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Effect of antibiotic use for acute bronchiolitis on new-onset asthma in children

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Early-life use of antibiotics is associated with asthma. We examined the effect of antibiotic use for early-life bronchiolitis on the development of new-onset asthma in children from Taiwan between 2005 and 2010. Data were from the National Health Insurance Research Database 2010, and diseases were coded using the International Classification of Disease (ICD). We classified the patients, all of whom had bronchiolitis, as having asthma or not having asthma. Asthma was diagnosed using ICD criteria and by use of an inhaled bronchodilator and/or corticosteroid twice in one year. We identified age at asthma onset, sex, residential area, history of atopy and NSAID use, age at first use of antibiotics, and the specific antibiotic, and adjusted for these factors using conditional logistic regression analysis. Among all individuals, there was a relationship between risk of new-onset asthma with use of a high dose of an antibiotic (adjusted odds ratio [aOR] = 3.33, 95% confidence interval [CI] = 2.67–4.15). Among the different antibiotics, macrolides (aOR = 2.87, 95% CI = 1.99–4.16), and azithromycin specifically (aOR = 3.45, 95% CI = 1.62–7.36), had the greatest effect of development of asthma.

Environmental and genetic factors play important roles in the development of asthma. In particular, the “hygiene hypothesis” proposes that growing up in a hygienic environment, with reduced exposure to microbes, promotes T-helper type 2 (Th2) immunity¹. The association of early-life use of antibiotics with wheezing symptoms and allergic rhinoconjunctivitis in childhood, and the lack of adverse effects of antibiotics on atopic diseases in childhood among infants who live in rural environments, are consistent with this hypothesis^{2,3}.

Among babies younger than 1 year-old, acute bronchiolitis (a lower respiratory tract infection) is the leading cause of hospitalization due to recurrent wheezing episodes, and a history of bronchiolitis during infancy is associated with an increased risk for development of asthma⁴. Infants hospitalized with bronchiolitis due to respiratory syncytial virus (RSV) infection have a 2 to 3-fold increased risk of developing asthma later in childhood⁵. Another study also demonstrated that rhinovirus-induced wheezing within the first 3 years of life was associated with a nearly 10-fold increased risk for development of asthma by age six⁶.

Although most cases of acute bronchiolitis are due to viral infections, antimicrobial drugs may be used if there is suspected co-infection by bacteria or for their anti-inflammatory effects. In fact, a high incidence of bacterial co-infection was reported in children with severe bronchiolitis who required mechanical ventilation⁷. Bacterial PCR of blood samples showed that 10% of patients with acute bronchiolitis may have bacteremia, and the major species are *Haemophilus influenzae* and *Streptococcus pneumoniae*⁸. However, use of antibiotics early in life and a history of bronchiolitis increase the risk for asthma in young adolescents⁹. Other studies reported that polymorphisms of Toll-like receptor 4 might modify the effect of environmental factors, such as use of antibiotics, on the

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| | Non-asthma group (n = 2082) | | Asthma group (n = 2082) | | p value |
|-----------------------|--------------------------------|--------|----------------------------|--------|---------|
| | N | (%) | N | (%) | |
| Age, mean \pm SD | 3.32 \pm 1.25 | | 3.34 \pm 1.26 | | 0.497 |
| Gender | | | | | |
| Female | 921 | (44.2) | 907 | (43.6) | 0.662 |
| Male | 1161 | (55.8) | 1175 | (56.4) | |
| Resident urbanization | | | | | |
| Urban | 463 | (22.2) | 451 | (21.7) | 0.807 |
| Suburban | 806 | (38.7) | 818 | (39.3) | |
| Rural | 813 | (39.0) | 813 | (39.0) | |
| Comorbidities | | | | | |
| Allergic rhinitis | 644 | (30.9) | 668 | (32.1) | 0.423 |
| Atopic dermatitis | 466 | (22.4) | 456 | (21.9) | 0.709 |
| Chronic rhinitis | 309 | (14.8) | 322 | (15.5) | 0.574 |
| Acute sinusitis | 1615 | (77.6) | 1628 | (78.2) | 0.627 |
| GERD | 31 | (1.5) | 23 | (1.1) | 0.273 |
| Medication | | | | | |
| NSAIDs | 482 | (23.2) | 471 | (22.6) | 0.685 |

Table 1. The characteristics of non-asthma and asthma group (N = 4,164).

development of asthma^{10,11}. Thus, reducing the use of antibiotics and prevention of bronchiolitis during infancy may prevent the development of asthma, especially in genetically susceptible subjects.

