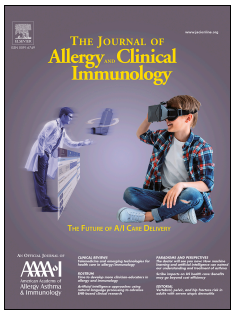
Journal Pre-proof



Association between early antibiotic treatment and clinical outcomes in children hospitalized for asthma exacerbation

Yusuke Okubo, MD, MPH, Kenta Horimukai, MD, Nobuaki Michihata, MD, MPH, PhD, Kojiro Morita, RN, PHN, MPH, Hiroki Matsui, MPH, Kiyohide Fushimi, MD, PhD, Hideo Yasunaga, MD, PhD

PII: S0091-6749(20)30750-8

DOI: https://doi.org/10.1016/j.jaci.2020.05.030

Reference: YMAI 14597

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 7 January 2020

Revised Date: 17 May 2020

Accepted Date: 19 May 2020

Please cite this article as: Okubo Y, Horimukai K, Michihata N, Morita K, Matsui H, Fushimi K, Yasunaga H, Association between early antibiotic treatment and clinical outcomes in children hospitalized for asthma exacerbation, *Journal of Allergy and Clinical Immunology* (2020), doi: https://doi.org/10.1016/j.jaci.2020.05.030.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology.

Journal Pre-proof

Association between early antibiotic treatment and clinical outcomes in children hospitalized for asthma exacerbation

Yusuke Okubo, MD, MPH[a*, b, c], Kenta Horimukai, MD[d], Nobuaki Michihata, MD, MPH, PhD[e], Kojiro Morita, RN, PHN, MPH [c], Hiroki Matsui, MPH[c], Kiyohide Fushimi, MD, PhD[f], and Hideo Yasunaga, MD, PhD[c]

a. Department of Epidemiology, University of California, Los Angeles, Fielding School of Public Health

b. Department of Social Medicine, National Center for Child Health and Development

c. Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo

d. Department of Pediatrics, Jikei University Katsushika Medical Center

e. Department of Health Services Research, Graduate School of Medicine, The University of Tokyo

f. Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine

*Corresponding Author: Yusuke Okubo

National Center for Child Health and Development,

2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan

Tel.: +81-3-3416-0181, Fax: +81-3-3416-2222, E-mail: sunning_dale@yahoo.co.jp

Short Title: Association between antibiotic use and clinical outcomes in asthma

Financial disclosure:
The authors have no financial relationships relevant to this article to disclose.

Funding source:
This work was supported by grants from the Ministry of Health, Labour, and Welfare, Japan. Yusuke Okubo is supported by the Wagatsuma Fellowship from the University of California, Los Angeles, Asia Pacific Center.

Journal Pre-proof

Journal Pre-proof

Potential conflict of interest:
The authors have no conflicts of interest relevant to this article to disclose.

Authorship statement:
Drs. Okubo and Michihata designed the data collection instruments, coordinated the data, drafted the initial manuscript, and performed the initial analyses. Drs. Horimukai, Matsui, and Morita and Profs. Fushimi and Yasunaga supervised the data collection, revised the manuscript, and approved the final manuscript as submitted. Each author has seen and approved the submission of the manuscript and takes full responsibility for its contents.

Journal Pre-proof

Journal Pre-proof

Abstract

Background: Professional society guidelines recommend against routine early antibiotic use in the treatment of asthma exacerbation without comorbid bacterial infection. However, high antibiotic prescribing rates have been reported in developed countries,

Objective: We assessed the effectiveness of this strategy in the routine care of children.

Methods: Using data on 48,743 children hospitalized for asthma exacerbation with no indication of bacterial infection during 2010–2018, we conducted a retrospective cohort study to compare clinical outcomes and resource utilization between children who received early antibiotic treatment and those who did not.

Results: Overall, 19,866 children (41%) received early antibiotic treatment. According to the propensity score matching analysis, children with early antibiotic treatment had longer hospital stay (mean difference, 0.21 days; 95% confidence interval [CI], 0.18–0.28), higher hospitalization costs (mean difference, 83.5 US dollars; 95% CI, 62.9–104.0), and higher risk of probiotic use (risk ratio, 2.01; 95% CI, 1.81–2.23) than children who did not receive early antibiotic therapy. Similar results were found from inverse probability of treatment weighting, G-computation, and instrumental variable methods and sensitivity analyses. The risks of mechanical ventilation and 30-day readmission were similar between the groups or slightly higher in the treated group, depending on the statistical models.

Conclusions: Antibiotic therapy may be associated with prolonged hospital stay, elevated hospitalization costs, and high risk of probiotic use without improving treatment failure and readmission. Our findings highlight the need for reducing inappropriate antibiotic use among children hospitalized for asthma.

Clinical implications:
Antibiotics may not be associated with better clinical outcomes and should not be routinely prescribed in children hospitalized for asthma and treated with corticosteroids and inhaled short-acting β-agonists.

Capsule summary:
Early antibiotic therapy was associated with prolonged hospital stay, elevated hospitalization costs, and risk of probiotic use without improving the risks of treatment failure and readmission among children hospitalized for asthma.

Abbreviation:
short-acting β_2-agonists, SABAs; the Diagnosis Procedure Combination, DPC; the International Classification of Diseases, 10th revision, ICD-10; US dollars, USD; propensity score, PS; inverse probability of treatment weighting, IPTW; instrumental variable, IV; standard deviation, SD; average treatment effects on the treated, ATT; average treatment effect, ATE; Japanese Yen, JPY; mean difference, MD; risk ratio, RR; Confidence interval, CI;

Journal Pre-proof

Key words;
Asthma, antibiotics, children, propensity score matching, inverse probability of treatment weighting, g-computation, instrumental variable

Journal Pre-proof

Introduction

Asthma is the most common chronic lung condition in children. Asthma exacerbation cases are responsible for a large number of emergency department visits, hospitalization, and healthcare expenditures each year in the most developed countries.(1,2) In Japan, asthma affects 8–13% of children.(3,4) Among them, approximately 15% were uncontrolled and < 5% experienced severe wheeze in the past year.(4,5) According to most guidelines for the treatment of patients hospitalized for asthma exacerbation,(6, 7) the standard treatments consist of oxygen administration, inhaled short-acting β_2-agonists (SABAs), and systemic corticosteroids. Some current guidelines(6,8) recommended against routine antibiotic prescription for asthma exacerbations in the absence of concurrent bacterial infections because respiratory viral infections are the major cause of asthma exacerbations.(9,10) Although a previous study based on a large database reported adherence to those guidelines and variation in treatment patterns in adults,(11) data derived from a pediatric population are still lacking.

Recent findings suggest the benefits of long-term antibiotic use for individuals with persistent uncontrolled asthma in terms of reducing the number of asthma exacerbation events and improving the quality of life of patients.(12–14) Additionally, several clinical trials suggested the potential benefits of early antibiotic treatment (especially for macrolides) for asthma exacerbation among adults and children.(13,15–17) However, caution is needed in interpreting the findings obtained from the ideal setting of randomized controlled trials because the real-world effectiveness under the usual circumstances of healthcare practice remain unclear owing to differences in the population of interest, illness severity, underlying conditions, and causative agents of asthma exacerbations.(9) Indeed, conflicting evidence have emerged from a

Journal Pre-proof

large observational study, suggesting that early antibiotic treatment has no clear benefits for adults with asthma execerbation.(1) Furthermore, comparative effectiveness studies on routine antibiotic use in pediatric asthma are still lacking. Therefore, we sought to evaluate the potential effects of antibiotics when added to corticosteroids and SABAs on clinical outcomes in the treatment of asthma exacerbation, to solve the issue of the limited generalizability of previous findings to the routine care of children. For this purpose, we conducted a retrospective cohort study among children hospitalized with asthma in the absence of indication for bacterial infections. We hypothesized that the addition of early antibiotic use to standard treatment would not produce further clinical benefits.

