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RESEARCH ARTICLE
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ASSOCIATION BETWEEN EARLY-LIFE ANTIBIOTIC EXPOSURE AND RECURRENT WHEEZING IN CHILDREN UNDER FIVE: A HOSPITAL-BASED CROSS-SECTIONAL STUDY IN THE AGRARIAN SETTING OF ADESH MEDICAL COLLEGE, HARYANA

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Abstract

Background

The prevalence of recurrent wheezing in preschool children is a growing public health concern in developing nations. The "gut-lung axis" hypothesis suggests that early-life antibiotic exposure (ELAE) induces intestinal dysbiosis, which may impair immune maturation and predispose infants to respiratory morbidity. In the agrarian belt of Kurukshetra, Haryana, this biological vulnerability is potentially exacerbated by environmental factors such as crop residue burning and biomass fuel use.

Objectives

To estimate the association between antibiotic exposure during the first 12 months of life and recurrent wheezing in children aged 12–60 months. Secondary objectives included analyzing antibiotic prescription patterns based on World Health Organization (WHO) indicators and assessing the impact of local environmental risk factors like stubble burning and indoor biomass fuel use.

Methodology

A hospital-based cross-sectional study was conducted at Adesh Medical College and Hospital (AMCH), Mohri, Shahabad, from February 2023 to November 2023. A systematic random sample of 400 children aged 1 to 5 years was selected from the Pediatric Department. Data were collected using a validated questionnaire adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase III. Antibiotic history was verified through medical records. Multivariate logistic regression was used to calculate Adjusted Odds Ratios (aOR).

Results

The prevalence of recurrent wheezing was 18.5%. Antibiotic use in the first year of life was significantly associated with recurrent wheezing (aOR: 2.18; 95% CI: 1.12–4.25; p=0.02). Children

receiving >3 courses of antibiotics faced a higher risk. Environmental analysis revealed that 70.2% of wheezers resided in areas with high exposure to agricultural smoke or used biomass fuel. Prescription analysis indicated a high reliance on third-generation cephalosporins (45%) for respiratory complaints.

Conclusion

Early-life antibiotic exposure acts as a significant, modifiable risk factor for recurrent wheezing in this rural population. The findings support the need for strict antimicrobial stewardship and public health interventions to mitigate environmental air pollution in Haryana.

Introduction

Respiratory morbidity constitutes a leading cause of death and disability among children under five globally. Recurrent wheezing, defined as three or more episodes of wheezing in the past year, is often the first clinical manifestation of asthma. While genetic predisposition is a key factor, the rapid rise in prevalence suggests a strong environmental component.[1]

The "hygiene hypothesis" and the more recent "microbiome depletion hypothesis" postulate that reduced microbial diversity in infancy—often driven by antibiotic use—disrupts the "gut-lung axis." This disruption fails to educate the naïve immune system, skewing it towards Th2-mediated allergic responses rather than tolerance.[2]

Regional Context: Haryana

This study is set in Adesh Medical College, located in the village of Mohri, Kurukshetra. This region presents a unique "double-hit" scenario:

1. **High Antibiotic Consumption:** India is one of the largest consumers of antibiotics worldwide. Studies from North India (2019–2021) indicate high rates of irrational prescribing for pediatric upper respiratory infections.[3]
2. **Environmental Stress:** The study area is an agricultural hub. The practice of burning paddy stubble (October–November) and wheat residue (April–May) releases massive particulate loads (PM2.5). Previous data (2016–2020) have linked these events to spikes in respiratory emergency visits.[4]

This research investigates whether antibiotic use in infancy acts as an independent driver of wheezing in a population already stressed by severe environmental pollution.

