EPH60

# Temporal Trends in Vaccination and Antibiotic Use Among Young Children in the United States, 2000-2019

Amanda L. Eiden[1]*; Qing Liu[2]; Yan Song[2]; Nicolae Done[2]; Yoonyoung Choi[1]; Travis Wang[2]; Goran Bencina[3]; Gary S. Marshall[4]; James Signorovitch[2]

[1]Merck & Co., Inc., Rahway, NJ, USA; [2]Analysis Group, Inc., Boston, MA, USA; [3]MSD Spain, Madrid; [4]Norton Children's and the University of Louisville School of Medicine, Louisville, KY, USA

*Presenting Author

## Background and objectives

- The widespread use and misuse of antibiotics are primary drivers of antimicrobial resistance (AMR), which is a top global public health threat[1]
- Vaccination programs, by preventing common diseases for which antibiotics are appropriately and inappropriately prescribed, have the potential to reduce antibiotic use and, consequently, the selection pressure towards AMR among bacterial pathogens[2]
- Real-world data on contemporaneous population-level trends between widespread vaccination and antibiotic prescribing are scarce. Ecological studies could serve as a valuable approach for investigating the role of vaccination in reducing antibiotic use
- This study aimed to describe temporal trends in vaccination status and uptake, rates of antibiotic prescriptions, and incidence of antibiotic-treated respiratory tract infections in children <5 years of age in the United States (US)

## Methods

### Study design and patient population

- This retrospective ecological study included US children from the Merative® MarketScan Commercial Claims and Encounters (CCAE) database (July 1, 2000-June 30, 2020) using 20 epidemiological years of data
- Each epidemiological year was defined as from July 1 of the current year through June 30 of the next year, from 2000 to 2019 (eg, the epidemiological year 2019 spans from July 1, 2019 through June 30, 2020)
- Children who had continuous enrollment from birth to at least 1 year of age from July 1, 2000 through June 30, 2020 were selected and were required to have full enrollment for the epidemiological year in which analyses were conducted
  - Additionally, children were censored from the study once they no longer contributed data or upon turning 5 years of age
- During each epidemiological year, eligible children were categorized into 3 groups based on the vaccination status of the following 4 respiratory pathogen vaccines:[3]
  - (1) 7-valent (PCV7) or 13-valent (PCV13) pneumococcal conjugate vaccine
  - (2) *Haemophilus influenzae* type b (Hib) vaccine
  - (3) diphtheria–tetanus–acellular pertussis (DTaP) vaccine
  - (4) influenza vaccine
- The 3 vaccination classification stratifications (groups), based on the Centers for Disease Control and Prevention (CDC) immunization schedule for children <5 years of age, were as follows:
  - Received 4 vaccines: defined as having received at least 1 dose of all 4 vaccine types
  - Received 1-3 vaccines: defined as having received at least 1 dose of 1-3 of the vaccine types
  - Unvaccinated: defined as no vaccination codes for any of the considered vaccine types
- Vaccination status was determined using Current Procedural Terminology (CPT) and codes from the National Drug Code (NDC) Directory

### Study outcomes and statistical analysis

- Antibiotic prescriptions for any reason were identified from pharmacy data using NDCs, and grouped into 8 drug classes: penicillins, cephalosporins, macrolides, tetracyclines, quinolones, sulfonamides/trimethoprim, lincosamides, and others
- 5 respiratory tract infections that commonly result in antibiotic prescription among children were assessed in the outpatient setting using the International Classification of Diseases, 10th Revision (ICD-10) codes: otitis media, pharyngitis, pneumonia (all-cause invasive and noninvasive pneumonia, excluding viral pneumonia), sinusitis, and viral respiratory infection (including viral pneumonia, influenza, and viral bronchitis, as well as others)[4,5]
- An infection episode was considered to be an antibiotic-treated episode if an antibiotic prescription was observed within 3 days of the start of the episode
- Antibiotic-treated urinary tract infection (UTI) episodes were used as an indicator of secular trends in antibiotic use (ie, negative control for the trend in antibiotic-treated episodes over time), as it may have been influenced by stewardship efforts, but not by vaccination programs
- The rates of antibiotic prescriptions and incidence of antibiotic-treated infection episodes per person-year were calculated for each epidemiological year and expressed as percentage changes relative to year 2000 baseline levels