Journal Pre-proof

Journal Pre-proof

Methods

Study design and data source

We conducted a retrospective cohort study using the Diagnosis Procedure Combination (DPC) inpatient database between July 1, 2010, and March 31, 2018. The details of the database have been described elsewhere.(18) Briefly, it contains data collected from > 1000 hospitals and covers up to 55% of all inpatient admissions to acute-care hospitals in Japan. The database stores hospital discharge records and administrative claims data for approximately 7 million inpatients per year. It includes information on the following: patient's diagnosis; preexisting comorbidities at admission; complications during hospitalization; patient's age, sex, and body weight and height; and dates of procedures and treatments. Approval for the present study was obtained from the institutional review board at The University of Tokyo. The board waived the requirement for informed consent because of the anonymous nature of the data.

We included pediatric inpatients aged between 3 months and 15 years with a diagnosis of asthma exacerbation. Hospitalizations for asthma exacerbation were defined using the International Classification of Diseases, 10th revision (ICD-10) code, as a primary diagnosis of asthma or a principal diagnosis of acute respiratory failure combined with a secondary diagnosis of asthma (Supplemental Table 1). To avoid misclassification and maximize the accuracy of the asthma diagnosis, we restricted the analyses to inpatients treated with intravenous systemic corticosteroids and short-acting β_2 stimulant inhalation, because these medications are currently considered the standard therapy for moderate to severe asthma exacerbation.(19) We excluded patients with potential indications for antibiotic treatment based on the diagnoses at admission (Supplemental Table 1), diagnostic procedures (computed tomography and blood culture), and

treatments (neuraminidase inhibitors and antifungal agents). Patients treated with neuraminidase inhibitors were excluded because children hospitalized for influenza treatment could have concurrent bacterial infections.(20) Patients with chronic medical conditions were also excluded from the analyses. Chronic medical conditions were defined according to the pediatric complex chronic conditions classification system version 2.(21) When a patient had more than one admission during the study period, we randomly selected one admission.

Measurements of variables

We defined early antibiotic treatment as antibiotic therapy initiated during the first 2 days of hospitalization. Antibiotics were categorized into the following groups: penicillin, macrolides, cephalosporins, quinolones, tetracyclines, and other types (Supplemental Table 2). In the primary analysis, patients who started antibiotic therapy after day 2 of hospitalization were considered the untreated group because later treatment could be a marker of patient deterioration and a mediator of the causal pathway from early treatment to the outcomes of interest.

Our primary outcome of interest was the mean length of hospital stay in days. The secondary outcomes were hospitalization costs in US dollars (USD), risk of invasive or noninvasive mechanical ventilation during hospitalization, risk of 30-day readmission, and risk of probiotic use after 2 days of hospitalization as an indication for antibiotic-associated diarrhea. In Japan, the payment for hospitalization cost is offered by a universal health care insurance and the fees are set by a government committee. The currency exchange rate was set at 100 Japanese yen per USD.

The patient characteristics included age, sex, weight status (thin, normal, overweight, or obese), preexisting comorbidities (food allergy, allergic rhinitis, and atopic dermatitis), admission to academic hospitals, ambulance use, residency in the ordinance-designated city, and

Journal Pre-proof

154 medications used within the first 2 days of hospitalization. These variables were selected as
155 potential confounders based on our best prior knowledge from previous study findings.(22–25)
156 The weight status was determined using z-scores of weight-for-length (for patients aged < 2
157 years), weight-for-height (for patients aged 2–5 years), or body mass index for age (for patients
158 aged > 5 years) calculated from the child growth references of the World Health
159 Organization.(26) Preexisting comorbidities were identified based on ICD-10 codes
160 (Supplemental Table 1). The medications used within the first 2 days of hospitalization included
161 antitussives, mucolytics, antihistamines, leukotriene receptor antagonists, xanthine, β-stimulants,
162 an inhaled corticosteroid, and acetaminophen (Supplemental Table 2 and 3).

163 **Statistical analysis**

164 Baseline characteristics are summarized as means and proportions for continuous and
165 categorical variables. We calculated the proportions of patients who received the initial antibiotic
166 treatment given all inpatients with asthma and ascertained the variabilities across hospitals that
167 had at least 50 inpatients over the study period.

168 To estimate the effects of initial antibiotic treatment on the outcomes of interest among
169 pediatric inpatients with asthma exacerbation, we used four different statistical methods:
170 propensity score (PS) matching, stabilized inverse probability of treatment weighting (IPTW), G-
171 computation algorithm, and instrumental variable (IV) method. PS matching is a statistical
172 technique used to account for potential confounders through matching based on the probability
173 of treatment assignment conditional on observed baseline covariates (PSs).(27) We calculated
174 PSs using multivariable logistic regression models and conducted one-to-one matching between
175 individuals of the treated and untreated groups using the nearest-neighbor methods within a
176 caliper distance of < 20% of standard deviation (SD) for PS. We checked the balance between

Journal Pre-proof

the two groups based on absolute standardized differences.(27) An absolute standardized difference of > 10% was considered a meaningful imbalance. After PS matching, we compared the outcomes of interest between the matched groups, which was considered the average treatment effects on the treated (ATTs).

As PS matching is unable to estimate average treatment effects (ATEs) and may have limited generalizability from the matched population to the overall population, we applied G-methods. The G-methods were designed to estimate the marginal causal effects using marginal structural models (MSMs).(28) The parameters of MSMs can be estimated using two classes of estimators: IPTW and the G-computation algorithm.(29) IPTW creates a pseudo-population in which the treatment is independent of the measured potential confounders so that the weighted treatment effect estimates will be unbiased.(30) IPTW can estimate ATEs and ATTs over the marginal distribution of observed covariates. We applied stabilized IPTW rather than unstabilized IPTW because stabilized IPTW can preserve the original sample size, produce appropriate variance estimates in the treatment effects, and adequately control type I errors.(31) Correct model specifications were checked according to the average of stabilized IPWs (IPW for the ATE model, mean 1.0 [SD, 0.3]; IPW for the ATT model, 1.0 [SD, 0.5]).

To check the robustness of parameters in MSMs from IPTW, we analyzed data using the G-computation algorithm. G-computation is commonly considered an alternative to IPTW because it produces more efficient and stable estimates and can better handle heterogeneity than IPTW.(28,32) G-computation can be conducted by creating pseudo-observations for each study participant and uniformly setting treatments of interest for all observations, and by imputing the counterfactual outcomes from the observed data.(28,32) For this method, we estimated both ATEs and ATTs, and estimated standard errors and confidence limits through bootstrapping.

Journal Pre-proof

The IV method can be employed to infer causal estimates even in the presence of unobserved confounders if the IV meets the following four assumptions: 1) relevance (IV has effects on exposure of interest), 2) exclusion restriction (IV affects the outcome only through exposure), 3) exchangeability (ignorable treatment assignment; IV does not share common causes with outcome), and 4) monotonicity.(33,34) We used a grouped-treatment approach, a form of IV analysis that assigns a probability of receiving antibiotic treatment at the hospital level as a valid instrument.(35) The ATEs were estimated using a two-stage least-square method.

We conducted several sensitivity analyses using IPTW and IV methods. First, we excluded patients who received antibiotic therapy after day 2 of hospitalization from the untreated group. Second, we excluded missing data on weight status. Third, we stratified the data based on age categories (< 2, 2–5, and 6–15 years), and types of antibiotics (penicillin, macrolides, and cephalosporin). Forth, we used generalized linear models with gamma distribution to deal with skewed distribution of continuous variables under stabilized IPTW. Fifth, we excluded patients who were admitted to the hospitals where > 90% or < 10% of inpatients received antibiotics. Sixth, we have accounted for the inflation of healthcare costs and currency valuations between JPY and USD during 2010–2018, with 2018 as a reference year, to estimate the mean difference in hospitalization costs. The effect estimates were reported with 95% confidence intervals (CIs). All data were analyzed using Stata software version 15.1 (StataCorp LP, College Station, TX, USA).