Review of Literature

Antibiotics and Asthma Risk

A growing body of evidence supports the link between ELAE and wheezing. A systematic review and meta-analysis of observational studies found that antibiotic exposure in the first two years of life was associated with an increased risk of childhood asthma (OR 1.37).[5] This aligns with findings from the Generation R study (Netherlands) and other cohorts which reported dose-dependent relationships.[6]

- **Mechanism:** The proposed mechanism involves the depletion of short-chain fatty acid (SCFA)-producing bacteria (e.g., Faecalibacterium, Bifidobacterium) in the infant gut. SCFAs like butyrate are essential for regulating pulmonary immune responses. Antibiotic-induced dysbiosis during the "critical window" of immune development (first 1000 days) appears to have lasting consequences.[2]

Prescription Patterns in India

Antibiotic overuse remains a critical challenge. A 2019 study analyzing antibiotic prescription rates in the public sector in India found that cephalosporins and penicillins accounted for the majority of prescriptions, often for viral fevers.[3] In Haryana, audits of primary care facilities (2021–2022) revealed that up to 89% of pediatric prescriptions for respiratory ailments contained antibiotics, often disregarding the WHO AWaRe (Access, Watch, Reserve) classification.[8]

Environmental Triggers in North India

The impact of crop residue burning on respiratory health is well-documented. Satellite data analyses (2016–2020) show distinct spikes in Aerosol Optical Depth (AOD) over Haryana during harvest seasons, correlating with increased respiratory symptoms in local populations.[4] Furthermore, the use of biomass fuel for cooking remains prevalent in rural households, contributing to indoor air pollution that acts synergistically with outdoor smog.[9]

Objectives

Primary Objective:

- To determine the association (Odds Ratio) between antibiotic use in the first 12 months of life and recurrent wheezing in children aged 12–60 months.

Secondary Objectives:

- To estimate the prevalence of recurrent wheezing in the pediatric outpatient population of Mohri, Haryana.
- To assess antibiotic prescription patterns for children under five, referencing WHO AWaRe classifications.
- To evaluate the association between environmental risk factors (biomass fuel, stubble burning proximity) and wheezing.

Methodology

Study Design and Setting

- **Design:** Hospital-based cross-sectional analytical study.
- **Setting:** Department of Paediatrics, Adesh Medical College and Hospital (AMCH), Mohri, Shahabad, Haryana
- **Duration:** March 2023, to November 2023.

Study Population and Sample Size

- **Population:** Children aged 12 to 60 months presenting to the Pediatric OPD or Ward.
- **Sample Size:** Based on a prevalence of childhood asthma/wheezing of approximately 7.9% in India [10], and allowing for amargin of error of 3% with 95% confidence, the calculated sample size was 310. To account for non-response and subgroup analysis, 400 children were enrolled.

Sampling Technique

Systematic random sampling was used. Every 3rd eligible child registered in the OPD on data collection days (Mon/Wed/Fri) was approached for inclusion.

Data Collection Tools

1. **Questionnaire:** A structured interview schedule was developed based on the **ISAAC Phase III** core questionnaire (translated into Hindi/Haryanvi).[11] It included sections on demographics, wheezing history, and environmental exposures.
2. **Medical Record Review:** Antibiotic exposure in the first year was ascertained by reviewing "baby files," vaccination cards, and discharge summaries provided by parents. Recall alone was not relied upon for antibiotic history.

Ethical Consideration

The study protocol was approved by the Institutional Ethics Committee (IEC) of Adesh Medical College.[12] Written informed consent was obtained from parents. The study adhered to ICMR National Ethical Guidelines 2017).[13]

Statistical Analysis

Data were analyzed using SPSS version 25.0.

- **Descriptive:** Frequencies and percentages for categorical variables.
- **Inferential:** Chi-square tests for univariate analysis. Binary logistic regression for multivariate

analysis to calculate Adjusted Odds Ratios (aOR), controlling for confounders like family history of atopy, mode of delivery, and smoke exposure. Significance was set at $p < 0.05$.

Results and Analysis

Socio-Demographic Profile

A total of 400 children were included. The mean age was 34.5 months. 58% were male, and 65% resided in rural villages surrounding Shahabad.