## Results

### Demographic characteristics

- In total, data were available for approximately 6.7 million children. The number of children included increased each year from 2000 through 2011 (from approximately 50,000 in 2000 to 564,000 children in 2011), then decreased from 2011 through 2019 (approximately 345,000 in 2019)
- Across the study timeframe the mean age of each cohort ranged 1.6-2.3 years with standard deviations of 1.1-1.3 years
- Per year, slightly over half of children were male, and the majority had preferred provider organization/point of service insurance coverage (ranging from 63.0%-74.3%)
- Most of the children lived in urban areas, with the proportions ranging from 73.5%-89.2% across the epidemiological years included in the study (**Table 1**)

**Table 1. Characteristics of the population of children <5 years of age between 2000-2019 with continuous health plan coverage for at least 12 months since birth**

| | Epidemiological year[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **2000** | **2001** | **2002** | **2003** | **2004** | **2005** | **2006** | **2007** | **2008** | **2009** |
| Number of children, n | 50,476 | 60,263 | 83,569 | 121,619 | 189,233 | 226,567 | 309,105 | 398,580 | 462,668 | 422,528 |
| Age, y, mean (SD) | 2.2 ± 1.3 | 2.2 ± 1.4 | 1.9 ± 1.3 | 1.6 ± 1.2 | 1.6 ± 1.1 | 1.8 ± 1.1 | 1.9 ± 1.2 | 2.0 ± 1.2 | 2.1 ± 1.2 | 2.2 ± 1.3 |
| Male, % | 51.6% | 51.6% | 51.4% | 51.3% | 51.2% | 51.3% | 51.2% | 51.2% | 51.2% | 51.2% |
| Urban area,[b] % | 73.5% | 80.6% | 80.2% | 79.1% | 79.8% | 84.8% | 85.7% | 85.5% | 86.0% | 86.7% |
| PPO/POS insurance plan, % | 74.3% | 68.6% | 67.3% | 67.8% | 63.0% | 66.4% | 68.4% | 69.9% | 71.4% | 67.8% |
| | **2010** | **2011** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019** |
| Number of children, n | 473,556 | 564,089 | 527,348 | 545,069 | 398,579 | 407,055 | 385,281 | 358,701 | 355,444 | 348,448 |
| Age, y, mean (SD) | 2.1 ± 1.3 | 2.1 ± 1.3 | 2.2 ± 1.3 | 2.2 ± 1.3 | 2.3 ± 1.3 | 2.3 ± 1.3 | 2.3 ± 1.3 | 2.3 ± 1.3 | 2.3 ± 1.3 | 2.3 ± 1.3 |
| Male, % | 51.3% | 51.5% | 51.5% | 51.4% | 51.4% | 51.3% | 51.3% | 51.3% | 51.1% | 51.2% |
| Urban area,[b] % | 88.0% | 86.8% | 87.0% | 84.2% | 89.2% | 90.0% | 75.9% | 74.9% | 75.9% | 75.2% |
| PPO/POS insurance plan, % | 68.9% | 67.8% | 65.0% | 66.1% | 63.9% | 63.7% | 58.8% | 55.2% | 55.6% | 55.6% |

POS, point of service; PPO, preferred provider organization; SD, standard deviation.
[a]Epidemiological year represents the 12-month period from July 1 of the current year to June 30 of the next year.
[b]Urban area was defined based on metropolitan statistical area (MSA) in the Merative® MarketScan Commercial Claims and Encounters database.

### Trends in vaccination status and uptake

- About 32.5% of children received 4 vaccines in 2004, following the recommendation for annual influenza vaccination, marking the first epidemiological year when all 4 vaccines were recommended. The uptake of 4 vaccines continued to increase in subsequent years, reaching 66.8% in 2019
- The proportion of unvaccinated children decreased from 8.4% in 2004 to 2.5% in 2019 (**Figure 1**)

