# Dose–Response Association Between Antibiotic Use and the Risk of Bullous Pemphigoid: A UK Population-Based Case-Control Study

MRes student: **Yasaman Hashtrodylar**

Supervisors: Sonia Gran, Mikolaj Swiderski, Roger Knaggs

Collaborators: Yana Vinogradova, Antonia Lloyd-Lavery, Vibhore Prasad

Patient Partners: Isobel Davies, Ingrid Thompson

# Background and rationale

# Background: Bullous Pemphigoid (BP)


- **Most common autoimmune blistering skin disease** [1].

- **Clinical course:**
  - Begins with a **prodromal phase** (nonspecific **pruritus**, **erythema**, **urticarial lesions**) [2].
  - Progresses over weeks to years to the **bullous phase** with tense blisters [2].

- **Epidemiology:**
  - Typically diagnosed between **75–80 years** [3].
  - **Highest prevalence** in the **8th–9th decades of life** [3].

- **Pathogenesis:**
  - **Multifactorial**, rooted in an underlying autoimmune mechanism [4].

- **Risk factors:**
  - Both **disease-related** and **drug-induced factors** [5].
  - **Antibiotics** have been identified as a **potential risk factor for BP** according to **Swiderski et al. (2025)** [6].
  - In the **UK**, **antibiotic prescribing patterns** reflect **high exposure in older adults**, with **35% of all prescriptions** issued to individuals aged **65 years and older**, and the **highest prescribing rates** observed among those aged **86 years and above** [7].

# Rationale

- **Clinical significance of BP:**
  - **Incidence is increasing globally** [1].
  - BP has a **marked impact on quality of life** and is linked with **multiple comorbidities** [8].
  - Associated with a **mortality rate 3.6× higher** than the **age-matched general population** [9].

- The **UK has an ageing population** [1].

- **Research gap:**
  - There is a **need to investigate** whether a **dose–response relationship** exists between **antibiotic use and BP** in a **representative population**.

- **Rationale:**
  - According to **Hill's criteria**, specifically the **biological gradient criterion**, if an association is **causal**, **greater exposure** should generally lead to a **higher incidence of the outcome** [10].
  - Identifying such a relationship would also be **clinically important**, as it may guide **risk minimisation** and **safer prescribing practices** in older adults.

# Methods

# Methods

- **Study design:**
  - **Population-based, nested case-control study.**

- **Setting and data:**
  - **UK general practices** contributing data to the Clinical Practice Research Datalink AURUM.

- **Participants:**
  - Adults (aged ≥18 years) diagnosed with BP (cases) between 1998-2021.
  - Matched to **up to five controls** by birth year, sex, and general practice.

- **Outcome:**
  - BP diagnosis identified using validated read codes [11].

# Methods

❖ **Exposures:**

- Focused on **antibiotics** that had been **previously linked to an increased risk of BP** [6].
- Antibiotic exposures were **classified hierarchically** according to the **BNF** into **group, class, subclass** and **individual drug substance** levels.

❖ **Exposure window:**

- **Antibiotic prescriptions per individual** were ascertained in the **6–12 months exposure window** before the **index date**.
- The **six months immediately preceding the index date** were **excluded** to mitigate **protopathic bias**.
- A **six-month exclusion period** was applied based on the **average diagnostic delay** observed for BP [12, 13].

| Group | Class | Subclass | Substance |
|---|---|---|---|
| **Antibiotics** | Cephalosporins | | Cefalexin, Cefuroxime, Ceftriaxone, Cefaclor, Cefadroxil, Cefixime, Cefradine |
| | Macrolides | | Erythromycin, Clarithromycin, Azithromycin |
| | Metronidazole | | Metronidazole |
| | Penicillins | Broad-spectrum penicillins | Amoxicillin, Pivampicillin, Pivmecillinam |
| | | Penicillinase-resistant penicillins | Flucloxacillin |
| | Sulphonamides and Trimethoprim | | Sulfamethoxazole/Trimethoprim and Trimethoprim |
| | Tetracyclines | | Doxycycline, Minocycline, Lymecycline, Oxytetracycline, Tetracycline |

# Methods

- **Data preparation:**
  - The remaining prescription records required **cleaning and standardisation** to ensure accurate calculation of **exposure measures**.
  - For data cleaning, the records were processed using the **DrugPrep algorithm** [14], which was able to:
    - Handle **implausible and missing quantities**
    - Handle **implausible and missing numerical daily doses**
    - **Calculate duration**
    - Handle **implausible and missing durations**
    - Resolve **clashing start dates**
    - Resolve **overlapping prescriptions**
    - Handle **small gaps between prescriptions**

- **Antibiotic exposure metrics:**
  - **Number of prescriptions**
  - **Cumulative number of defined daily doses (DDDs)** = (Daily Dose / WHO DDD) × Number of Days
  - **Cumulative duration**
  - **Interval between last antibiotic use and BP onset (drug free interval)**
  - Calculation of exposure metrics were performed separately at the **group**, **class**, **subclass**, and **individual substance** levels (except for the cumulative duration).

