Antibiotic Prophylaxis for Children With Sickle Cell Anemia

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abstract

BACKGROUND: Children with sickle cell anemia (SCA) are at increased risk for invasive pneumococcal disease; antibiotic prophylaxis significantly reduces this risk. We calculated the proportion of children with SCA who received ≥300 days of antibiotic prophylaxis and identified predictors of such receipt.

METHODS: Children aged 3 months to 5 years with SCA were identified by the presence of 3 or more Medicaid claims with a diagnosis of SCA within a calendar year (2005–2012) in Florida, Illinois, Louisiana, Michigan, South Carolina, and Texas. Receipt of antibiotics was identified through claims for filled prescriptions. The outcome, receipt of ≥300 days of antibiotics, was assessed annually by using varying classifications of antibiotics. By using logistic regression with generalized estimating equations, we estimated the odds of receiving ≥300 days of antibiotics, with potential predictors of age, sex, year, state, and health services use.

RESULTS: A total of 2821 children contributed 5014 person-years. Overall, only 18% of children received ≥300 days of antibiotics. Each additional sickle cell disease-related outpatient visit (odds ratio = 1.01, 95% confidence interval: 1.01–1.02) and well-child visit (odds ratio = 1.08, 95% confidence interval: 1.02–1.13) was associated with incrementally increased odds of receiving ≥300 days of antibiotics.

CONCLUSIONS: Despite national recommendations and proven lifesaving benefit, antibiotic prophylaxis rates are low among children with SCA. Numerous health care encounters may offer an opportunity for intervention; in addition, such interventions likely need to include social factors that may affect the ability for a child to receive and adhere to antibiotic prophylaxis.

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Dr Reeves conducted the initial analyses, drafted the initial manuscript, and revised the manuscript; Dr Tribble assisted with analyses, and reviewed and revised the manuscript; Mr Madden performed the data collection, and reviewed the manuscript; Dr Freed conceptualized and designed the study, and reviewed the manuscript; Dr Dombkowski conceptualized and designed the study, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Children with sickle cell anemia are at substantially increased risk for invasive pneumococcal disease; daily antibiotic prophylaxis until the age of 5 significantly reduces this risk.

WHAT THIS STUDY ADDS: We assessed rates and predictors of antibiotic prophylaxis among children with sickle cell anemia. In doing so, our goal was to characterize opportunities for intervention to increase rates of antibiotic prophylaxis among this high-risk population.

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Sickle cell disease affects predominately racial and ethnic minority populations in the United States; 1 in 375 African American infants are diagnosed with this recessive genetic condition.[1–5] Children with sickle cell disease are affected by numerous morbidities, such as an increased risk of invasive pneumococcal disease (IPD), caused by *Streptococcus pneumoniae*.[5,6]

Although children and adults with sickle cell disease are at an increased risk of IPD, children with the sickle cell anemia (SCA) subtype (hemoglobin SS) are at greatest risk for both the disease and related case fatality.[7,8] Without intervention, children with SCA have up to 100 times the risk of IPD as compared with children with normal hemoglobin.[7] Daily receipt of penicillin is an effective method to reduce the incidence of IPD among children with SCA. The Prophylactic Penicillin Study revealed an 84% reduction in the risk of infection among children that received daily penicillin as compared with those receiving the placebo.[9] More recently, the National Heart, Lung, and Blood Institute (NHLBI) reiterated the importance of penicillin prophylaxis in updated recommendations for the management of sickle cell disease indicating that children with SCA receive twice-daily oral penicillin until age 5.[10,11]

Although the effectiveness of daily penicillin prophylaxis has been known for decades, limited evidence indicates low rates of compliance among children.[12,13] Although the authors of these studies offer some insight into penicillin prophylaxis among children with sickle cell disease, they do not focus specifically on the NHLBI-specified target population of children with SCA. In addition, the classification of antibiotic prophylaxis varies between studies, making comparability difficult.[12–14] To address these issues, we assessed rates of antibiotic prophylaxis among children with SCA by using varying definitions of antibiotic prophylaxis. We also explored predictors of receipt of ≥300 days of antibiotics, with the goal of characterizing opportunities for intervention to increase rates of antibiotic prophylaxis among this population.