There is strong evidence of an association between acute bronchiolitis and asthma, but it is unclear whether this is a causal relationship. Although antibiotic use in early life increases the risk of asthma, the effect of antibiotic use by children for treatment of early-life bronchiolitis on the development of new-onset asthma is unknown. The aim of this study, which used the Taiwan National Health Insurance Research Database (NHIRD) 2010 database, was to assess the relationship of early-life antibiotic use for bronchiolitis with new-onset asthma in children.

Methods

Data source. This study examined claims data from the NHIRD, which includes the medical records of 99% of the 23.74 million residents of Taiwan, and 97% of Taiwanese hospitals and clinics who have contracts with the National Health Research Institute in Taiwan. The NHIRD contains comprehensive healthcare information, including demographic data of insured individuals, dates of clinical visits, diagnostic codes, and prescription details. All data in this study were from the NHIRD 2010, and all diseases were classified using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). Patients with records indicating a diagnosis of bronchiolitis (ICD-9:466.19) during the first 2 years of life from 2000 to 2010 were included. New-onset asthma was diagnosed using the criteria of ICD-9:493 and receipt of selective beta-2 agonists and/or inhaled corticosteroid treatments twice within one year from age 2 to 18 years-old. This study was approved by the Institutional Review Board of Kaohsiung Medical University (KMUHIRB-E (I)-20150168). All methods were performed in accordance with the relevant guidelines and regulations.

Use of antibiotics. The use of antibiotics was obtained from the outpatient prescription database, which listed the name of the drug and had data on dosage, date, and duration of prescription. To investigate the effect of antibiotic dosage, the cumulative defined daily dose (DDD) was calculated. Antibiotic use was defined as the prescription of at least one antibiotic (anatomical therapeutic chemical [ATC] code J01*) in the 5 years before onset of asthma. We analyzed data on 3 individual common classes of antibiotics—penicillins (ATC code J01C*), cephalosporins (ATC code J01D*), and macrolides (ATC code J01F*). Other types of antibiotics (quinolones, sulphonamides, glycopeptides, lincosamides) were analyzed separately.

Potential confounders. The potential confounders of asthma included urban residence, allergic rhinitis (ICD9-CM: 477.8, 477.9), atopic dermatitis (ICD9-CM: 691.8), chronic rhinitis (ICD9-CM:472.0), acute sinusitis (ICD9-CM:461), gastroesophageal reflux disease (GERD) (ICD9-CM:530.81), and use of a nonsteroidal anti-inflammatory drug (NSAID) in the 120 days before the onset of asthma.

Statistical analysis. Pearson's chi-square test or Fisher's exact test and the independent *t* test were used to evaluate the significance of differences of categorical and continuous variables in patients with and without asthma. Conditional logistic regression analysis was used to calculate the association between asthma and antibiotic use. As recommended by the World Health Organization (WHO), cumulative DDD was used to quantify the cumulative dose of antibiotics, and the categories were "low dose", "moderate dose", and "high dose". Several co-variables, including age, sex, residential area, history of atopy, and use of NSAIDs, were included in the statistical model. The effect of antibiotic class was also analyzed by adjusting for co-variables and type of antibiotic, except for penicillins, cephalosporins, and macrolides. Odds ratios (ORs), adjusted ORs (aORs) and 95% confidence intervals (CIs) were calculated to show the risk for development of asthma. We further used false discovery