### Trends in antibiotic prescription rates and incidence of antibiotic-treated respiratory tract infections

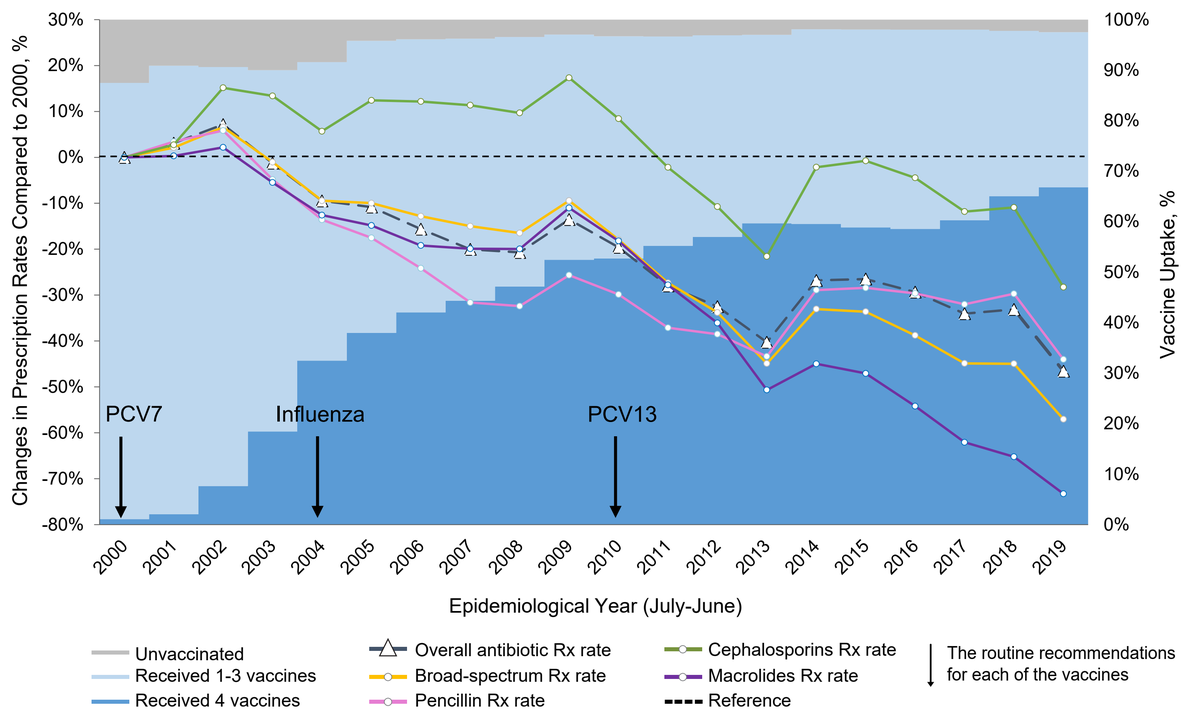
- The rate of overall antibiotic prescriptions decreased by 46.6% from 2000 to 2019
  - The greatest rate reduction was observed for macrolides (73.3%), followed by broad-spectrum antibiotics (57.0%), penicillins (44.0%), and cephalosporins (28.3%) (**Figure 1**)
- The incidence of overall antibiotic-treated respiratory tract infections decreased by 33.8% in 2019 compared to 2000
  - The greatest rate reduction was observed for sinusitis (64.7%), followed by pharyngitis (39.8%), otitis media (38.3%), pneumonia (32.1%), and viral respiratory infection (17.1%)
  - In contrast, antibiotic-treated UTI incidence remained relatively stable during the study period, only showing a notable decrease of 4.9%-24.0% during 2016-2019, similar to the 3.8%-17.1% decrease observed for viral respiratory infections (**Figure 2**)
- During 2004-2008, when all 4 of the study vaccines were recommended, rates of most antibiotic prescriptions and all respiratory tract infection episodes decreased
- Notable decreases in antibiotic prescriptions and infection episodes during 2010-2013 coincided with the recommendation for use of PCV13 and the recommendation for universal influenza vaccination[6]

## Limitations

- While this study explored the relationship between vaccine uptake and changes over time in antibiotic use, it could not establish causality, due to its ecological design. The study is potentially subject to confounding biases, including temporal effects and variations in the number and characteristics of the selected population over the study period
- Like all claims database studies, this analysis has inherent limitations including coding inaccuracies, potential misclassification of diagnoses and vaccination status, incomplete capture of antibiotic prescriptions, and missing pharmacy records
- Only children covered by commercial health plans were included in the analyses, therefore the results cannot be generalized to the more vulnerable Medicaid population with likely lower vaccine uptake
- This study did not consider other factors that may have contributed to decreased antibiotic use, such as increased antibiotic stewardship initiatives and the increased availability of these tests at the point of care

**Figure 1. Antibiotic prescription and vaccine uptake among children <5 years of age by epidemiological year, 2000-2019[a]**