METHODS

We conducted a multistate analysis of antibiotic prophylaxis among children with SCA by using administrative claims data (University of Michigan Institutional Review Board HUM00120422).

Data Source

Our target population was drawn from the Medicaid programs for the following 6 states that had an average to high prevalence of SCA: Florida, Illinois, Louisiana, Michigan, South Carolina, and Texas. Medicaid Analytic eXtract (MAX) administrative data were acquired from the Centers for Medicare and Medicaid Services; at the time of the study, these states only contained valid data through 2012. Administrative data (2005–2012) included enrollment history and all paid claims for inpatient, outpatient, emergency department (ED), laboratory, and outpatient pharmacy services.[15] Authors of previous studies have indicated ∼90% of children with SCA are enrolled in Medicaid at some point in time, and we expect that Medicaid data will capture a large proportion of the children with SCA.[16,17]

Study Population

We identified children with SCA using a case definition of the presence of at least 3 claims for a child within a calendar year that were SCA-related (282.61, 282.62). This case definition was previously demonstrated to have a high level of sensitivity (91.4%) and specificity (80%) as compared with the gold standard of newborn screening records.[17,18] Continuous enrollment in the Medicaid program for at least 1 calendar year within this time period was required. For each year a child was eligible for the study population, we restricted our analysis to children with no other forms of health insurance (ie, private insurance) during the study period to maximize the completeness of claims available. Children were eligible to contribute multiple nonsequential years to the study population (eg, 2005 and 2007). Children were <5 years old throughout each contributed person-year, consistent with NHLBI recommendations for penicillin prophylaxis.[11]

Definitions of Antibiotic Prophylaxis

Oral penicillin is recommended by the NHLBI for prophylaxis against IPD. However, the American Academy of Pediatrics recommends erythromycin for children with a suspected or proven penicillin allergy, and amoxicillin is sometimes prescribed for practical reasons and is equally effective against *S pneumoniae*. Therefore, we classified antibiotics by using the following 4 definitions:

1. oral penicillin;
2. oral penicillin or erythromycin;
3. oral penicillin, erythromycin, or amoxicillin; and
4. any antibiotic likely to protect against *S pneumoniae* (including penicillin, erythromycin, amoxicillin).[19–23]

Antibiotics were identified in pharmacy claims by using relevant national drug codes associated with an antibiotic (Supplemental Table 4). An author with expertise in pediatric infectious diseases (A.T.) reviewed these records and classified them as described above.

Antibiotic Prophylaxis

The total number of days' supply of antibiotics within a year was

determined by summing the days' supply reported within each filled prescription. Adequate antibiotic prophylaxis was defined as having filled antibiotic prescriptions that would cover ≥300 days of the year; this definition of adequate antibiotic adherence has been endorsed by the National Quality Forum.[18] As such, this quality assessment should be viewed as a "best case" assessment because some children still would not have prophylaxis for all days in a given year.

Predictors of Antibiotic Adherence

We evaluated potential associations between receiving ≥300 days' supply of antibiotics and the following predictors: age, sex, use of health services (sickle cell disease-related inpatient, outpatient, ED, or well-child visits), calendar year, and state of residence.[24] Our approach adjusted for state of residence as a confounder to partially account for the unmeasured variation of these factors between states. Classification of health care encounters was expanded to include any mention of sickle cell disease to account for potential misclassification of sickle cell subtype within the encounter.

Statistical Analysis

Frequencies and percentages (or means, medians, and SDs) were determined for demographic characteristics obtained from the MAX enrollment files. The total number of days' supply of antibiotics for each child within the study population was calculated by definition, as well as the proportion of children that received ≥300 days' supply within the calendar year, for each year and state.

Means, SDs, and interquartile ranges of the number of annual health services visits were assessed. Logistic regression was used to estimate the bivariate associations between each potential predictor and receiving ≥300 days of antibiotics. For the purposes of this analysis, Definition 3 (penicillin, erythromycin, or amoxicillin) was used because this definition was permissive without being all-inclusive. Because multiple periods of enrollment were allowed for each child, generalized estimating equation models with robust SEs accounted for correlation among children. Counts of health care services and age were modeled continuously; predictors showing an association ($P < .20$) were included in a final multivariable model. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the final associations. For all models, regression diagnostics were performed to assess normality of error variances.