| Antibiotic use | Non-asthma group (n = 2082) | | Asthma group (n = 2082) | | Unadjusted Model | | Adjusted Model | |
|-----------------------|--------------------------------|--------|----------------------------|--------|------------------|---------|-----------------|---------|
| | N | (%) | N | (%) | OR (95% CI) | p value | OR (95% CI) | p value |
| J01 antibiotic* | | | | | | | | |
| No | 419 | (20.1) | 233 | (11.2) | 1.00 | | 1.00 | |
| Yes | 1663 | (79.9) | 1849 | (88.8) | 2.00(1.68–2.38) | <0.001 | 2.10(1.75–2.52) | <0.001 |
| Cumulative DDDs | | | | | | | | |
| <3.50 | 648 | (31.1) | 557 | (11.2) | 1.55(1.27–1.88) | <0.001 | 1.64(1.35–2.01) | <0.001 |
| 3.50–10.00 | 544 | (26.1) | 589 | (26.8) | 1.95(1.60–2.37) | <0.001 | 2.23(1.81–2.74) | <0.001 |
| >10.00 | 471 | (22.6) | 703 | (33.8) | 2.68(2.20–3.27) | <0.001 | 3.33(2.67–4.15) | <0.001 |
| p for trend | | | | | | <0.001 | | <0.001 |
| J01C Penicillin** | | | | | | | | |
| No | 419 | (24.5) | 233 | (13.7) | 1.00 | | 1.00 | |
| Yes | 1293 | (75.5) | 1468 | (86.3) | 2.04(1.71–2.44) | <0.001 | 1.77(1.43–2.20) | <0.001 |
| Cumulative DDDs | | | | | | | | |
| <3.00 | 572 | (33.4) | 505 | (29.7) | 1.59(1.30–1.94) | <0.001 | 1.48(1.18–1.87) | 0.001 |
| 3.00–7.55 | 351 | (20.5) | 412 | (24.2) | 2.11(1.70–2.62) | <0.001 | 2.00(1.55–2.57) | <0.001 |
| >7.55 | 370 | (21.6) | 551 | (32.4) | 2.68(2.18–3.30) | <0.001 | 2.62(2.02–3.39) | <0.001 |
| p for trend | | | | | | <0.001 | | <0.001 |
| J01D Cephalosporins** | | | | | | | | |
| No | 419 | (27.0) | 233 | (15.2) | 1.00 | | 1.00 | |
| Yes | 113 | (73.0) | 1297 | (84.8) | 2.06(1.73–2.47) | <0.001 | 1.67(1.32–2.11) | <0.001 |
| Cumulative DDDs | | | | | | | | |
| <1.25 | 420 | (27.1) | 446 | (29.2) | 1.91(1.55–2.35) | <0.001 | 1.61(1.26–2.06) | <0.001 |
| 1.25–3.31 | 351 | (22.7) | 401 | (26.2) | 2.05(1.66–2.55) | <0.001 | 1.71(1.31–2.23) | <0.001 |
| >3.31 | 359 | (23.2) | 450 | (29.4) | 2.25(1.82–2.77) | <0.001 | 1.85(1.40–2.45) | <0.001 |
| p for trend | | | | | | <0.001 | | <0.001 |
| J01F Macrolides** | | | | | | | | |
| No | 419 | (43.2) | 233 | (23.8) | 1.00 | | 1.00 | |
| Yes | 551 | (56.8) | 745 | (76.2) | 2.43(2.00–2.95) | <0.001 | 2.02(1.48–2.76) | <0.001 |
| Cumulative DDDs | | | | | | | | |
| <1.50 | 240 | (24.7) | 234 | (23.9) | 1.75(1.38–2.23) | <0.001 | 1.57(1.12–2.20) | 0.009 |
| 1.50–3.00 | 140 | (14.4) | 205 | (21.0) | 2.63(2.01–2.44) | <0.001 | 2.38(1.66–3.41) | <0.001 |
| >3.00 | 171 | (17.6) | 306 | (31.3) | 3.22(2.56–4.12) | <0.001 | 2.87(1.99–4.16) | <0.001 |
| p for trend | | | | | | <0.001 | | <0.001 |
| J01 Others** | | | | | | | | |
| No | 419 | (77.9) | 233 | (61.6) | 1.00 | | 1.00 | |
| Yes | 119 | (22.1) | 145 | (38.4) | 2.19(1.64–2.93) | <0.001 | 1.40(0.71–2.75) | 0.466 |
| Cumulative DDDs | | | | | | | | |
| <1.00 | 45 | (8.4) | 54 | (14.3) | 2.16(1.41–3.31) | <0.001 | 1.40(0.67–2.97) | 0.466 |
| 1.00–2.00 | 30 | (5.6) | 35 | (9.3) | 2.10(1.26–3.51) | <0.001 | 1.34(0.61–2.96) | 0.466 |
| >2.00 | 44 | (8.2) | 56 | (14.8) | 2.29(1.50–3.51) | <0.001 | 1.45(0.67–3.12) | 0.466 |
| p for trend | | | | | | <0.001 | | 0.485 |