Journal Pre-proof

Results

We identified a total of 48,743 children eligible for our study. Overall, 19,866 patients (40.8%) received antibiotics within the first 2 days of their hospitalization. The most commonly prescribed antibiotics were macrolide (7986 patients [40.2%]), cephalosporin (4802 patients [24.2%]), and penicillin (4150 patients [20.9%]) (Supplemental Table 4), with wide variations in antibiotic use across hospitals (Figure 1). A total of 1452 patients (3.0%) received antibiotics after hospital day 2 (Supplemental Table 5).

The baseline characteristics are summarized in Table 1. Children with early antibiotic treatment were more likely to be younger (4.1 vs. 4.8 years); more likely to receive tipepidine (a synthetic, non-opioid antitussive of thiambutenes class) (36.3% vs. 22.1%), first-generation antihistamine (9.5% vs. 3.5%), leukotriene receptor antagonist (74.5% vs. 69.5%), β_2 receptor-stimulant tape (46.1% vs. 35.4%), or acetaminophen (16.9% vs. 8.9%); and less likely to be admitted to academic hospitals (5.9% vs. 10.4%). After PS matching, the baseline characteristics were well balanced between the two groups.

According to the PS matching analysis (Supplement Table 6), children in the early treatment group had slightly longer hospital stay (mean difference [MD], 0.21 days; 95% CI, 0.17–0.25; Figure 2A), higher hospitalization costs (MD, 83.5 USD; 95% CI, 62.9–104; Figure 2B), and higher risks of requiring mechanical ventilation (risk ratio [RR], 2.06; 95% CI, 0.02–0.18; Figure 2C). Treatment with injection drugs was the most important contributor to increased hospitalization costs (Supplemental Table 7). The risk of 30-day readmission was almost identical between the treated and untreated groups (RR, 0.90; 95% CI, 0.70–1.16; Figure 2D), whereas the risk of probiotic use was higher in the early treatment group (RR, 2.01; 95% CI,

Journal Pre-proof

1.81–2.23). Similar results were observed when we applied IPTW and the G-computation algorithm for ATEs and ATTs. IV analyses did not show the same findings in the risks of mechanical ventilation and 30-day readmission, whereas the length of stay, costs, and risk of receiving probiotics were almost similar to those in other statistical methods.

Sensitivity analyses were conducted using IPTW (ATE and ATT) and IV methods. First, when we excluded patients with delayed antibiotic treatment (Supplemental Table 8), early antibiotic treatment did not show any clear benefits in terms of the duration of hospitalization; healthcare costs; and risks of mechanical ventilation, 30-day readmission, and probiotic use (Supplemental Table 8). Second, similar patterns were found when we excluded patients with missing data on weight status (Supplemental Table 9). Third, when we stratified the data on types of antibiotics (Supplemental Table 10 and Figure 3A), the RR of probiotic use was higher in those treated with cephalosporin and penicillin than in those treated with macrolides. When we stratified the data by age categories (Supplemental Table 11), the RRs of mechanical ventilation among children aged 2–5 and > 6 years showed the same direction across different statistical models; however, the estimates were imprecise with wide CIs (Figure 3B). Fourth, when we used generalized linear models with gamma distribution, similar results were obtained (Supplemental Table 12). Fifth, we observed similar effect estimates when we exclude data for patients who were admitted to hospitals that had < 10% of inpatients or > 90% of inpatients who received antibiotics (Supplemental Table 13). Sixth, when we accounted for inflation of healthcare costs in Japan and currency valuations between Japan and USD, we observed higher hospitalization costs in the early antibiotic treatment groups (Supplemental Table 14).

Journal Pre-proof

Discussion

In this large study based on a national database with approximately 48,000 children hospitalized for asthma exacerbation, we found that nearly 41% of children hospitalized for asthma received early antibiotic treatment in the absence of indications for bacterial infection. We observed wide variations in antibiotic use at the hospital level. Early antibiotic treatment did not show any clear clinical benefits but was rather associated with very slightly longer hospital stay and healthcare costs, and slightly higher risk of mechanical ventilation. These results were consistent among different statistical models and sensitivity analyses performed to reduce the potential selection bias, misclassification, unmeasured confounding, and model misspecification. Our findings reflect the setting of routine care for children with asthma and strongly support the current recommendation against routine antibiotic use in the absence of comorbid bacterial infection. Additionally, our findings highlight the need for further interventions to promote appropriate antibiotic treatment in the setting of pediatric asthma exacerbation.

Evidence about antibiotic treatment for asthma exacerbation has been limited and derived from randomized controlled trials, mainly in adults.(12,17) For example, one trial in adults with asthma exacerbation revealed that treatment with macrolides (telithromycin) was associated with improvement of respiratory function; however, approximately 60% of individuals had either *Mycoplasma pneumoniae or Chlamydophila pneumoniae* infections, while the findings suggest antimicrobial effects when specific organisms are present.(17) In addition, generalizability of the results to children hospitalized with asthma exacerbation could be limited because respiratory viral infections are the major cause of asthma exacerbations.[8–10] Several clinical trials in preschool children with a history of wheeze showed that early administration of azithromycin reduced the duration of symptoms and mitigated the illness severity, suggesting anti-

inflammatory and/or immunomodulation effects.(13,16) Recently, a retrospective observational study in approximately 20,000 adults with asthma exacerbation found that antibiotic therapy could be related to longer hospital stay, higher hospital cost, and similar risks of treatment failure(1). Correspondingly, similar findings were observed from a retrospective observational study with approximately 5000 children hospitalized for asthma exacerbation(36); however, these findings were limited by the small sample size of the antibiotic therapy group (n = 174) and the use of only one type of antibiotic (azithromycin). Our results extend the prior findings and confirm the lack of benefits of early treatment with antibiotics, including macrolide, cephalosporin, and penicillin, when added to systemic corticosteroids and SABA inhalation among children hospitalized for asthma exacerbation in the absence of evidence of bacterial infection.

The overuse and misuse of antibiotics are important public health problems because they can be responsible for the increase in healthcare expenditure, elevated risks of adverse events, and development of antimicrobial resistance.(37) Recent data on the consumption of antibiotic formulations in children showed that Japan was the worst country among 36 high-income countries in terms of appropriate use of antibiotics.(37) These findings were consistent with those of our previous studies with respect to overuse and physician preference of broad-spectrum antibiotics in common pediatric infectious diseases.(38–41) The discontinuation of ineffective, inappropriate, or potentially harmful treatment may be necessary for sustainable medicine. A previous study in the US based on a large database reported that 60% of adults hospitalized with asthma received antibiotics in the absence of an indication for antibiotics with a wide variation in antibiotic treatment patterns in adults.(11) Correspondingly, our study found that approximately 40% of pediatric inpatients with asthma exacerbation received antibiotic treatments, and this

Journal Pre-proof

practice was highly variable across different hospitals (some hospitals rarely used antibiotics, whereas other hospitals almost always used antibiotics), suggesting a clear need for education on best practices. The potential reasons for the different rates of antibiotic use at the hospital level include the difficulty of differentiating bacterial from nonbacterial infections, fear of treatment failure, and gaps in knowledge about the benefits of antibiotic therapy. Our findings on the widely different practice patterns across hospitals at a national level clearly indicate the need for further study to understand what institutional characteristics drove these differences and the promotion for discontinuation of unnecessary antibiotics in children with asthma exacerbation to optimize antibiotic use because early antibiotic treatment lacks sufficient evidence for effectiveness, is against the epidemiological evidence on the role of viral infections in asthma exacerbation,(9) and could lead to the emergence of resistant strains.

