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Factors contributing to missed opportunities for human papillomavirus vaccination among adolescents, ages 11 to 13, in Iowa

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ABSTRACT

Introduction: Rates of human papillomavirus (HPV) vaccination remain low and missed opportunities for HPV vaccination are widespread. Researchers have identified factors related to HPV vaccination, but less is known about missed opportunities.

Methods: We used medical claims data from a large Midwestern insurance provider to explore relationships between adolescent and provider characteristics and missed opportunities for HPV vaccination. We stratified models by initiation status with adolescents who had received one or more HPV vaccinations in one group (n = 6,123) and adolescents with no record of an HPV vaccination in the other (n = 8,107).

Results: There were significant differences in comparisons of all variables between initiators and non-initiators. Notably, non-initiators had lower rates of vaccination for HPV and other adolescent vaccinations, and fewer well-child visits. For all adolescents, birth year, having other recommended vaccines, and number of well-child visits were significantly associated with missed opportunities. Additionally, among initiators, pediatrician as a primary care provider and being in a rural area were significantly associated.

Discussion: Overall, adolescents with greater healthcare utilization had more missed opportunities, indicating that, despite increased numbers of visits, providers are not taking advantage of these opportunities to vaccinate. Future research should prioritize developing a deeper understanding of why these missed opportunities are occurring and implementing new and existing strategies to prevent them. Reducing missed opportunities will help to prevent future HPV-related cancers and the significant morbidity and mortality that they can cause.

Introduction

The human papillomavirus (HPV) vaccine has been studied extensively and is highly effective at preventing HPV-related cancers [1-3], yet less than 60% of adolescents in the United States are not considered up-to-date on the HPV vaccine series [4]. The fact that rates for other adolescent vaccines (those for tetanus, diphtheria, and pertussis and meningococcal disease) are significantly higher indicates a need for further research to understand these low rates for HPV vaccination. One phenomenon that is relatively unresearched, is the occurrence of missed opportunities (MOs) for HPV vaccination and what factors might be related to them. Missed opportunities can generally be defined as clinical encounters in which a patient does not receive care for which they are eligible [5] For HPV vaccination, MOs occur when an eligible adolescent does not receive a needed dose in the vaccine series. It is important to note that there are contraindications for HPV vaccination (e.g. severe illness) and these visits would not be classified as MOs. Existing research reveals that MOs may be a widespread issue [6-9]. A limited number of studies have explored what factors are associated with increased numbers of MOs. For example,

Abbreviations: ACIP, Advisory Committee on Immunization Pratices; EHR, Electronic Health Record; HPV, Human Papillomavirus; MO, Missed Opportunity; MSA, Metropolitan Statistical Area; PCP, Primary Care Provider.

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analyses of electronic health record (EHR) data have found that MOs are associated with patient characteristics such as race or language spoken [10], lack of preventive care visits [11], and type of visit, with non-preventive visits being more likely to result in a MO [6]. Additionally, analyses of medical claims data demonstrated associations between MOs and non-preventive care visits [12], visits for another vaccine [6], and at visits to non-pediatricians [12]. While this prior research offers important insights into how individual and contextual factors may contribute to MOs, it is limited by either a focus on small subsets of patient populations or definitions of MOs that do not capture all types of visits.

In the literature on adolescent and provider characteristics associated with either initiation or completion of HPV vaccination, clear patterns have emerged as to what impacts initiation and completion. Commonly cited adolescent-level factors that are predictive of higher HPV vaccine uptake are receipt of other recommended vaccines (Tdap and MenACWY) [13-15], having well-child visits [16], and being female [4]. Among the strongest predictors of uptake is provider recommendation [17]. Additionally, provider type [18,19] and provider age [20,21] have been identified as a correlate of vaccination recommendation behavior, with pediatricians (compared to family physicians and gynecologists) and younger providers being more likely to recommend HPV vaccination. Finally, another factor frequently cited in literature on HPV vaccine uptake is rurality. As in previous years, the most recently available data from the NIS-Teen found that adolescents living in non-metropolitan statistical areas (MSAs) had lower vaccination rates than those living in MSAs [4].

Given the strong impact that these factors have on HPV initiation and completion, it is reasonable to question whether there would be similar associations with the number of MOs experienced by adolescents. Identifying what these associations are could help researchers, practitioners, and providers to better target certain populations to eliminate MOs and ensure adolescents are vaccinated at all eligible visits. The aim of this study was to use multivariable regression analyses to explore associations between adolescent and provider characteristics and the number of MOs adolescents experience between ages 11 and 13.