Table 2. The association between antibiotics cumulative DDDs exposure categories and the risk of new-onset asthma in ever-diagnosed bronchiolitis population (n = 4,164). *Adjusted age, gender, resident urbanization, other comorbidities and medication. **Adjusted age, gender, resident urbanization, other comorbidities, medication and other subtype antibiotics. ***p value was performed by Benjamini-Hochberg P-values.

correction to evaluate each variables and Benjamini-Hochberg P-values were showed in tables. All statistical analyses were performed using SAS 9.3, and p value below 0.05 was considered significant.

Results

After propensity score matching, the non-asthma and asthma groups each had 2082 children (Table 1). Due to matching, these 2 groups had similar distributions of age, sex, urbanization of residence, comorbidities, and use of NSAIDs.

Univariable and multivariable analysis indicated significant associations between use of any antibiotic and cumulative DDDs of any antibiotic with development of new-onset asthma (aOR = 2.10, 95% CI = 1.75–2.20) (Table 2). Analysis of the different classes of antibiotics also indicated significant associations between the cumulative DDDs for penicillins, cephalosporins, and macrolides with the development of new onset asthma. Use of other antibiotics (quinolones, sulphonamides, glycopeptides, lincosamides) had no effect on the development of asthma.

| Exposure age | Non-asthma group | | asthma group | | Model I | | |
|---------------|------------------|--------|--------------|--------|----------------------|---------|----------|
| | N | (%) | N | (%) | Adjusted OR (95% CI) | p value | p value* |
| Overall | 2082 | | 2082 | | | | |
| No exposure | 426 | (20.5) | 256 | (12.3) | 1.00 | | |
| <=1 years old | 1371 | (65.9) | 1396 | (67.1) | 1.01(0.78–1.30) | 0.955 | 0.955 |
| 2 years old | 242 | (11.6) | 361 | (17.3) | 1.67(1.27–2.19) | <0.001 | <0.001 |
| 3 years old | 43 | (2.1) | 69 | (3.3) | 1.99(1.29–3.09) | 0.002 | 0.003 |
| 3–4 y/o | 1735 | | 1721 | | | | |
| No exposure | 400 | (23.1) | 239 | (13.9) | 1.00 | | |
| <=1 years old | 1130 | (65.1) | 1128 | (65.5) | 0.90(0.68–1.19) | 0.463 | 0.463 |
| 2 years old | 182 | (10.5) | 300 | (17.4) | 1.78(1.32–2.39) | <0.001 | <0.001 |
| 3 years old | 23 | (1.3) | 54 | (3.1) | 2.95(1.72–5.07) | <0.001 | <0.001 |
| >4 y/o | 347 | | 361 | | | | |
| No exposure | 26 | (7.5) | 17 | (4.7) | 1.00 | | |
| <=1 years old | 241 | (69.5) | 268 | (74.2) | 1.26(0.59–2.71) | 0.552 | 0.871 |
| 2 years old | 60 | (17.3) | 61 | (16.9) | 1.18(0.52–2.64) | 0.696 | 0.871 |
| 3 years old | 20 | (5.8) | 15 | (4.2) | 0.92(0.35–2.43) | 0.871 | 0.871 |