- By assessing **multiple dimensions of antibiotic exposure**, the study aimed to capture **different aspects of antibiotic prescribing** that could influence the **risk of developing BP**.

# Methods

- **Confounders and covariates:**
  - **Matched on:** age, sex, GP practice.
  - **A priori confounder: skin infections.**
  - **Potential confounders: stroke**, **dementia**, **Parkinson's disease**, **Index of Multiple Deprivation**, **ethnicity**.
  - **Covariates: medications previously shown to be associated with BP** [6]**.**

- **Statistical analysis:**
  - **Models:**
    - **Evaluating exposure–outcome associations and testing for linearity:**
      - Conducted using **conditional logistic regression** with **fractional polynomials (FP)**.
    - **Estimation of ORs for categorical exposure variables:**
      - **Exposure variables** were **categorised** based on **clinical judgement** and **pharmacological rationale**.
      - Conducted using **conditional logistic regression**
    - **Bonferroni correction** was applied for multiple testing ($p < 0.001$).

  - **Model levels:**
    - Models were developed for **therapeutic group**, **classes**, **subclasses**, and **individual substances**.

# Results

# Study population

| | Cases | Controls |
|---|---|---|
| N | 11156 | 52201 |
| Age at index date (years), mean (SD) | 76.58 (14.26) | 75.99 (14.28) |
| Age group (years) | | |
| < 60 | 1252 (11.22%) | 6124 (11.73%) |
| 60–69 | 1247 (11.18%) | 6088 (11.66%) |
| 70–79 | 2957 (26.51%) | 14323 (27.44%) |
| 80–89 | 4172 (37.4%) | 19528 (37.41%) |
| ≥ 90 | 1528 (13.7%) | 6138 (11.76%) |
| Sex | | |
| Female | 6162 (55.2%) | 28957 (55.5%) |
| Male | 4994 (44.8%) | 23244 (44.5%) |
| Ethnicity | | |
| Asian | 436 (3.9%) | 1121 (2.1%) |
| Black | 209 (1.9%) | 673 (1.3%) |
| White | 9309 (83.4%) | 40505 (77.6%) |
| Other | 124 (1.1%) | 479 (0.9%) |
| Unknown | 1078 (9.7%) | 9423 (18.1%) |
| Index of Multiple Deprivation | | |
| 1 (most affluent) | 2426 (21.7%) | 11772 (22.6%) |
| 2 | 2322 (20.8%) | 10903 (20.9%) |
| 3 | 2299 (20.6%) | 10387 (19.9%) |
| 4 | 2048 (18.4%) | 9446 (18.1%) |
| 5 (most deprived) | 1796 (16.1%) | 8133 (15.6%) |
| Unknown | 265 (2.4%) | 1560 (3%) |
| Neurological comorbidities * | | |
| Dementia | 1008 (9%) | 1775 (3.4%) |
| Stroke | 1769 (15.9%) | 5502 (10.5%) |
| Parkinson disease | 264 (2.4%) | 547 (1%) |

# Exposure–Outcome Associations: Continuous Variables

- **Adjusted conditional logistic regression using fractional polynomial models** showed **statistically significant associations** between BP risk and multiple antibiotic exposure metrics (number of prescriptions, cumulative number of DDDs, cumulative duration, and drug-free interval) across almost all antibiotic group, classes, subclasses and substances, except for clarithromycin and oxytetracycline.
- In the adjusted model, **most associations** between antibiotic exposure metrics and BP risk followed a **linear pattern**.

# Exposure–Outcome Associations: Categorical Variables

## Antibiotics

| Number of prescriptions | | |
|---|---|---|
| Categories | Mutually adjusted | |
| | OR (95% CI) | P-value |
| 0 | 1 | - |
| 1 | 1.81 (1.68-1.95) | <0.001* |
| 2 or 3 | 2.27 (2.06-2.49) | <0.001* |
| 4 or more | 2.76 (2.36-3.24) | <0.001* |

| Cumulative number of DDDs | | |
|---|---|---|
| Categories | Mutually adjusted | |
| | OR (95% CI) | P-value |
| 0 | 1 | - |
| <= 7 | 1.82 (1.68-1.96) | <0.001* |
| > 7 and <= 14 | 2.24 (2.01-2.50) | <0.001* |
| > 14 and <= 28 | 2.32 (2.03-2.65) | <0.001* |
| > 28 | 2.35 (2.00-2.76) | <0.001* |

| Time interval from the last antibiotic prescription | | |
|---|---|---|
| Categories | Mutually adjusted | |
| | OR (95% CI) | P-value |
| > 12 | 1 | - |
| => 6 and < 8 | 2.21 (2.04-2.39) | <0.001* |
| => 8 and < 10 | 1.89 (1.71-2.09) | <0.001* |
| => 10 and < 12 | 1.85 (1.66-2.07) | <0.001* |