We performed a sensitivity analysis to account for potential limitations of pharmacy claims data pertaining to the dispensed days' supply reported on claims. If pharmacy claims for filled prescriptions are missing, our results would be an underestimate of the true proportion of children receiving antibiotic prophylaxis. First, we assessed the number of person-years that included 0 fills for penicillin, erythromycin, or amoxicillin. Then, we explored how our results would be impacted if we assumed that observation with less than a 30 days' supply of antibiotics was because of incomplete claims records. We excluded any person-years that had fewer than 30 days' supply reported for penicillin, erythromycin, or amoxicillin within a calendar year. Among this restricted population, we calculated the proportion of children that had ≥300 days of antibiotics filled; these results were compared with those for the full study population for each year by using 2-proportion *z* tests.

RESULTS

A total of 2821 children with SCA between the ages of 3 months and 5 years of age were identified from the MAX data set from 2005 to 2012, contributing a total of 5014 person-years. The number of person-years varied by state as follows: Florida (1619, 32%), Texas (897, 18%), Louisiana (855, 17%), Illinois (622, 12%), Michigan (580, 12%), and South Carolina (441, 9%). The study population was comprised of 48% girls ($n = 1364$) and 52% boys ($n = 1457$). In 2005, the average age was 1.6 years (SD = 1.1); this was consistent across each year of observation (Table 1). Across states, the median age was 2 years, with the exception of South Carolina, in which the median age was 1 year.

The mean number of days of filled antibiotic prescriptions varied by definition and by year (Fig 1A). The average number of days of filled prescriptions was as follows: 162 days of penicillin (SD = 117; median: 160), 164 days of penicillin or erythromycin (SD = 117; median: 160), 178 days of penicillin, erythromycin, or amoxicillin (SD = 113; median: 180), and 193 days of any *S pneumoniae* antibiotic (SD = 116; median: 194).

The proportion of children that received ≥300 days of antibiotics also varied by definition and year (Fig 1B): 16% of children received ≥300 days of penicillin, 16% of children received ≥300 days of penicillin or erythromycin, 18% of children received ≥300 days of penicillin, erythromycin, or amoxicillin, and 22% of children received ≥300 days of any *S pneumoniae* antibiotic.

The proportion of children receiving ≥300 days of penicillin, erythromycin, or amoxicillin (Definition 3) varied by state (Fig 2). This proportion ranged from 19% (2009, 2012) to 27% (2005, 2007), with South Carolina having the lowest proportion of children with receiving ≥300 days of antibiotic prophylaxis at any time point (6% in 2009).

TABLE 1 Demographic Characteristics of Children With SCA Enrolled in Medicaid by Year, 2005–2012

	2005	2006	2007	2008	2009	2010	2011	2012
	n = 496	*n* = 503	*n* = 534	*n* = 563	*n* = 690	*n* = 723	*n* =756	*n* = 749
Sex, *n* (%)								
Girl	231 (47)	248 (49)	267 (50)	276 (49)	336 (49)	349 (48)	348 (46)	353 (47)
Boy	265 (53)	255 (51)	267 (50)	287 (51)	354 (51)	374 (52)	408 (54)	396 (53)
State, *n* (%)								
Florida	170 (34)	160 (32)	122 (23)	145 (26)	233 (34)	270 (37)	266 (35)	253 (34)
Illinois	53 (11)	75 (15)	69 (13)	69 (12)	96 (14)	75 (10)	82 (11)	103 (14)
Louisiana	101 (20)	87 (17)	122 (23)	124 (22)	115 (17)	116 (16)	106 (14)	84 (11)
Michigan	41 (8)	55 (11)	68 (13)	70 (12)	92 (13)	90 (13)	85 (11)	79 (11)
South Carolina	49 (10)	52 (10)	57 (11)	33 (6)	35 (5)	41 (6)	64 (9)	110 (15)
Texas	82 (17)	74 (15)	96 (18)	122 (22)	119 (17)	113 (18)	153 (20)	120 (16)

TABLE 2 Annual Health Care Use Among Children Ages 3 Months to 5 Years With SCA (*n* = 5014 Person-Years)

Type of Visit	Mean No. Encounters (SD)	Interquartile Range (25th, 75th)
SCD-related inpatient	1.7 (1.8)	2 (0, 2)
SCD-related outpatient	13.2 (11.1)	11 (6, 17)
ED	3.8 (3.4)	4 (1, 5)
Well-child visits	1.6 (1.5)	2 (0, 2)

Study consisted of 2281 individual children that could contribute multiple person-years to the study population. SCD, sickle cell disease.

