



Disproportionate Exposure to Antibiotics in Children at Risk for Invasive Pneumococcal Disease: Potential for Emerging Resistance and Opportunity for Antibiotic Stewardship

Tamar F. Barlam,^{1a} Jake R. Morgan,^{2a} Warren A. Kaplan,³ Kevin Outterson,⁴ and Stephen I. Pelton^{5,6}

Sections of ¹Infectious Diseases and ²Pediatric Infectious Diseases, Boston University School of Medicine, Massachusetts; ³Department of Health Policy and Management and ⁴Center for Global Health and Development, Boston University School of Public Health, Massachusetts; ⁵Boston University School of Law, Massachusetts; and ⁶Maxwell Finland Laboratory for Infectious Diseases, Boston Medical Center, Massachusetts

We compared antibiotic prescribing for children with and those without an underlying chronic condition associated with increased risk for invasive pneumococcal disease. Children with a chronic condition had significantly greater cumulative exposure to antibiotics and higher rates of prescriptions per person-year than those without a chronic condition; this population is at increased risk for the emergence of multidrug-resistant pathogens.

Keywords. antibiotic resistance; antibiotic stewardship; antibiotic use; children's health; physician; prescribing patterns.

Children with a specific underlying comorbid condition have been recognized to be at increased risk of invasive pneumococcal disease [1]. We hypothesized that those children might represent a population likely to have disproportionate exposure to antibiotics compared with children without such a condition and could represent a target population for interventions to reduce inappropriate antibiotic prescribing. We compared the cumulative burden of antibiotic exposure and rates of antibiotic prescribing for children with and those without a specific condition that predisposed them to invasive pneumococcal disease during the first 6 years of life.

Received 18 January 2017; editorial decision 3 August 2017; accepted 7 August 2017.

Correspondence: T. F. Barlam, MD, Boston Medical Center, Section of Infectious Diseases, 771 Albany St, Dowling 3 North, Boston, MA 02118 (tbarlam@bu.edu).

^aT. F. B. and J. R. M. contributed equally to this article.

Journal of the Pediatric Infectious Diseases Society 2017;00(00):1–3

© The Author 2017. Published by Oxford University Press on behalf of The Journal of the Pediatric Infectious Diseases Society. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/jpids/pix070

METHODS

Data from the Truven Health Analytics MarketScan Commercial Claims Database for the years 2007 to 2013 were used for the study. MarketScan includes claims for inpatient and outpatient care from more than 100 commercial health insurance plans covering working adults younger than 65 years and their dependents and represents nearly half of the US health insurance plans. Children born in 2007 or 2008 with pharmacy coverage for the duration of their enrollment in the health insurance plan were included and followed longitudinally from birth to either the end of the observation period (December 31, 2013) or until they dropped out of the cohort (eg, changed insurers). The Boston University Institutional Review Board deemed this project exempt from review.

The International Classification of Diseases, Ninth Revision, and Current Procedural Terminology diagnosis and procedural codes were used to identify conditions recognized by the American Academy of Pediatrics Committee on Infectious Diseases as predisposing to invasive pneumococcal infection [2]. Children with at least 1 inpatient or 2 outpatient records documenting 1 of these specific chronic conditions were categorized as having that condition from the earliest coding occurrence. For analyses according to age, only children with full enrollment during the corresponding age range were included. Children were categorized as having a comorbid condition if their condition was diagnosed before the age considered in the analysis. For example, for the analysis of antibiotic prescribing at the age of 2 years, only children diagnosed with a chronic condition before their second birthday were included.

Prescription data were from outpatient visits only. We categorized antibiotics according to their National Drug Code and evaluated use within 5 therapeutic classes, namely, penicillins, cephalosporins, macrolides, sulfonamides, and fluoroquinolones. Cumulative antibiotic exposure was the sum of unique drug prescriptions for each year of life and according to specific chronic condition. The rate of antibiotic prescribing was calculated by dividing the total number of antibiotic prescriptions by total person-time. To compare rates, we used the large-sample χ^2 test. We also performed a sensitivity analysis that excluded conditions that could be an indication for chronic antibiotic prophylaxis, and it did not change our results.

RESULTS

A total of 512 400 infants were enrolled in the study, and the average follow-up time was 2.8 years. Of these children, 17% were identified with 1 or more of the risk conditions included in our analysis (Supplementary Table 1). Low birth weight (7.97%), recurrent wheezing/asthma (6.01%), chronic heart disease (2.43%), and chronic lung disease (2.38%) were the most common diagnoses.