# Exposure–Outcome Associations: Categorical Variables

## Flucloxacillin

| Number of prescriptions | | |
|---|---|---|
| Categories | Mutually adjusted | |
| | OR (95% CI) | P-value |
| 0 | 1 | - |
| 1 | 2.22 (1.96-2.50) | <0.001* |
| 2 or more | 3.44 (2.80-4.23) | <0.001* |

| Cumulative number of DDDs | | |
|---|---|---|
| Categories | Mutually adjusted | |
| | OR (95% CI) | P-value |
| 0 | 1 | - |
| <= 7 | 2.28 (2.02-2.57) | <0.001* |
| > 7 and <= 14 | 3.26 (2.54-4.19) | <0.001* |
| > 14 | 2.97 (2.11-4.19) | <0.001* |

| Cumulative duration | | |
|---|---|---|
| Categories | Mutually adjusted | |
| | OR (95% CI) | P-value |
| 0 | 1 | - |
| <= 7 | 2.14 (1.89-2.43) | <0.001* |
| > 7 and <= 14 | 3.56 (2.84-4.46) | <0.001* |
| > 14 | 3.13 (2.28-4.30) | <0.001* |

| Time interval from the last antibiotic prescription | | |
|---|---|---|
| Categories | Mutually adjusted | |
| | OR (95% CI) | P-value |
| > 12 | 1 | - |
| => 6 and < 8 | 2.91 (2.49-3.40) | <0.001* |
| => 8 and < 10 | 2.35 (1.96-2.83) | <0.001* |
| => 10 and < 12 | 1.97 (1.60-2.43) | <0.001* |

# Exposure–Outcome Associations: Categorical Variables

## Trimethoprim

| Number of prescriptions | | |
|---|---|---|
| Categories | Mutually adjusted | |
| | OR (95% CI) | P-value |
| 0 | 1 | - |
| 1 | 1.47 (1.27-1.69) | <0.001* |
| 2 or 3 | 1.98 (1.58-2.49) | <0.001* |

| Cumulative number of DDDs | | |
|---|---|---|
| Categories | Mutually adjusted | |
| | OR (95% CI) | P-value |
| 0 | 1 | - |
| <= 7 | 1.47 (1.27-1.69) | <0.001* |
| > 7 and <= 14 | 2.25 (1.65-3.06) | <0.001* |
| > 14 and <= 28 | 1.38 (0.85-2.26) | 0.19485 |
| > 28 | 2.03 (1.28-3.21) | 0.00265 |

| Cumulative duration | | |
|---|---|---|
| Categories | Mutually adjusted | |
| | OR (95% CI) | P-value |
| 0 | 1 | - |
| <= 7 | 1.44 (1.25-1.67) | <0.001* |
| > 7 and <= 14 | 2.00 (1.47-2.73) | <0.001* |
| > 14 | 2.03 (1.50-2.75) | <0.001* |

| Time interval from the last antibiotic prescription | | |
|---|---|---|
| Categories | Mutually adjusted | |
| | OR (95% CI) | P-value |
| > 12 | 1 | - |
| => 6 and < 8 | 1.85 (1.54-2.21) | <0.001* |
| => 8 and < 10 | 1.33 (1.06-1.67) | 0.0126 |
| => 10 and < 12 | 1.70 (1.36-2.13) | <0.001* |

# Discussion

# Discussion

- Key results:
  - A **statistically significant association** was observed between **antibiotic exposure metrics** (number of prescriptions, cumulative number of DDDs, and cumulative duration) **and the development of BP** at most antibiotic levels **(except for clarithromycin and oxytetracycline)**, **consistent with Hill's criteria for causation** [10]**.**

  - **BP risk exceeded clinical relevance (adjusted OR > 2) only after specific exposure thresholds of frequency, cumulative dose, and duration were reached** for selected antibiotics (including flucloxacillin and trimethoprim).

  - **Dose-Response Trends Across Exposure Metrics:**

    - BP risk **increased** with a higher number of antibiotic prescriptions.
    - BP risk **increased** with higher cumulative number of DDDs or duration, often reaching a **plateau or declining at higher exposure levels**, suggesting a **saturation threshold.**
    - BP risk **attenuated** over time after exposure, indicating a **temporal effect.**

# Discussion

- **Strengths**
  - **Comprehensive exposure data:** CPRD Aurum captures every primary care antibiotic prescription with dosage, quantity, duration, and issue date.
  - **Representative database:** Reflects the UK general population.
  - **Large study population:** Provides strong statistical power.
  - **Robust data processing:** Prescription data cleaned using the *DrugPrep* algorithm.
  - **Confounder and covariate adjustment**
  - **Multiple exposure metrics**
  - **Detailed classification:** Allows analysis across therapeutic group, classes, subclasses, and individual substances.