Table 3. The association between childhood antibiotics exposure and the risk of new-onset asthma in ever-diagnosed bronchiolitis population (n = 4164). Adjusted age, gender, resident urbanization, other comorbidities and medication. *Benjamini-Hochberg P-values.

| Antibiotic use | Non-asthma group | | Asthma group | | Unadjusted Model | | | Adjusted Model | | |
|-----------------------|------------------|--------|--------------|--------|------------------|---------|------------|------------------|---------|------------|
| | N | (%) | No | (%) | OR (95% CI) | p value | p value*** | OR (95% CI) | p value | p value*** |
| Less than 5 years old | | | | | | | | | | |
| J01 Antibiotics* | 1335 | (76.9) | 1496 | (86.9) | 1.99(1.67–2.38) | <0.001 | <0.001 | 2.07(1.82–2.50) | <0.001 | <0.001 |
| J01C Penicillin** | 1007 | (71.6) | 1155 | (83.7) | 2.04(1.70–2.45) | <0.001 | <0.001 | 1.73(1.38–2.17) | <0.001 | <0.001 |
| J01D Cephalosporins** | 855 | (68.1) | 1001 | (81.6) | 2.08(1.73–2.51) | <0.001 | <0.001 | 1.68(1.31–2.14) | <0.001 | <0.001 |
| J01F Macrolides** | 408 | (50.5) | 558 | (71.3) | 2.43(1.98–2.99) | <0.001 | <0.001 | 1.97(1.41–2.75) | <0.001 | <0.001 |
| J01 Others** | 83 | (17.2) | 94 | (29.5) | 2.01(1.44–2.82) | <0.001 | <0.001 | 1.30(0.64–2.65) | 0.474 | 0.474 |
| More than 5 years old | | | | | | | | | | |
| J01 Antibiotics* | 328 | (94.5) | 353 | (97.8) | 2.56(1.10–5.92) | 0.028 | 0.029 | 2.85(1.21–6.69) | 0.016 | 0.032 |
| J01C Penicillin** | 286 | (93.8) | 313 | (97.5) | 2.60(1.12–6.03) | 0.026 | 0.029 | 2.53(0.98–6.53) | 0.055 | 0.092 |
| J01D Cephalosporins** | 275 | (93.5) | 296 | (97.4) | 2.56(1.10–5.94) | 0.029 | 0.029 | 1.85(0.70–4.91) | 0.218 | 0.267 |
| J01F Macrolides** | 143 | (88.3) | 187 | (95.9) | 3.11(1.32–7.30) | 0.009 | 0.015 | 2.72(0.87–8.53) | 0.085 | 0.121 |
| J01 Others** | 36 | (65.5) | 51 | (86.4) | 3.37(1.33–8.53) | 0.011 | 0.016 | 5.17(0.33–80.22) | 0.240 | 0.267 |

Table 4. The association between the species of antibiotics and the risk of new-onset asthma in ever-diagnosed bronchiolitis population by age-stratified analysis (n = 4,164). *Adjusted age, gender, resident urbanization, other comorbidities and medication. **Adjusted age, gender, resident urbanization, other comorbidities, medication and other subtype antibiotics. ***Benjamini-Hochberg P-values.