This study had several limitations. Although we conducted several different statistical analyses to control for potential confounders and model misspecification, these biases could be inherent in our study. For example, the diagnoses of preexisting comorbidities may have been underestimated because of possible underreporting or potential misclassification of ICD-10 codes, resulting in biases toward either direction. The detailed clinical presentation (e.g., the length of symptoms preceding the admission), laboratory data, prescriptions before admission, and patient information were unavailable in the DPC database, which may have resulted in residual confounding and confounding by the indication of therapy. For instance, the choice to treat with early antibiotics could be associated with severity on presentation, while we were trying to account for illness severity by adjusting for baseline characteristics and adjunctive treatment as a proxy of severity. Propensity score matching and all G-methods were not able to account for the unmeasured confounders. However, IV analyses could account for these

unobserved covariates, although some findings from IV analyses were imprecise with wide CIs, possibly owing to rare outcomes. Although we checked for correct model specifications for PS and IPTW, model misspecification might induce some bias. However, the findings from G-computation analyses reached the same results, suggesting the robustness of our results. In one of the sensitivity analyses, we excluded children who received antibiotics after 2 days of their hospitalization referring to the methods in previous study. However, this method could lead to block the causal pathway from the treatment of interest to outcome and induce collider-stratification bias, although our findings in the sensitivity analyses were closer to the main results. Caution is needed to interpret the timing of antibiotic use because we defined early antimicrobial therapy based on any antibiotic use within 2 days of hospitalization, not based on the start of asthma symptoms. Also, careful interpretation is required for healthcare costs for pediatric inpatients with asthma based on the difference between Japan (mean healthcare costs, 2000 USD per pediatric inpatient) and the US (mean healthcare cost, 10000 USD per pediatric inpatient).(25) We observed difference in healthcare costs between the early antibiotic group and control group by 50-80 USD per patient, but this could be clinically insignificant. Although the utilization of a national representative inpatient database was the strength of our study in terms of generalizability, the translatability of our findings to external populations may still be uncertain. Further studies are desirable to select patients for whom antibiotics are indicated based on asthma phenotypes.(42,43)

In summary, early antibiotic treatment for pediatric asthma exacerbation was associated with longer hospital stay, higher healthcare costs, and higher risks of probiotic use without improving the risks of treatment failure and 30-day readmission. Our results support the current clinical guidelines that recommend against the routine use of antibiotics for asthma exacerbation.

Further studies and interventions are needed to reduce inappropriate antibiotic use in children hospitalized for asthma exacerbation.

Figure Legends

Figure 1. Proportions of antibiotic use among children hospitalized for asthma at the hospital level, with 95% confidence intervals

Figure 2. Associations between early antibiotic use and clinical outcomes in terms of length of hospital stay (A), hospitalization cost (B), mechanical ventilation (C), 30-day readmission (D), and probiotic use (E)

Figure 3. Sensitivity analyses for the association between early antibiotic use and risk of probiotic use by antibiotic types (A) and risk of mechanical ventilation by age categories (B)

Reference List:

1. Stefan MS, Shieh MS, Spitzer KA, Pekow PS, Krishnan JA, Au DH, et al. Association of Antibiotic Treatment with Outcomes in Patients Hospitalized for an Asthma Exacerbation Treated with Systemic Corticosteroids. JAMA Intern Med. 2019;179(3):333–9.

2. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: The Asthma Insights and Reality in Europe (AIRE) study. Eur Respir J. 2000;16(5):802–7.

3. Morikawa E, Sasaki M, Yoshida K, Adachi Y, Odajima H, Akasawa A. Nationwide

survey of the prevalence of wheeze, rhino-conjunctivitis, and eczema among Japanese children in 2015. Allergol Int . 2019;(xxxx). Available from: https://doi.org/10.1016/j.alit.2019.08.010

4. Sasaki M, Morikawa E, Yoshida K, Adachi Y, Odajima H, Akasawa A. The change in the prevalence of wheeze, eczema and rhino-conjunctivitis among Japanese children: Findings from 3 nationwide cross-sectional surveys between 2005 and 2015. Allergy Eur J Allergy Clin Immunol. 2019;1572–5.

5. Yoshida K, Sasaki M, Adachi Y, Itazawa T, Odajima H, Saito H, et al. Childhood asthma control in Japan: A nationwide, cross-sectional, web-based survey. Asian Pacific J Allergy Immunol. 2018;36(1):16–21.

6. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention . Global Strategy for Asthma Management and Prevention. 2018 [cited 2019 Apr 28]. p. 1–32. Available from: https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-tracked_v1.3.pdf

7. Arakawa H, Hamasaki Y, Kohno Y, Ebisawa M, Kondo N, Nishima S, et al. Japanese guidelines for childhood asthma 2017. Allergol Int . 2017;66(2):190–204. Available from: http://dx.doi.org/10.1016/j.alit.2016.11.003

8. British Thoracic Society/Scottish Intercollegiate Guideline Network. British Guideline on the Management of Asthma . 2016 [cited 2019 Nov 11]. Available from: http://www.globalasthmanetwork.org/management/guides/bosnia_and_herzegovina/British guideline for asthma.pdf

9. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al.

Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. BMJ . 1995 May 13;310(6989):1225–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7767192

10. Chauhan AJ, Inskip HM, Linaker CH, Smith S, Schreiber J, Johnston SL, et al. Personal exposure to nitrogen dioxide (NO 2) and the severity of virus-induced asthma in children. Lancet. 2003;361(9373):1939–44.

11. Lindenauer PK, Stefan MS, Feemster LC, Shieh M-S, Carson SS, Au DH, et al. Use of Antibiotics Among Patients Hospitalized for Exacerbations of Asthma. JAMA Intern Med . 2016 Sep 1;176(9):1397–400. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2016.4050

12. Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet . 2017;390(10095):659–68. Available from: http://dx.doi.org/10.1016/S0140-6736(17)31281-3

13. Bacharier LB, Guilbert TW, Mauger DT, Boehmer S, Beigelman A, Fitzpatrick AM, et al. Early Administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses a randomized clinical trial. JAMA - J Am Med Assoc. 2015;314(19):2034–44.

14. LEWIS-FANING E, DAVIES W. A controlled trial of tetracyc-line (Achromycin) therapy in asthmatic children during the winter period. Acta Allergol . 1960;15(6):492–516. Available from: http://www.ncbi.nlm.nih.gov/pubmed/13761762

15. Koutsoubari I, Papaevangelou V, Konstantinou GN, Makrinioti H, Xepapadaki P, Kafetzis D, et al. Effect of clarithromycin on acute asthma exacerbations in children: an open randomized study. Pediatr Allergy Immunol . 2012 Jun;23(4):385–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22433020

16. Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Pedersen TM, Vinding RK, et al. Azithromycin for episodes with asthma-like symptoms in young children aged 1-3 years: A randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2016;4(1):19–26.

17. Johnston SL, Blasi F, Black PN, Martin RJ, Farrell DJ, Nieman RB. The Effect of Telithromycin in Acute Exacerbations of Asthma. N Engl J Med. 2006;354(15):1589–600.

18. Matsuda S, Fujimori K, Kuwabara K, Ishikawa KB, Fushimi K. Diagnosis Procedure Combination as an Infrastructure for the Clinical Study. Asian Pacific J Dis Manag. 2013;5(4):81–7.

19. Arakawa H, Hamasaki Y, Kohno Y, Ebisawa M, Kondo N, Nishima S, et al. Japanese guidelines for childhood asthma 2017. Allergol Int. 2017;66(2):190–204.

20. Uda K, Okubo Y, Shoji K, Miyairi I, Morisaki N, Michihata N, et al. Trends of neuraminidase inhibitors use in children with influenza related respiratory infections. Pediatr Pulmonol . 2018 Jun [cited 2019 Apr 6];53(6):802–8. Available from: http://doi.wiley.com/10.1002/ppul.24021

21. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: Updated for ICD-10 and complex medical technology dependence and transplantation. BMC Pediatr. 2014;14(1):1–7.

Journal Pre-proof

22. Sasaki M, Yoshida K, Adachi Y, Furukawa M, Itazawa T, Odajima H, et al. Factors associated with asthma control in children: Findings from a national Web-based survey. Pediatr Allergy Immunol. 2014;25(8):804–9.