Overall, children in the study population had an annual mean of 1.7 SCD-related inpatient hospitalizations (SD = 1.8), 13.2 SCD-related outpatient visits (SD = 11.1), 3.8 ED visits (SD = 3.4), and 1.6 well-child visits (SD = 1.5) (Table 2). Bivariate analysis indicated that the number of sickle cell disease-related outpatient visits (OR = 1.01, $P < .0001$), well-child visits (OR = 1.09, $P = .0008$), ED visits (OR = 1.05, $P < .0001$), state of residence (ORs varied by state), and calendar year (ORs varied by year) were independently associated with receiving ≥300 days of antibiotics; age (OR = 0.98, $P = .67$) and number of sickle cell disease-related inpatient visits were not associated (OR = 1.02, $P = .39$). The final multivariable model indicated that the number of sickle cell disease-related outpatient visits, well-child visits, and state of residence continued to be associated with the outcome. Each additional well-child visit was associated with incrementally increased odds of receiving ≥300 days of antibiotics (OR = 1.08, 95% CI: 1.02–1.13), as was each additional sickle cell disease-related outpatient visit (OR = 1.01, 95% CI: 1.01–1.02). A child that was at the third quartile of sickle cell disease-related outpatient visits (17 annual visits) had 15% greater odds of receiving ≥300 days of antibiotics as a child in the first quartile of sickle cell disease-related outpatient visits (6 visits). The odds of receiving ≥300 days of antibiotics did not differ in any year as compared with 2005 (Table 3).

Sensitivity Analysis

A total of 286 person-years (5.7%) had 0 fills for penicillin, erythromycin, or amoxicillin. Furthermore, only 544 person-years (10.8%) had pharmacy claims for fewer than 30 days' supply of penicillin, erythromycin, or amoxicillin. On exclusion of these children, there were 4470 person-years (89.2%) in the restricted population; 20.1% of these person-years had ≥300 days filled compared with 17.9% in the full study population. There was no statistically significant difference in the proportion of children receiving ≥300 days of antibiotics as compared with the full study population in any year.

DISCUSSION

In this multistate analysis, receipt of antibiotic prophylaxis among children with SCA was persistently low, irrespective of year or state. We found that the majority of children with SCA do not receive ≥300 days of antibiotics within a year, even when broadened definitions of antibiotic prophylaxis were considered. These findings are particularly troubling given the elevated risk and case fatality rate of IPD among children with SCA, even with the introduction of the pneumococcal conjugate vaccine.[7,8,25] The methods we applied in this study establish a framework in which to assess the proportion of children adequately protected against IPD, providing an important first step toward identifying opportunities for improvement.

Our findings indicate that a substantial gap exists between use of prophylactic antibiotics among children with SCA and NHLBI recommendations, which indicate penicillin prophylaxis until age 5.[10,11] Although the NHLBI guidelines indicate that oral penicillin is the most appropriate prophylaxis against IPD,[11] we reasoned that it was important to understand if children were protected with alternative antibiotics because intervention approaches to increase rates of