Over the first 6 years of life, the average child received 9 antibiotic prescriptions (Figure 1). Children with a chronic condition were prescribed antibiotics more intensively than children without a chronic condition by their sixth birthday (cumulative means: 12.50 vs 7.91 antibiotic prescriptions, respectively). Prescribing between the 2 groups diverged soon after birth. When stratified according to specific chronic condition, the average cumulative exposures to antibiotics by the age of 6 years were 11.71 prescriptions for children with low birth weight, 12.97 prescriptions for children with chronic heart disease, 13.57 prescriptions for children with recurrent wheezing/asthma, and 15.99 prescriptions for children with chronic lung disease. Children with both low birth weight and recurrent wheezing/asthma had greater cumulative antibiotic exposure (average, 16.95 prescriptions by 6 years of age) than those with either condition alone.

The overall rate of antibiotic prescribing was 1.55 prescriptions per person-year. Children with a chronic condition received 2.12 antibiotic prescriptions per person-year, whereas those without a chronic condition were given 1.39 prescriptions per person-year ($P < .001$). For each year of life, children with

a chronic condition had significantly higher rates of antibiotic prescriptions than children without any of the designated conditions (Supplementary Table 2). Children with chronic lung disease (2.70 prescriptions), recurrent wheezing/asthma (2.43 prescriptions), low birth weight (1.87 prescriptions), or both recurrent wheezing/asthma and low birth weight (2.87 prescriptions) had significantly higher prescribing rates than children without any of these conditions.

According to the average cumulative prescriptions by 6 years of age, penicillins were prescribed most often for children with and those without a chronic condition (6.31 and 4.45 prescriptions, respectively), followed by cephalosporins (3.20 and 2.00 prescriptions, respectively) and macrolides (2.99 and 1.52 prescriptions, respectively) (Supplementary Figure). The mean and median durations of each prescription were comparable in the children without a chronic condition (9.7 and 9.9 days, respectively) and in those with a comorbidity (9.9 and 10 days, respectively). The proportion of children prescribed more than 28 or 60 days of antibiotics in each year of life was greater in those with a designated comorbid condition (Supplemental Table 3).

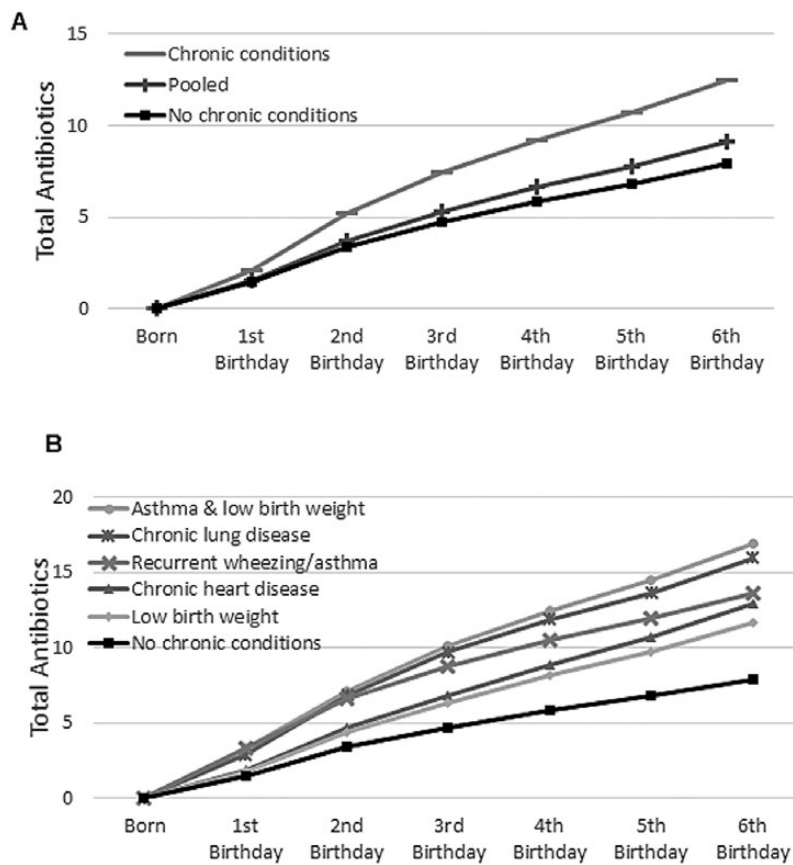


Figure 1. Cumulative number of antibiotic prescriptions for the first 6 years of life. (A) Mean antibiotic exposure between children with and those without any chronic condition compared with that of the pooled cohort. (B) Mean antibiotic exposure for children with a specific chronic condition compared with children without any chronic condition.