23. Okubo Y, Michihata N, Yoshida K, Morisaki N, Matsui H, Fushimi K, et al. Impact of pediatric obesity on acute asthma exacerbation in Japan. Pediatr Allergy Immunol. 2017;

24. Okubo Y, Nochioka K, Testa MA. The impact of pediatric obesity on hospitalized children with lower respiratory tract infections in the United States. Clin Respir J . 2018 Apr [cited 2019 Apr 6];12(4):1479–84. Available from: http://doi.wiley.com/10.1111/crj.12694

25. Okubo Y, Nochioka K, Hataya H, Sakakibara H, Terakawa T, Testa M. Burden of Obesity on Pediatric Inpatients with Acute Asthma Exacerbation in the United States. J Allergy Clin Immunol Pract. 2016;4(6).

26. WHO. The World Health Organization (WHO) Child Growth Standards.

27. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46(3):399–424.

28. Snowden JM, Rose S, Mortimer KM. Implementation of G-computation on a simulated data set: Demonstration of a causal inference technique. Am J Epidemiol. 2011;173(7):731–8.

29. Wang A, Nianogo RA, Arah OA. G-computation of average treatment effects on the treated and the untreated. BMC Med Res Methodol . 2017;17(1):1–5. Available from: http://dx.doi.org/10.1186/s12874-016-0282-4

30. Hernán MA, Robins JM. Estimating causal effects from epidemiological data. J Epidemiol Community Health. 2006 Jul;60(7):578–86.

31. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Heal . 2010;13(2):273–7. Available from: http://dx.doi.org/10.1111/j.1524-4733.2009.00671.x

32. Wang A, Nianogo RA, Arah OA. G-computation of average treatment effects on the treated and the untreated. BMC Med Res Methodol. 2017;17(1):1–5.

33. Greenland S. An introduction to instrumental variables for epidemiologists. Int J Epidemiol. 2000;29(4):722–9.

34. Lousdal ML. An introduction to instrumental variable assumptions, validation and estimation. Emerg Themes Epidemiol . 2018;15(1):1–7. Available from: https://doi.org/10.1186/s12982-018-0069-7

35. Johnston SC, Henneman T, McCulloch CE, Van Der Laan M. Modeling treatment effects on binary outcomes with grouped-treatment variables and individual covariates. Am J Epidemiol. 2002;156(8):753–60.

36. Douglas LC, Choi J, Esteban-Cruciani N. Azithromycin treatment in children hospitalized with asthma: a retrospective cohort study. J Asthma . 2019 Apr 1;0(0):1–7. Available from: https://doi.org/10.1080/02770903.2019.1590590

37. Hsia Y, Sharland M, Jackson C, Wong ICK, Magrini N, Bielicki JA. Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve

(AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries. Lancet Infect Dis . 2019;19(1):67–75. Available from: http://dx.doi.org/10.1016/S1473-3099(18)30547-4

38. Okubo Y, Michihata N, Morisaki N, Kinoshita N, Miyairi I, Urayama KY, et al. Recent patterns in antibiotic use for children with group A streptococcal infections in Japan. J Glob Antimicrob Resist . 2018 Jun [cited 2019 Apr 6];13:55–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213716517302151

39. Okubo Y, Michihata N, Morisaki N, Uda K, Miyairi I, Ogawa Y, et al. Recent trends in practice patterns and impact of corticosteroid use on pediatric Mycoplasma pneumoniae-related respiratory infections. Respir Investig . 2018;56(2):158–65. Available from: http://dx.doi.org/10.1016/j.resinv.2017.11.005

40. Okubo Y, Miyairi I, Michihata N, Morisaki N, Kinoshita N, Urayama KY, et al. Recent Prescription Patterns for Children With Acute Infectious Diarrhea. J Pediatr Gastroenterol Nutr. 2019;68(1):13–6.

41. Uda K, Okubo Y, Kinoshita N, Morisaki N, Kasai M, Horikoshi Y, et al. Nationwide survey of indications for oral antimicrobial prescription for pediatric patients from 2013 to 2016 in Japan. J Infect Chemother . 2019 Jun 21; Available from: https://linkinghub.elsevier.com/retrieve/pii/S1341321X19300698

42. Froidure A, Mouthuy J, Durham SR, Chanez P, Sibille Y, Pilette C. Asthma phenotypes and IgE responses. Eur Respir J . 2016;47(1):304–19. Available from: http://dx.doi.org/10.1183/13993003.01824-2014

43. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat

503 Med . 2012 May 4;18(5):716–25. Available from:

504 http://www.ncbi.nlm.nih.gov/pubmed/22561835

505

506

Journal Pre-proof

Journal Pre-proof

Table1. Baseline characteristics between those who received antibiotics and those who did not within 2 days of hospitalization before and after propensity score (PS) matching.