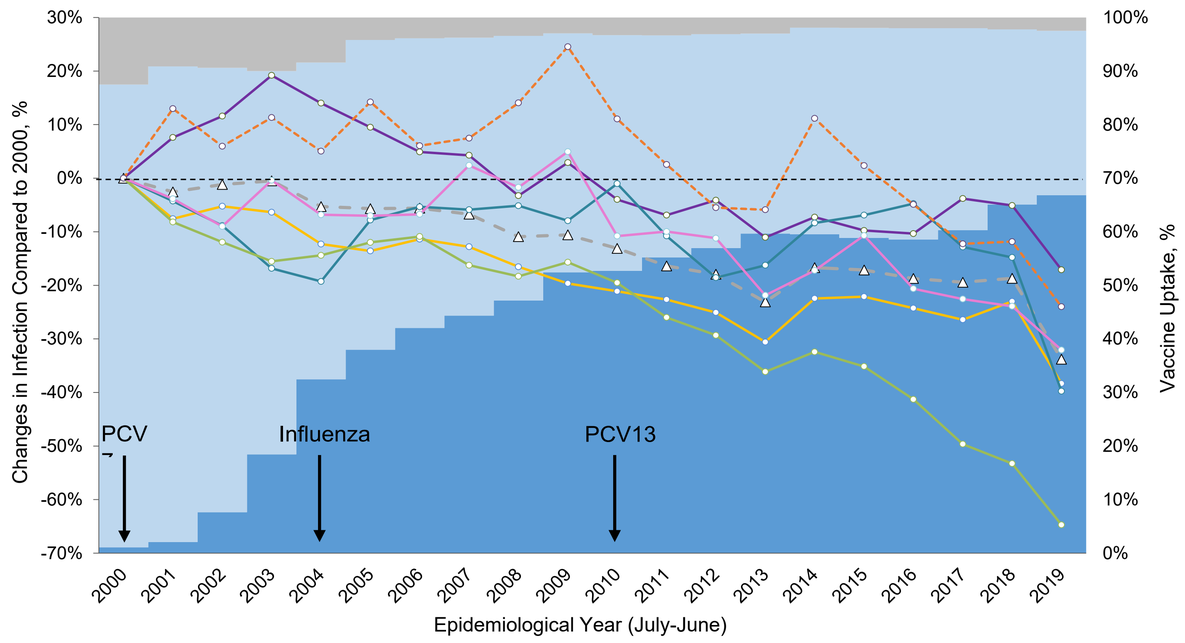
Change in antibiotic prescription rates compared to 2000 (left axis) and vaccine uptake[b] (right axis).




Rx, prescription.
[a]Epidemiological year represents the 12-month period from July 1 of the current year through June 30 of the next year.
[b]Vaccine uptake was assessed by categorizing children into 3 groups: "received 4 vaccines" if they received at least 1 dose of all 4 vaccine types (pneumococcal, Hib, DTaP, and influenza); "received 1-3 vaccines" if they received at least 1 dose of 1 to 3 of the vaccines under study; and "unvaccinated" if they had no vaccination codes for any of the considered vaccines.

**Figure 2. Respiratory tract infection and vaccine uptake among children <5 years of age by epidemiological year, 2000-2019[a]**

Change in incidence of antibiotic-treated infections compared to 2000 (left axis) and vaccine uptake[b] (right axis).




OM, otitis media; PCV, pneumococcal conjugate vaccines; UTI, urinary tract infection.
[a]Epidemiological year represents the 12-month period from July 1 of the current year through June 30 of the next year.
[b]Vaccine uptake was assessed by categorizing children into 3 groups: "received 4 vaccines" if they received at least one dose of all 4 vaccine types (pneumococcal, Hib, DTaP, and influenza); "received 1-3 vaccines" if they received at least 1 dose of 1 to 3 of the vaccines under study; and "unvaccinated" if they had no vaccination codes for any of the considered vaccines.

## Conclusions

- During the epidemiological years 2000-2019, as uptake of vaccines increased, antibiotic prescriptions and antibiotic-treated respiratory tract infections declined. The trends observed in this ecological study indicate that vaccination programs may contribute to reduced antibiotic use in young children
- These findings align with and reinforce similar conclusions drawn from previous controlled analyses conducted on smaller samples
- While the reduced antibiotic use may not be solely attributed to vaccines against bacterial diseases and other factors may also influence empiric antibiotic prescribing and overall antibiotic use, future research utilizing longitudinal patient-level data is necessary to further validate this trends

### References

1. Walsh TR, et al. *PLoS Med.* 2023;20(7):e1004264.
2. Lipsitch M., *mBio.* 2016;7(3):10-128.
3. Centers for Disease Control and Prevention. Vaccines & Immunizations. https://www.cdc.gov/vaccines/by-age/index.html. Accessed November 7, 2024.
4. Tong S, et al. *BMC Health Serv Res.* 2018;18:1-8.
5. Watson JR, et al. *Clin Infect Dis.* 2017;64(11):1479-1485.
6. Immunize.org. Vaccine History Timeline. https://www.immunize.org/vaccines/vaccine-timeline/. Accessed November 7, 2024.

### Funding

This work was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. The content is the sole responsibility of the authors and does not necessarily represent the official views of Merck & Co., Inc., Rahway, NJ, USA.

Presented at ISPOR Europe; Barcelona, Spain; 17-20 November 2024