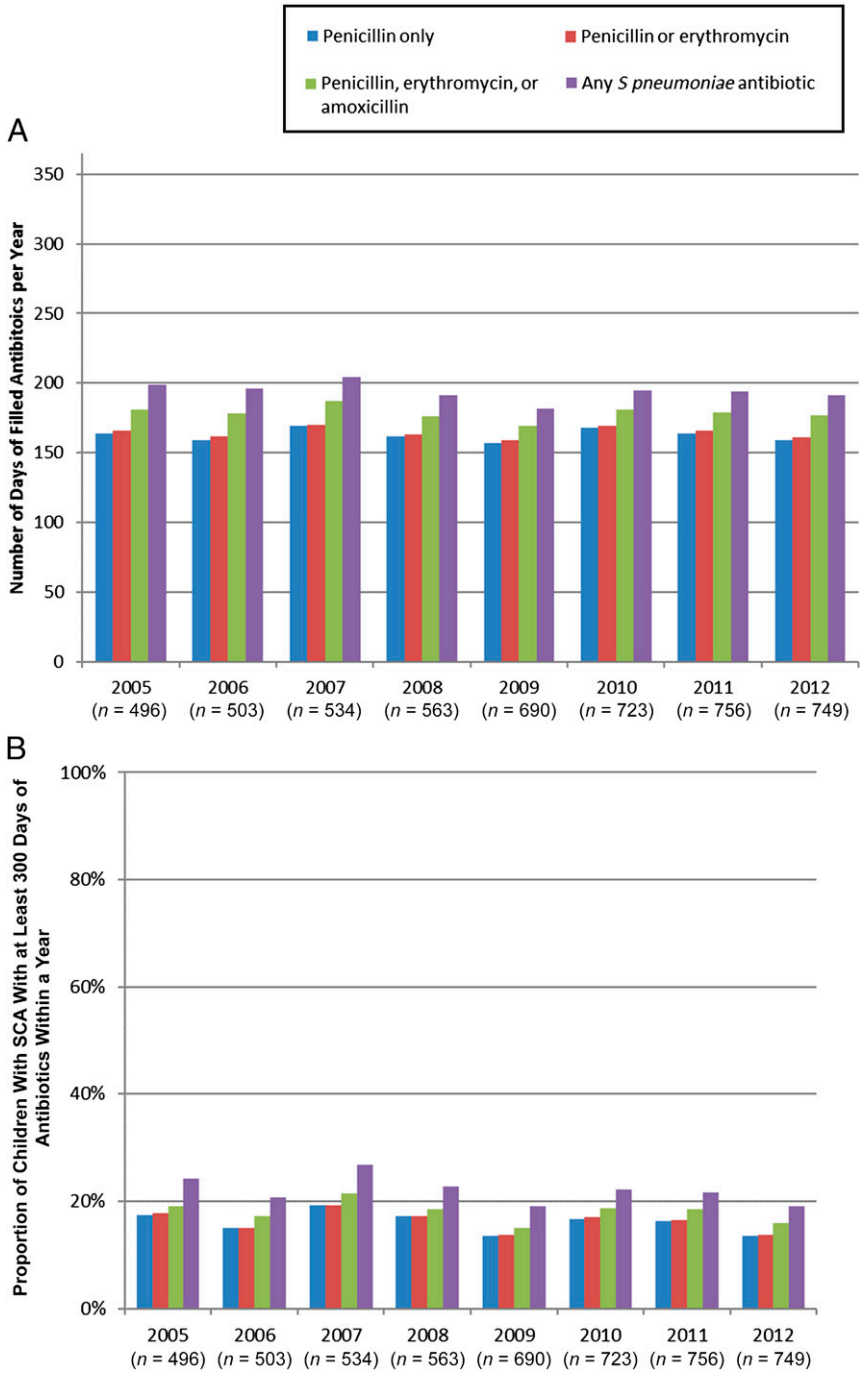

FIGURE 1

A, Mean number of days of dispensed antibiotics per child with SCA, by definition and year. B, Proportion of children with SCA dispensed ≥300 days of antibiotics within a year, by definition and year.

prophylaxis would depend on if children were adequately protected (even if by nonrecommended methods), or if the children were not receiving any antibiotics to protect against IPD. However, even considering the broadest definition of antibiotic prophylaxis, fewer than one-third of children received ≥300 days of these antibiotics across the study period. Although these results are remarkably low, they are consistent with other studies of medication adherence among young pediatric populations enrolled in Medicaid, such as hydroxyurea therapy among children with SCA or asthma controllers among children with persistent asthma.[26,27]