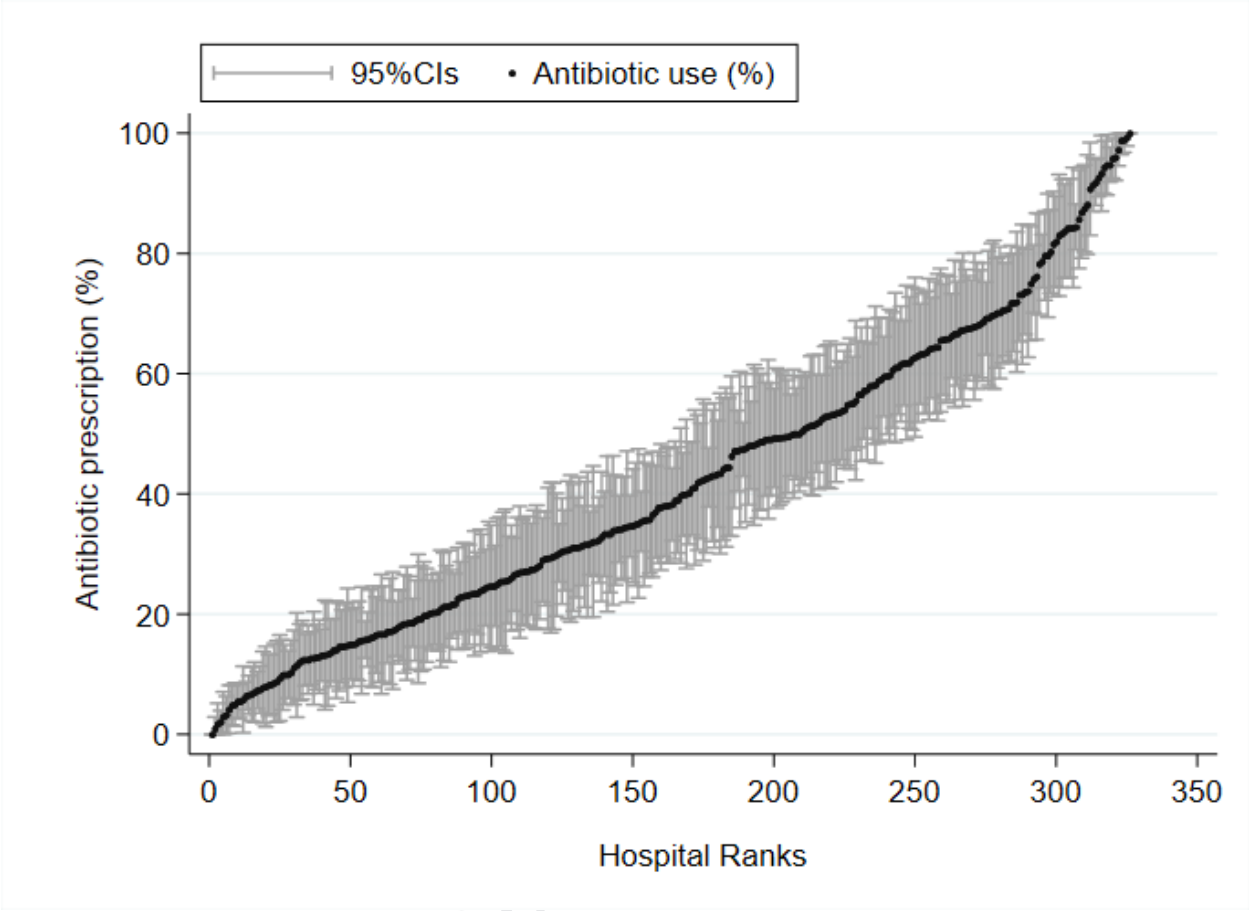
	Before PS matching			After PS matching		
Antibiotics	Untreated (N = 28,877)	Treated (N = 19,866)	StdDiff (%)	Untreated (N = 17,596)	Treated (N = 17,596)	StdDiff (%)
Patient characteristics						
Age, mean (SD)	4.8 (3.5)	4.1 (3.2)	19.8	4.3 (3.2)	4.3 (3.3)	0.1
Male, N (%)	18,048 (63.8)	12,102 (60.9)	5.9	10,858 (61.7)	10,852 (61.7)	0.07
Weight status, N (%)						
Thin	1732 (6.0)	1304 (6.6)	-2.3	1138 (6.5)	1147 (6.5)	-0.2
Normal	16,285 (56.4)	11,052 (55.6)	1.2	9831 (55.9)	9861 (56.0)	-0.32
Overweight	2295 (8.0)	1490 (7.5)	1.7	1328 (7.5)	1329 (7.6)	-0.02
Obesity	2326 (8.1)	1462 (7.4)	2.6	1332 (7.6)	1333 (7.6)	-0.02
Missing	6239 (21.6)	4558 (22.9)	-3.2	3967 (22.5)	3926 (22.3)	0.56
Past medical history						
Food allergy, N (%)	430 (1.5)	244 (1.2)	2.3	215 (1.2)	228 (1.3)	-0.6
Allergic rhinitis, N (%)	1323 (4.6)	1159 (5.8)	-5.7	938 (5.3)	899 (5.1)	1.0
Atopic dermatitis, N (%)	855 (3.0)	559 (2.8)	0.9	502 (2.9)	505 (2.9)	-0.1
Ambulance use, N (%)	1785 (6.2)	931 (4.7)	6.6	854 (5.0)	872 (5.0)	-0.5
Academic hospital, N (%)	3000 (10.4)	1175 (5.9)	16.4	1181 (6.6)	1156 (6.6)	0.6
Ordinance-designated city, N (%)	6915 (23.9)	4164 (21.0)	7.2	3767 (21.5)	3777 (21.5)	-0.1
Seasonality						
Spring, N (%)	6125 (21.2)	4069 (20.5)	1.8	3566 (20.3)	3617 (20.6)	-0.7
Summer, N (%)	6266 (21.7)	4767 (24.0)	-5.5	4118 (23.4)	4124 (23.4)	-0.1
Fall, N (%)	12,485 (43.2)	8219 (41.4)	3.8	7436 (42.3)	7401 (42.1)	0.4
Winter, N (%)	4001 (13.9)	2811 (14.1)	-0.1	2476 (14.1)	2454 (13.9)	0.4
Treatment, N (%)						
Dextromethorphan	448 (1.6)	497 (2.5)	-6.8	382 (2.2)	375 (2.1)	0.3
Tipepidine	6377 (22.1)	7211 (36.3)	-31.6	5504 (31.3)	5441 (30.9)	0.7
Other antitussives	664 (2.3)	628 (3.2)	-5.3	534 (3.0)	533 (3.0)	0.03
Mucolytics	19,670 (68.1)	15,006 (75.5)	-16.5	13,106 (74.2)	13,047 (74.2)	0.8
Airway lubricant	11,875 (41.1)	8237 (41.5)	-0.7	7424 (42.3)	7473 (42.5)	-0.6
Tranexamic acid	130 (0.5)	167 (0.8)	-4.9	118 (0.7)	116 (0.7)	0.1
1st generation AH	1017 (3.5)	1893 (9.5)	-24.5	894 (5.6)	805 (4.6)	4.6
2nd generation sedative AH	603 (2.1)	770 (3.9)	-10.5	529 (3.0)	497 (2.8)	1.0
2nd generation non-sedative AH	1255 (4.4)	1060 (5.4)	-4.7	888 (5.0)	901 (5.1)	-0.3
Leukotriene receptor antagonist	20,072 (69.5)	14,716 (74.5)	-10.1	12,823 (72.9)	12,860 (73.1)	-0.5
Other antiallergic medication	11,773 (40.8)	8416 (42.4)	-3.3	7384 (42.0)	7318 (41.6)	0.8
Xanthine	2129 (7.4)	1614 (8.2)	-2.9	1393 (7.9)	1395 (7.9)	-0.04
Beta-2 receptor-stimulant, i.v.	322 (1.1)	259 (1.3)	-1.6	221 (1.3)	228 (1.3)	-0.4
Beta-2 receptor-stimulant, p.o.	6780 (23.5)	5314 (26.7)	-7.5	4622 (26.3)	4685 (26.6)	-0.8
Beta-2 receptor-stimulant, tape	10,207 (35.4)	9147 (46.1)	-21.9	7553 (42.9)	7541 (42.9)	0.1
Inhaled corticosteroid	2845 (9.6)	2350 (11.9)	-6.5	1945 (11.1)	1957 (11.1)	-0.2
H2 blocker	163 (0.6)	224 (1.3)	-6.1	135 (0.7)	124 (0.7)	0.7
Acetaminophen	2568 (8.9)	3369 (16.9)	24.2	2300 (13.1)	2169 (12.3)	2.2
Clinical outcomes						
Length of hospital stay, day (SD)	5.5 (2.4)	5.7 (2.2)		5.5 (2.4)	5.7 (2.2)	
Mechanical ventilation, N (%)	31 (0.11)	36 (0.18)		17 (0.09)	35 (0.2)	
Healthcare cost, mean USD (SD)	2254.2 (1012)	2304.2 (964.4)		2221.6 (994)	2305 (734.3)	
30-day readmission, N (%)	191 (0.66)	135 (0.67)		125 (0.71)	112 (0.63)	
Probiotics prescription, N (%)	763 (3.1)	1137 (5.7)		494 (2.8)	992 (5.6)	

Journal Pre-proof

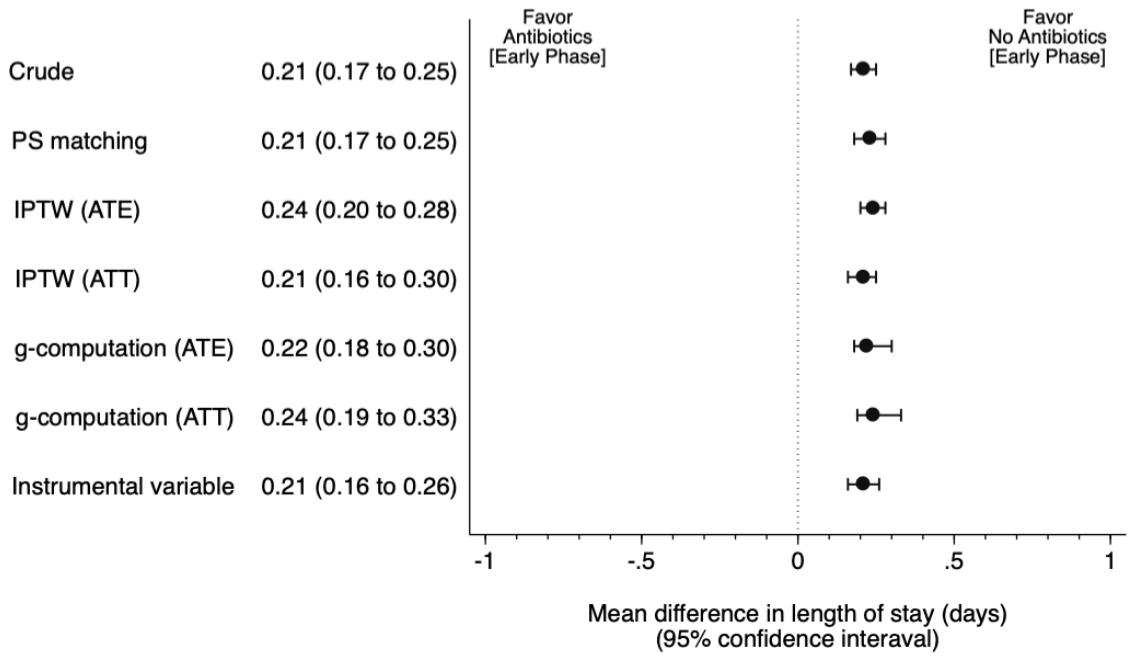
Journal Pre-proof

Std Diff, standardized difference; SD, standard deviation; AH, antihistamine; i.v., intravenous; p.o., per os; USD, Japanese yen