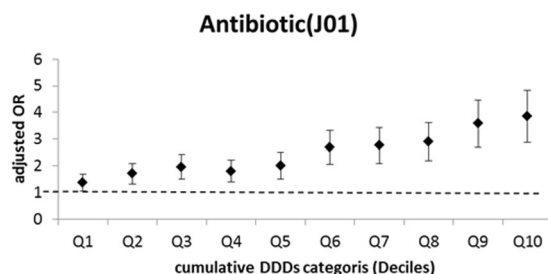


Figure 1. The relationship of cumulative DDDs of antibiotics and new-onset asthma.

| Antibiotic use | Non-asthma group | | Asthma group | | Unadjusted Model | | | Adjusted Model | | |
|----------------------|------------------|--------|--------------|--------|------------------|---------|----------|-----------------|---------|----------|
| | N | (%) | N | (%) | OR (95% CI) | p value | p value* | OR (95% CI) | p value | p value* |
| J01C Penicillin | | | | | | | | | | |
| J01CA Amoxicillin | 1712 | | 1701 | | | | | | | |
| No | 419 | (24.5) | 233 | (13.7) | 1.00 | | | 1.00 | | |
| Yes | 1293 | (75.5) | 1468 | (86.3) | 2.04(1.71–2.44) | <0.001 | <0.001 | 1.77(1.43–2.20) | <0.001 | <0.001 |
| Cumulative DDDs | | | | | | | | | | |
| <3.00 | 573 | (33.5) | 506 | (29.7) | 1.59(1.30–1.94) | <0.001 | <0.001 | 1.49(1.18–1.87) | 0.001 | 0.002 |
| 3.00–7.50 | 338 | (19.7) | 394 | (23.2) | 2.10(1.69–2.60) | <0.001 | <0.001 | 1.99(1.54–2.56) | <0.001 | <0.001 |
| >7.50 | 382 | (22.3) | 568 | (33.4) | 2.67(2.18–3.29) | <0.001 | <0.001 | 2.61(2.02–3.38) | <0.001 | <0.001 |
| J01CA01 Ampicillin | 467 | | 293 | | | | | | | |
| No | 419 | (89.7) | 233 | (79.5) | 1.00 | | | 1.00 | | |
| Yes | 48 | (10.3) | 60 | (20.5) | 2.25(1.49–3.39) | <0.001 | <0.001 | 0.97(0.41–2.31) | 0.948 | 0.948 |
| Cumulative DDDs | | | | | | | | | | |
| <0.50 | 24 | (5.1) | 28 | (9.6) | 2.10(1.19–3.70) | 0.011 | 0.013 | 1.04(0.41–2.62) | 0.943 | 0.948 |
| 0.50–1.00 | 5 | (1.1) | 10 | (3.4) | 3.60(1.22–10.65) | 0.021 | 0.022 | 1.82(0.43–7.69) | 0.413 | 0.508 |
| >1.00 | 19 | (4.1) | 22 | (7.5) | 2.08(1.10–3.93) | 0.023 | 0.023 | 0.68(0.22–2.09) | 0.506 | 0.578 |
| J01F Macrolides | | | | | | | | | | |
| J01FA10 Azithromycin | 544 | | 462 | | | | | | | |
| No | 419 | (77.0) | 233 | (50.4) | 1.00 | | | 1.00 | | |
| Yes | 125 | (23.0) | 229 | (49.6) | 3.29(2.51–4.32) | <0.001 | <0.001 | 2.53(1.41–4.53) | 0.002 | 0.003 |
| Cumulative DDDs | | | | | | | | | | |
| <1.67 | 49 | (9.0) | 48 | (10.4) | 1.76(1.15–2.71) | 0.010 | 0.012 | 1.43(0.72–2.82) | 0.306 | 0.408 |
| 1.67–2.50 | 48 | (8.8) | 109 | (23.6) | 4.08(2.81–5.94) | <0.001 | <0.001 | 3.39(1.80–6.38) | <0.001 | <0.001 |
| >2.50 | 28 | (5.1) | 72 | (15.6) | 4.62(2.91–7.36) | <0.001 | <0.001 | 3.45(1.62–7.36) | 0.001 | 0.002 |
| J01FA01 Erythromycin | 840 | | 767 | | | | | | | |
| No | 419 | (49.9) | 233 | (30.4) | 1.00 | | | 1.00 | | |
| Yes | 421 | (50.1) | 534 | (69.6) | 2.28(1.86–2.80) | <0.001 | <0.001 | 2.00(1.40–2.85) | <0.001 | <0.001 |
| Cumulative DDDs | | | | | | | | | | |
| <1.50 | 202 | (24.0) | 218 | (28.4) | 1.94(1.51–2.49) | <0.001 | <0.001 | 1.77(1.21–2.59) | 0.003 | 0.004 |
| 1.50–3.00 | 80 | (9.5) | 107 | (14.0) | 2.41(1.73–3.35) | <0.001 | <0.001 | 2.18(1.41–3.38) | <0.001 | <0.001 |
| >3.00 | 139 | (16.5) | 209 | (27.2) | 2.70(2.07–3.53) | <0.001 | <0.001 | 2.44(1.61–3.37) | <0.001 | <0.001 |