DISCUSSION

Our analysis of a large claims database reveals that children with a chronic condition that predisposes them to invasive pneumococcal infection are exposed to antibiotics more than 1.5 times more often than children without such a condition. Children with chronic lung disease or recurrent wheezing/asthma have the highest antibiotic exposures, and this exposure is amplified when more than 1 condition is present. Despite a declining incidence of pneumococcal disease in children after the introduction of first- and second-generation pneumococcal conjugate vaccines [3] and decreasing rates of antibiotic prescribing associated with nationwide programs for judicious use of antibiotics [4, 5], significantly higher rates of antibiotic prescribing were documented for children with a comorbidity than for children without a comorbidity.

Evidence supports the theory that higher exposure to antibiotics in a specific geographic area results in a prevalence of antibiotic resistance among respiratory pathogens that is higher than that in areas with lower exposure, which suggests that children with increased risk for invasive pneumococcal disease might be a population at higher risk for the emergence of resistant pathogens [6, 7]. The mechanisms proposed include unmasking of bacterial pathogens already present or acquisition of resistant pathogens during treatment episodes [8].

Our study had several limitations. The database we used tracks filled prescriptions, not actual use, so we cannot know whether the children ingested all of their prescribed doses. We also do not know if the prescriptions were appropriate. Our sample did not include children insured by Medicaid, who might exhibit different characteristics than those who are commercially insured. Also, children with a chronic condition might change insurers at different rates than the balance of the population, which would make this longitudinal sample less representative. Finally, our data cannot be generalized to all comorbid conditions, such as those identified using the classification by Feudtner et al [9]. The American Academy of Pediatrics classification includes conditions that pose particular risk for invasive pneumococcal diseases, which we believe is appropriate when examining antibiotic use.

CONCLUSION

In summary, children in our study were exposed, on average, to more than 9 antibiotic prescriptions from birth to the age of 6 years; children with a chronic illness had significantly greater exposure than those without a chronic condition. Targeted antibiotic stewardship in this population might identify inappropriate use that could be reduced safely, and microbial surveillance could provide early warning of the emergence of new resistance among potential pathogens.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

Note

Potential conflicts of interest. K. O. has received grants from the BARDA (CARB-X) and the European Union (Drive-AB) and has served on an advisory board for Roche/Genentech and Pure Tech. S. I. P. reports grants and personal fees from Pfizer, Inc, and personal fees from Merck, Inc, Sequiris, and GSK Bio. T. F. B., J. R. M., and W. A. K.: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Pelton SI, Weycker D, Farkouh RA, et al. Risk of pneumococcal disease in children with chronic medical conditions in the era of pneumococcal conjugate vaccine. *Clin Infect Dis* 2014; 59:615–23.
2. American Academy of Pediatrics. Pneumococcal infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015; 626–38.
3. Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. *Lancet Infect Dis* 2015; 15:301–9.
4. Hersh AL, Jackson MA, Hicks LA; American Academy of Pediatrics Committee on Infectious Diseases. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. *Pediatrics* 2013; 132:1146–54.
5. Greene SK, Kleinman KP, Lakoma MD, et al. Trends in antibiotic use in Massachusetts children, 2000–2009. *Pediatrics* 2012; 130:15–22.
6. Goossens H, Ferech M, Vander Stichele R, Elseviers M; ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; 365:579–87.
7. Perz JF, Craig AS, Coffey CS, et al. Changes in antibiotic prescribing for children after a community-wide campaign. *JAMA* 2002; 287:3103–9.
8. Schrag SJ, Beall B, Dowell SF. Limiting the spread of resistant pneumococci: biological and epidemiologic evidence for the effectiveness of alternative interventions. *Clin Microbiol Rev* 2000; 13:588–601.
9. Feudtner C, Feinstein JA, Zhong W, et al. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr* 2014; 14:199.