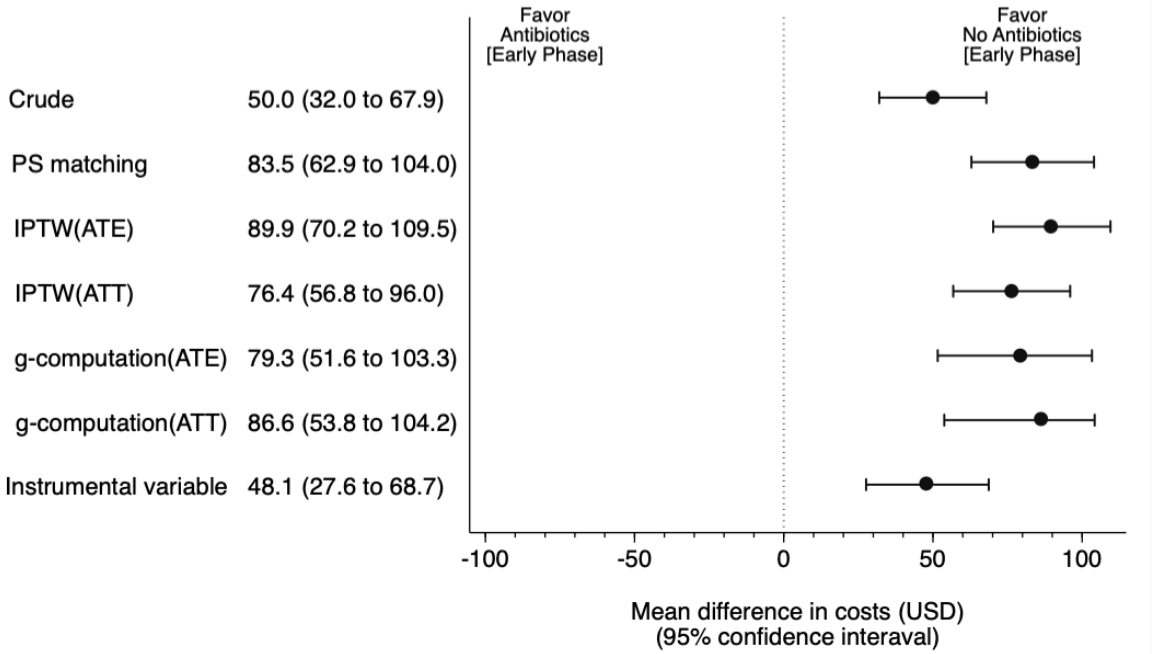
Journal Pre-proof


95%CIs
Antibiotic use (%)
Antibiotic prescription (%)
0
20
40
60
80
100
0
50
100
150
200
250
300
350
Hospital Ranks