Prevalence of Wheezing

- **Recurrent Wheezing (>3 episodes/year):** 18.5% (n=74).
- **Ever Wheezed:** 26.0%. Antibiotic Exposure
- **Prevalence:** 62% (248/400) received at least one antibiotic course in infancy.
- **Prescription Pattern:** The most frequently verified antibiotics were third-generation Cephalosporins (45%) and Macrolides (15%), often categorized as "Watch" group antibiotics by WHO.

Risk Factor Analysis (Logistic Regression)

Table 1: Multivariate Analysis of Risk Factors for Recurrent Wheezing

Risk Factor	aOR (95% CI)	p-value
Antibiotic Use (<1 yr)	**2.18 (1.12 – 4.25)**	**0.02**
>3 Antibiotic Courses	**2.85 (1.45 – 5.60)**	**0.003**
Family Hx of Asthma	2.90 (1.60 – 5.25)	<0.001
Biomass Fuel Use	2.20 (1.25 – 3.80)	0.005
Stubble Burning Proximity	2.45 (1.35 – 4.40)	0.002
C-Section Delivery	1.95 (1.10 – 3.45)	0.02

- **Key Finding:** Antibiotic exposure in the first year was an independent predictor of recurrent wheezing, with the risk doubling for exposed children.
- **Dose-Response:** A "dose-response" relationship was observed; children with >3 courses had a higher odds ratio (2.85) than those with 1-2 courses.
- **Environment:** Proximity to stubble burning and biomass fuel use were significant independent risk factors, confirming the high environmental burden.

Discussion

Antibiotics and the Vulnerable Lung

The study demonstrates a significant association (aOR 2.18) between early-life antibiotic use and recurrent wheezing. This is consistent with the meta-analysis by Slob et al. (2017) [6] and recent findings from 2021–2022.[5] The high utilization of broad-spectrum cephalosporins in this cohort is concerning, as these agents are known to cause severe collateral damage to the infant microbiome, depleting protective bacterial strains that regulate immune tolerance.[7]

The Environmental "Double Hit"

The results highlight a unique challenge in Haryana. The significant association with stubble burning proximity (aOR 2.45) suggests that children here face a "double hit": internal immune

dysregulation from antibiotics and external airway inflammation from particulate matter (PM2.5). Studies utilizing satellite data (2016–2020) have previously established the massive pollutant load in this region during harvest seasons.[4] Our data confirms that children living closest to these emission sources are at the highest risk.

Rational Prescribing Gap

The prescription analysis reveals a deviation from stewardship principles. The preference for "Watch" group antibiotics (Cephalosporins, Azithromycin) over "Access" group drugs (Amoxicillin) mirrors trends reported in other North Indian studies.[3] This practice, often driven by the desire for rapid recovery in a competitive private healthcare market, contributes not only to antimicrobial resistance but potentially to the chronic disease burden of asthma.

Conclusion

This study provides evidence that **early-life antibiotic exposure is an independent risk factor for recurrent wheezing** among children in rural Haryana. This risk is compounded by environmental factors, specifically biomass fuel use and exposure to crop residue burning. The findings suggest that the rising burden of pediatric respiratory morbidity in this region is likely driven by the intersection of irrational antibiotic prescribing and environmental pollution.

Recommendations

- **Antimicrobial Stewardship:** Implementation of strict antibiotic policies at Adesh Medical College and surrounding clinics, prioritizing "Access" group antibiotics and discouraging empirical use for viral ARIs.
- **Public Awareness:** Education campaigns for parents in Mohri/Shahabad regarding the long-term respiratory risks of unnecessary antibiotics.
- **Pollution Control:** Continued policy enforcement against stubble burning and promotion of clean cooking fuels (LPG) to protect pediatric lung health.

Limitations

- **Recall Bias:** While medical records were used, some antibiotic history may have been missed or inaccurately recalled if records were lost.
- **Confounding by Indication:** Children who received antibiotics might have been inherently more prone to infections ("reverse causation"), although the multivariate model attempted to adjust for this.

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