In other studies of antibiotic prophylaxis in children with sickle cell disease, authors report similar results, even when varying definitions of antibiotic prophylaxis and study populations are taken into consideration.[12–14] In the Wisconsin Medicaid program, only 23% of children with SCA received penicillin and/or amoxicillin for 80% of the year (292 days).[13] Although our results do not differ substantially from these studies, this study provides an updated benchmark for receipt of antibiotic prophylaxis among children with SCA. Children with SCA receive suboptimal preventive care in other areas as well. For example, ~30% of children with sickle cell disease have not received recommended pneumococcal conjugate vaccine by 59 months of age.[28] Transcranial Doppler ultrasonography, recommended to identify children at a high risk of stroke, also has low rates among these states, with only 45% of children screened annually. However, unlike our rates of antibiotic prophylaxis, which did not increase over time, transcranial Doppler screening rates increased from 2005 to 2012.[24] Although policy differences may exist across states within this study, all children benefited from the Early and Periodic Screening, Diagnostic, and Treatment program, which are federally mandated to provide robust Medicaid benefits to children. Although state was included as an independent variable in our models, it is possible that differences between states in the availability and accessibility to health care services could contribute to the variation seen across time within states.

Given the consistent finding that antibiotic prophylaxis rates are

TABLE 3 Multivariable Model Predicting Receipt of ≥300 Days of Penicillin, Erythromycin, or Amoxicillin Among Children With SCA (n = 5014 person-years)

Variable	OR	Lower 95% CI	Upper 95% CI
Type of visit			
ED	1.02	0.99	1.04
SCD-related outpatient	1.01*	1.01	1.02
Well child	1.08*	1.03	1.14
State			
Florida	0.51*	0.39	0.68
Illinois	1.00	Reference	Reference
Louisiana	0.57*	0.41	0.78
Michigan	0.60*	0.42	0.85
South Carolina	0.62*	0.43	0.89
Texas	1.01	0.76	1.35
Year			
2005	1.00	Reference	Reference
2006	0.92	0.69	1.23
2007	1.21	0.91	1.60
2008	0.98	0.72	1.33
2009	0.80	0.59	1.09
2010	0.99	0.73	1.33
2011	0.98	0.73	1.31
2012	0.85	0.63	1.15

Study consisted of 2821 children. SCD, sickle cell disease.
* $P < .05$.

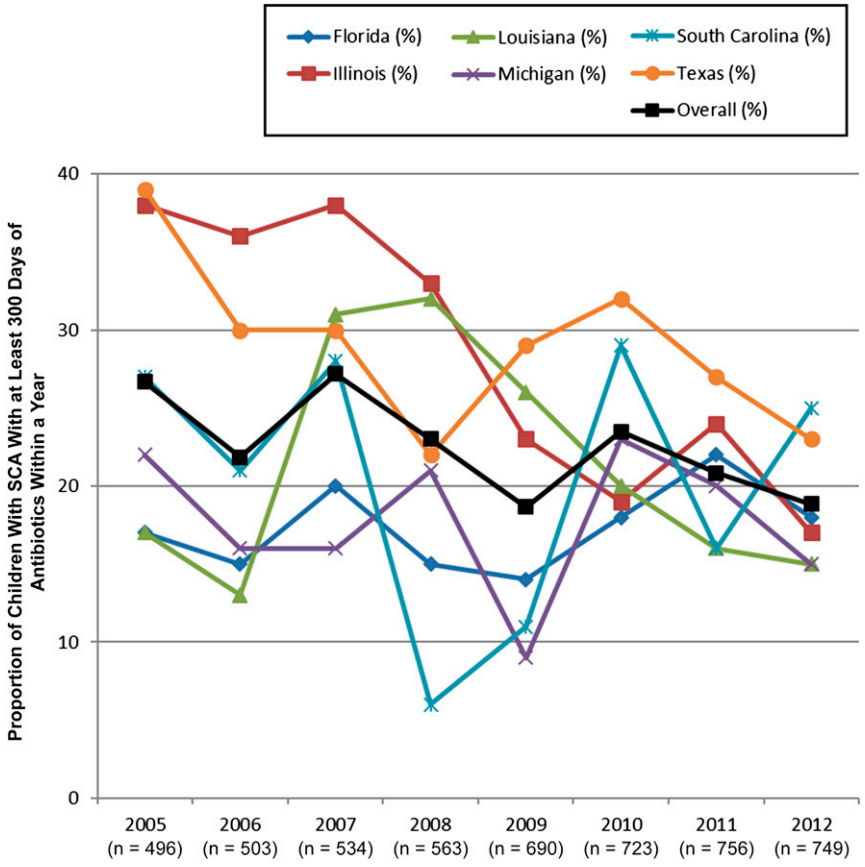

FIGURE 2
Proportion of children with SCA with ≥300 days of filled antibiotics within a year. Antibiotics are defined as penicillin, erythromycin, or amoxicillin.