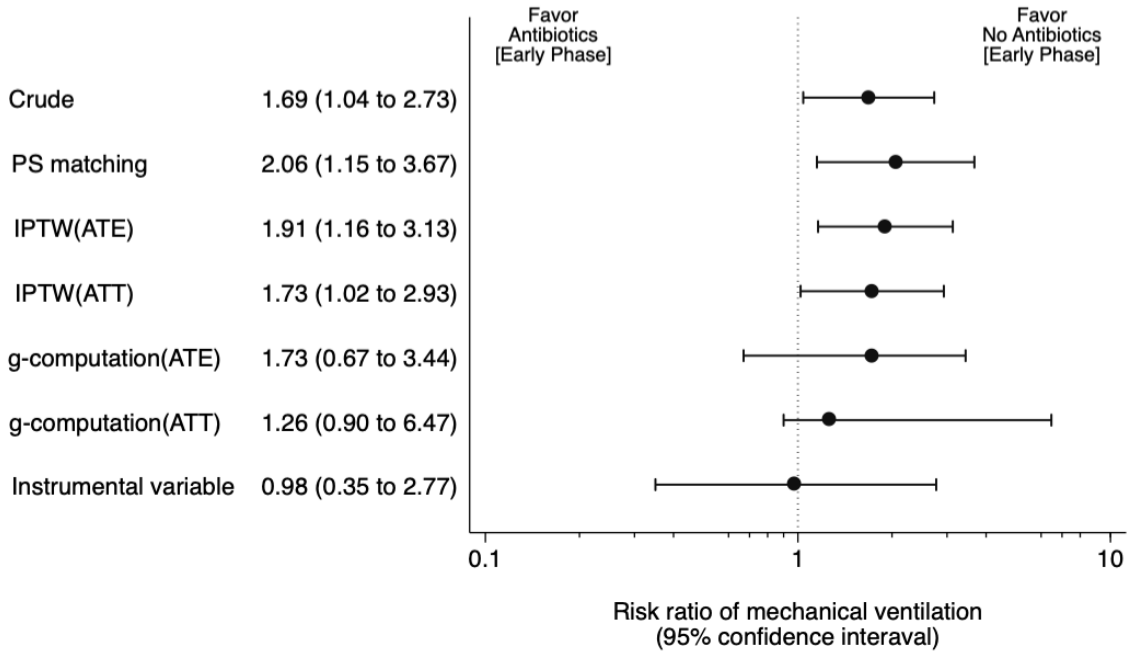
Journal



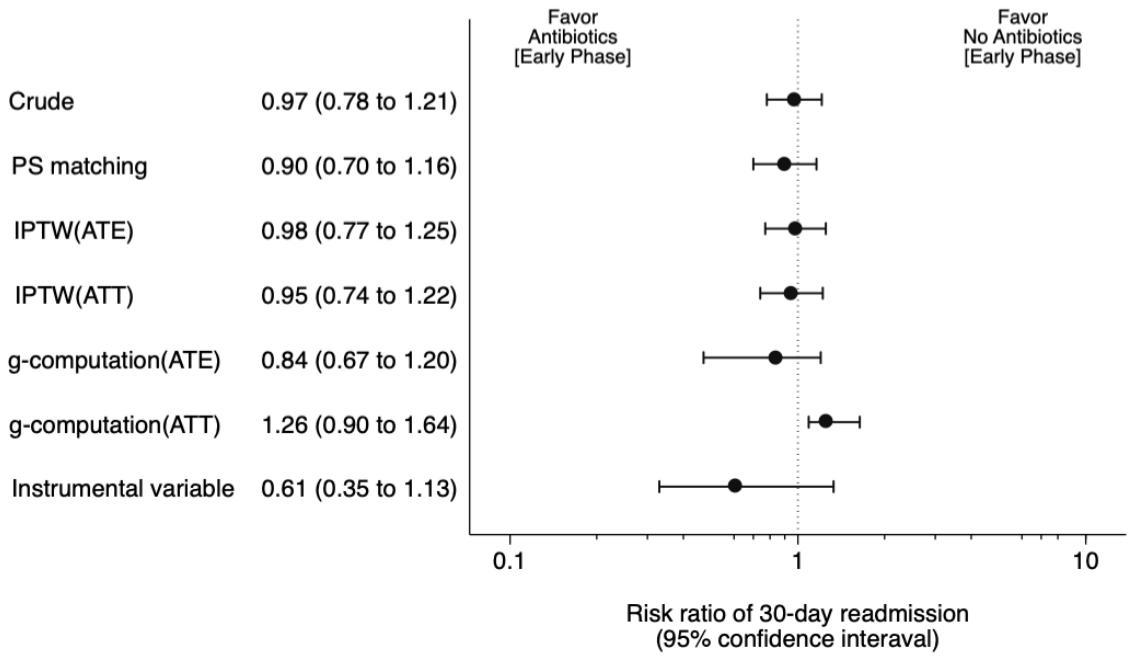
Journal Pre-proof



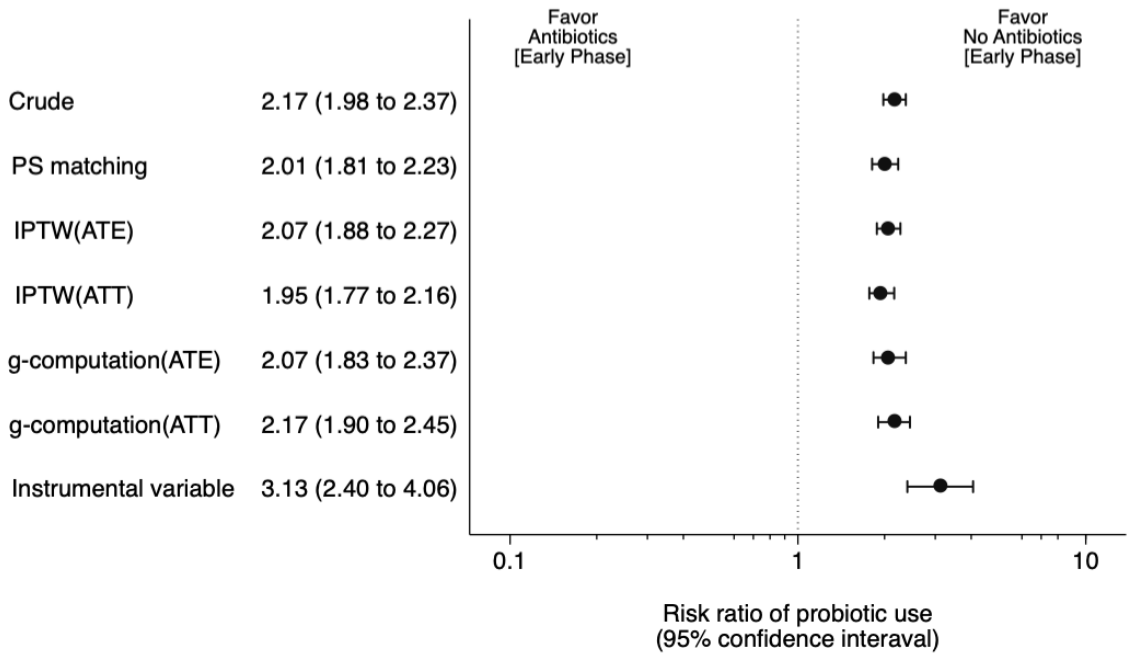
Journal Pre-proof



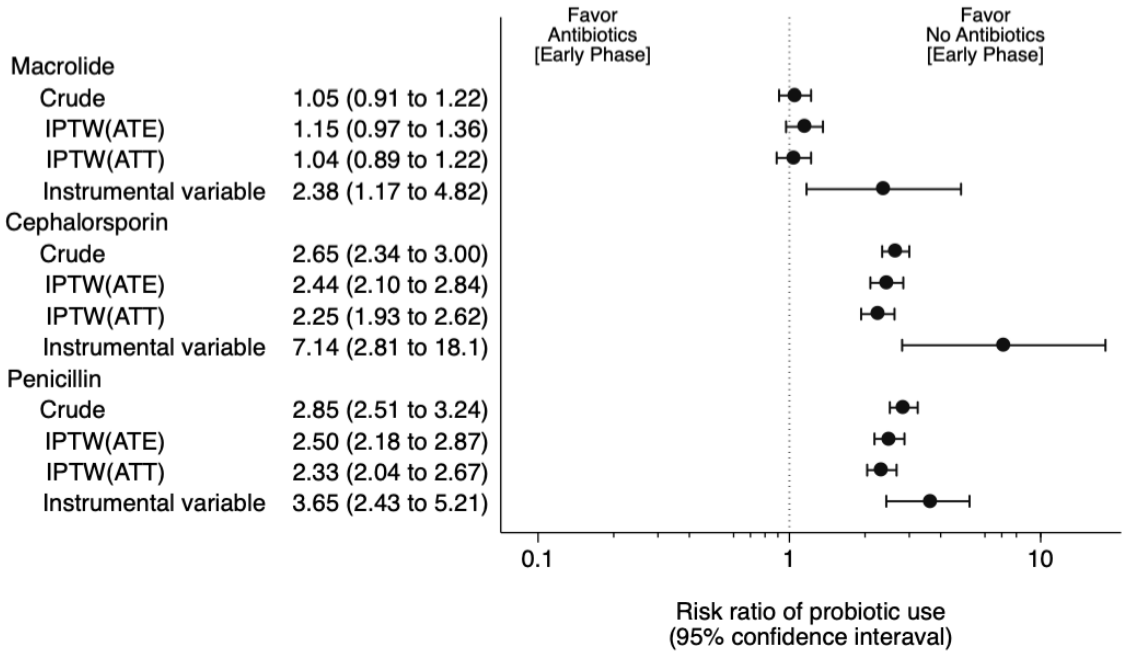
Journal Pre-proof



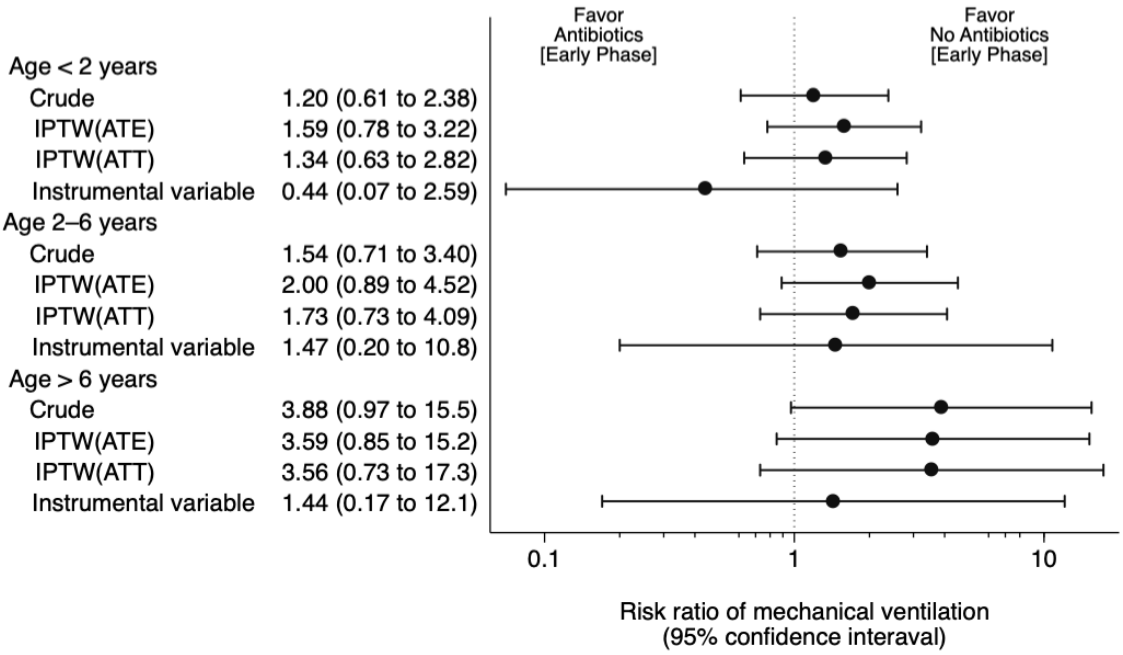
Journal Pre-proof



Journal Pre-proof



Journal Pre-proof



Journal Pre-proof