Table 5. The association between the subtype of antibiotics and the risk of new-onset asthma in ever-diagnosed bronchiolitis population (n = 4164). Adjusted age, gender, resident urbanization, other comorbidities, medication and other subtype antibiotics. *Benjamini-Hochberg P-values.

Overall, individuals who first received an antibiotic by age 2 (aOR = 1.67, 95% CI = 1.27–2.19) or by age 3 (aOR = 1.99, 95% CI = 1.29–3.09) were more significantly more likely to develop new-onset asthma (Table 3). Age-stratified analysis indicated that children who were diagnosed with new-onset asthma at age 3–4 were significantly more likely to have used antibiotics by age 2 (aOR = 1.78, 95% CI = 1.32–2.39) and by age 3 (aOR = 2.95, 95% CI = 1.72–5.07). This relationship was not significant for children who had new-onset asthma when older than age 4.

Separation of patients into 3 groups based on cumulative DDDs of antibiotic used indicated the frequency of overall antibiotic use in the asthma group was 11.2% (low dose), 26.8% (moderate dose), and 33.8% (high dose) (Table 2). There was also dose-dependent relationship of cumulative DDDs of antibiotic use with the aOR for new-onset asthma (Fig. 1).

Age-stratified analysis indicated that children younger than 5 who used any antibiotic (aOR = 2.07, 95% CI = 1.82–2.50), a penicillin (adjusted OR 1.73, 95% CI 1.73–2.17), a cephalosporin (adjusted OR 1.68, 95% CI 1.31–2.14), or a macrolide (adjusted OR 1.97, 95% CI 1.41–2.75) had an increased risk for development of new-onset asthma (Table 4). There was no such effect for children older than 5.

Further analysis of the cumulative DDDs of specific penicillins and macrolides indicated that a high doses of amoxicillin (aOR = 2.61 95% CI = 2.02–3.38), erythromycin (aOR = 2.44 95% CI = 1.61–3.37), and azithromycin (aOR = 3.45 95% CI = 1.62–7.36) were associated with increased risk for development of new-onset asthma (Table 5).

Discussion

Our results indicate that early use of antibiotics in children with acute bronchiolitis is significantly associated with the development of new-onset asthma. In addition, our comparison of the effects of individual antibiotics indicated that use of high-dose azithromycin had the greatest impact on the development of new-onset asthma.

Bronchiolitis is the most common reason for hospitalization of infants and young children. The respiratory syncytial virus (RSV) and rhinovirus are the two most common pathogens in acute bronchiolitis¹², and infection

with either virus increases the risk for allergic diseases. Previous research reported that azithromycin can reduce wheezing episodes during RSV-mediated bronchiolitis due to its anti-inflammatory effect¹³. In Taiwan, antibiotics may be prescribed to children younger than age 2 for treatment of acute bronchiolitis, in an effort to prevent bacterial supra-infection or to reduce wheezing. In recent decades, there has been a high rate of antibiotic use by children with lower respiratory tract infections, especially during infancy¹⁴. Use of antibiotics during infancy increases the risk of childhood asthma^{15,16}. Moreover, when pregnant women use antibiotics in the third trimester of pregnancy, their children have a slightly increased risk of asthma when in preschool¹⁷.