- **Limitations**
  - **No confirmation of adherence:** Prescriptions may not have been dispensed or taken as prescribed.
  - **Confounding by indication:** Underlying infections prompting antibiotic use may themselves be linked to BP risk.
  - **Limited power in smaller subgroups:** Some classes, subclasses, or individual substances had few exposures.

# Discussion

- **Comparison with Existing Literature**
  - No previous studies have investigated the **dose–response relationship** between antibiotic use and BP development.

- **Clinical Implications**

•**Identification of exposure thresholds** (prescription frequency, cumulative number of DDDs, and duration) provides **actionable insight for antibiotic stewardship.**

•**Caution is warranted with repetitive, high-dose, or long-duration antibiotic use**, particularly in patients with established BP risk factors:

- •Older age
- •Female sex
- •Neurological comorbidities (stroke, dementia, Parkinson's disease)
- •Concomitant use of other BP-associated medicines [6]

•**Alternative antibiotics should be considered where clinically appropriate**, especially for flucloxacillin and trimethoprim which showed **strong and consistent associations** across multiple exposure metrics.

# References


[1]. Persson MSM, Harman KE, Vinogradova Y, et al. Incidence, prevalence and mortality of bullous pemphigoid in England 1998-2017: a population-based cohort study. *Br J Dermatol* 2021;184(1):68-77. doi: 10.1111/bjd.19022

[2]. Martinez N, Gadler T, Benson A, Lalicata K, Truman L. Bullous Pemphigoid: A Multifactorial Review of a Dermatologic Mystery. Adv Emerg Nurs J. 2021;43(4):272-8.

[3]. Sadik CD, Schmidt E. Resolution in bullous pemphigoid. Semin Immunopathol. 2019;41(6):645-54.

[4]. Geng RSQ, Wei E, Wilken B, Sibbald RG, Sibbald C. Serum Biomarkers in Bullous Pemphigoid: A Systematic Review. J Cutan Med Surg. 2024;28(5):463-7.

[5]. Bernard P, Antonicelli F. Bullous Pemphigoid: A Review of its Diagnosis, Associations and Treatment. Am J Clin Dermatol. 2017;18(4):513-28.

[6]. Swiderski M, Vinogradova Y, Knaggs RD, Harman K, Harwood RH, Prasad V, et al. Association between drugs and vaccines commonly prescribed to older people and bullous pemphigoid: a case-control study. Br J Dermatol. 2025;192(3):440-9.

[7]. Waterlow NR, Ashfield T, Knight GM. Observational study of antibiotic prescribing patterns by age and sex in primary care in England: why we need to take this variation into account to evaluate antibiotic stewardship and predict AMR variation. JAC Antimicrob Resist. 2025;7(1):dlae210.

[8]. Werth VP, Murrell DF, Joly P, Ardeleanu M, Hultsch V. Bullous pemphigoid burden of disease, management and unmet therapeutic needs. J Eur Acad Dermatol Venereol. 2025;39(2):290-300.

[9]. Kridin K, Schwartz N, Cohen AD, Zelber-Sagi S. Mortality in bullous pemphigoid: A systematic review and meta-analysis of standardized mortality ratios. J Dermatol. 2018;45(9):1094-100.

[10]. Hill AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? Proc R Soc Med. 1965;58(5):295-300.

[11]. Persson MSM, Harman KE, Vinogradova Y, et al. Validation study of bullous pemphigoid and pemphigus vulgaris recording in routinely collected electronic primary healthcare records in England. BMJ Open 2020;10(7):e035934. doi: 10.1136/bmjopen-2019-035934

[12]. della Torre R, Combescure C, Cortés B, Marazza G, Beltraminelli H, Naldi L, Borradori L. Clinical presentation and diagnostic delay in bullous pemphigoid: a prospective nationwide cohort. Br J Dermatol. 2012;167(5):1111-7.

[13]. Welsh B. Blistering skin conditions. Aust Fam Physician. 2009;38(7):484-90.

[14]. Pye SR, Sheppard T, Joseph RM, Lunt M, Girard N, Haas JS, et al. Assumptions made when preparing drug exposure data for analysis have an impact on results: An unreported step in pharmacoepidemiology studies. Pharmacoepidemiol Drug Saf. 2018;27(7):781-8.

University of Nottingham
UK | CHINA | MALAYSIA

# Thank you

**Contact:**
yasamanhsh75@gmail.com
www.linkedin.com/in/yasaman-hashtrodylar

NIHR | National Institute for Health and Care Research