low among children with SCA, development of practical and effective interventions are key. These interventions should be focused at both the provider and the patient and parent level to ensure a more comprehensive approach to reducing the barriers associated with antibiotic prophylaxis among this population.[25] Provider-focused strategies to increase adherence could capitalize on the numerous annual outpatient encounters with the health care system that children with SCA are already experiencing.[24,29] For example, previously successful interventions to increase medication adherence within health care encounters have targeted physician prescribing habits and provider-led adherence promotion.[30,31] In previous research, authors have also indicated that primary care physicians have a lower level of self-efficacy and knowledge in the provision of preventive care of children with SCA. As such, education of primary care physicians in the importance of these preventive services is necessary.[32] Patient and parent-focused interventions may be most effective when focused on family and social factors that may impact receipt of filled prescriptions at the pharmacy and administration of the antibiotics to the child. For example, the typical formulation of prophylactic antibiotics requires that refills be obtained frequently given the limited shelf life.[33] Although none of the state Medicaid programs included in this analysis require a co-payment for pediatric prescriptions, social factors such as the availability of transportation to pharmacies, and the time required to pick up medications, may be a significant barrier to families because numerous trips to the pharmacy each year are required for refills.[34,35] Families with children with SCA already face a substantial burden of care, which is coupled with challenges of administering daily antibiotics to a young child that may by all outward signs appear healthy. Therefore, assessment of the

knowledge and perceptions regarding the risk of IPD among caregivers, particularly after introduction of the pneumococcal conjugate vaccine, may provide key information for focused interventions to increase administration of antibiotics.[36,37]

There are several limitations to this study. First, the presence of a filled antibiotic prescription does not necessarily indicate that the medication was actually administered to the patient for whom it was prescribed. This limitation suggests that our results may be an overestimate of the true proportion of children with SCA protected against IPD. Second, our study population consisted of children with at least 3 annual claims for SCA; although this definition had a high sensitivity and specificity for identifying cases, children with less interaction with the health care system would not be included. We anticipate these children would also be less likely to receive ≥300 days of antibiotics within a year, indicating another overestimation of the true rates. Third, the use of administrative data to assess quality of care among children with SCA is advantageous given the broad potential for application and low cost. As with other administrative claims methods that are commonly used in quality of care assessments, these methods are subject to the limitations of coding accuracy and claims completeness.[38] However, our administrative claims-based SCA case definition was previously validated by using newborn screening as a gold standard, demonstrating a high degree of accuracy in Michigan.[17] We would expect this definition to perform similarly across the United States because of similar claims-based definitions to identify children with SCA in other states, as well as similarly high levels of health care use across states.[17,24,29,39–41] Fourth, although our data were only complete through 2012, we do not expect that care has improved markedly since that time, absent a coordinated and directed quality improvement program. Finally, we were unable to ascertain pneumococcal vaccination coverage among our study population, which may provide additional protection against IPD.

CONCLUSIONS

Despite long-standing national recommendations, antibiotic prophylaxis against IPD remains low among children with SCA, and efforts aimed at increasing adherence are urgently needed. It is unknown which mechanisms will be the most effective; however, numerous health care encounters may offer an opportunity for intervention. In addition, such interventions likely need to include social factors that may affect the ability for a child to receive and adhere to antibiotic prophylaxis.

ABBREVIATIONS

CI: confidence interval
ED: emergency department
IPD: invasive pneumococcal disease
MAX: Medicaid Analytic eXtract
NHLBI: National Heart, Lung, and Blood Institute
OR: odds ratio
SCA: sickle cell anemia

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