Asthma is a multifactorial disease, and genetic and environmental factors can affect the risk for developing asthma. The diagnosis of asthma early in a child's life is particularly difficult, because cooperation during functional testing is difficult and frequent wheezing episodes may occur due to respiratory infections. Thus, clinicians diagnose asthma in young children based on symptoms using a differential diagnosis, and response to anti-asthmatic medications. Over-diagnosed asthma is sometimes found in Taiwan due to the policy of national health insurance and the diagnosis of real asthma is difficult in young age. In our study, we examined children with diagnoses of asthma who received selective beta-2 agonists and/or inhaled corticosteroids twice within 1 year to discriminate asthma from transient wheezing.

During gestation, the immune phenotype is skewed toward Th2 cells, which protect the developing embryo from the maternal immune response and thereby prevent miscarriage and premature labor¹⁸. Thus, Th2-associated chemokines—CCL17 and CCL22—are highest in neonates, and decline gradually during the following 2 years¹⁹. The presence of environmental stimuli during pregnancy and early life may potentially affect Th1/Th2 immunity and programming by affecting chromatin remodeling processes²⁰. In particular, Th2 dominance can shift to Th1 dominance following exposure to infectious microorganisms. However, disruption of the normal Th1/Th2 realignment during infancy may lead to the development of atopic disease and allergy²⁰.

Most interactions between the host immune system and the microbiome occur in the gut. Symbiotic or pathogenic microorganisms in the human gut can affect the immune response through gut-associated lymphoid tissues and Toll-like receptors, ultimately leading to various inflammatory disorders²¹. Antibiotic use during early life can alter the gut microbiota, and lead to inflammatory and allergic diseases. These adverse effects of antibiotic use diminish with age, based on the results of the present study (Table 4) and a previous cohort study, which reported that the risk of developing asthma in children was greater when they used antibiotics during the first year of life¹⁵.

No previous studies have examined the simultaneous presence of acute bronchiolitis and antibiotic use on the development of asthma in children. However, previous cohort studies in Europe and Canada reported associations in the use of ampicillin, cephalosporin, and macrolides with the development of asthma, and positive correlations of the accumulative antibiotic dose with asthma^{9,16}. We found that use of azithromycin, relative to other antibiotics, led to a greater risk of new-onset asthma among children younger than age 5 who ever had acute bronchiolitis. A previous multi-center cohort study reported that macrolide use during the first year of life was associated with an increased risk for wheezing by 36 months⁹. Macrolides have anti-bacterial effects and immunomodulatory properties, in that they inhibit T-cell activation, down-regulate pro-inflammatory cytokines, decrease mucus synthesis, and promote apoptosis of inflammatory cells in the bronchial epithelium^{22,23}. In addition, macrolides can reduce the frequency of exacerbations in eosinophilic asthma²⁴, and is given to infants who have wheezing symptoms resulting from acute bronchiolitis. However, the mechanism by which macrolide administration during infancy induces new-onset asthma during childhood is unknown. Further studies of this important topic are necessary.

Our study had several limitations in that we did not consider confounding by socioeconomic status, exposure to second-hand smoke, and the presence of atopic diseases in parents and siblings. Moreover, definitive diagnosis of asthma in preschool children is difficult, and under-diagnosis may have led to the inappropriate exclusion of certain children.

In conclusion, our results provide evidence that infants with acute bronchiolitis who use a penicillin, a cephalosporin, or a macrolide—especially azithromycin—have an increased risk for developing new-onset asthma during childhood. These results are consistent with the predictions of the hygiene hypothesis.

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Author Contributions

I-Lun Chen and Hsin-Chun Huang: wrote the main manuscript text. Yu-Han Chang, Hsin-Yi Huang, Wei-Ju Yeh, Ting-Yi Wu: collect and analyze data. Jau-Ling Suen: prepare figure San-Nan Yang, Chih-Hsing Hung: revised whole article. All authors reviewed the manuscript.

Additional Information

Competing Interests: The authors declare no competing interests.

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