Methods

We used deidentified medical claims data provided by a large midwestern insurance provider for all analyses. This study received a determination of not human subjects research from the University of Iowa Institutional Review Board. To create a cohesive cohort of adolescents, we applied several criteria to the data provided (Fig. 1). To avoid temporal effects related to changes to recommendations for the HPV vaccine, we only included adolescents born between 2001 and 2005. Prior to 2010, the vaccine was not routinely recommended for males; therefore, males born prior to 2001 would not have been offered the HPV vaccine. Additionally, in 2016 the recommendation changed from three doses for all adolescents to two doses (in certain circumstances), therefore adolescents born after 2005 likely received different messaging from providers on the HPV vaccine. We then limited data to only adolescents living in Iowa with continuous insurance enrollment between ages 11 and 13 to ensure all eligible visits and vaccinations would be captured. This criterion of continuous enrollment has been used in previous studies analyzing vaccination behaviour [22,23]. Finally, this dataset contained a variable that identified individuals covered under the same healthcare plan. As sibling vaccination behavior is often similar to each other [24,25], we only included the eldest sibling to avoid a potential clustering effect between related family members. All adolescents included in this analysis had claims data for the time at which they were between ages 11 and 13; for the entire cohort this data spanned 2012 to 2018.

Table 1 contains full variable definitions and any relevant International Classification of Disease (ICD) or Current Procedural Terminology (CPT) codes used. Briefly, adolescent characteristics included both demographic characteristics, gender and birth year, and variables about healthcare utilization between ages 11 and 13 including other immunizations received and number of well-child visits. Provider characteristics included in this analysis refer to provider demographics. To determine these, we assigned each adolescent a primary provider. Given that almost all adolescents visited more than one provider, it was necessary to determine which one to use as their primary care provider (PCP). There is significant debate among researchers using medical claims data as to how best to determine this with no firm conclusion on best practice [26]. Common methods include assigning the provider to whom the majority dollar amount of the claims is ascribed [27], or identifying the provider at which either the majority or plurality of the visits occur [26,28]. Each of these methods has limitations; however, one study found concordance between identification through the plurality method and self-report of primary physician to be as high as 83% [28]. Therefore, for this analysis, we chose to use the plurality method of primary care provider assignment and determined the provider at which the adolescent had a plurality of visits that were identified as missed opportunities. To determine this, we calculated the total number of providers seen for MO visits and assigned the provider with the most MO visits as the PCP. In the event that an adolescent had more than one provider with the same number of visits as the plurality, the provider who had the most recent visit date was assigned. By assigning a primary care provider, we could include provider birth year and specialty. To make the provider birth year variable more interpretable, we recoded values by decade of birth year. We then created a dichotomous variable for provider to indicate whether the assigned primary care provider was a pediatrician or any other type of provider (this included General Practice, Family Practice, Internal Medicine, Obstetrics/Gynecology, Physician Assistant, Nurse Practitioner). For physician assistants and nurse practitioners this data set did not delineate what type of practice they worked at so we were unable to determine whether they worked at a pediatric practice and they were classified as "non-pediatricians".

The outcome variable used in regression analyses was the number of MOs between ages 11 and 13. To create this variable, we used the following process. We first recruited three primary care physicians to advise the research team on types of visits to exclude as opportunities due to moderate or severe illness. We provided these three physicians with a list of reasons for visit (operationalized through a review of diagnosis codes to create a clinically meaningful condition/reason for visit) that was provided in data set. These physicians marked off visits at which they would not vaccinate adolescents and when two or more physicians both marked the same condition, we excluded those visits as opportunities for vaccination. We identified visits (1) at which an HPV vaccination did not occur, (2) that fell within one of the categories identified by physicians as a vaccine opportunity, (3) that occurred at a provider who would typically be expected to vaccinate, and (4) that did not fall too close to other HPV vaccines (according to the Advisory Committee on Immunization Practices (ACIP) recommendations current in 2016). Visual inspection of the distribution of total MOs was highly positively skewed. To avoid issues of bias by including adolescents who had high levels of interaction with the healthcare system, we removed adolescents whose total MOs were at or above the 95th percentile (n = 1,398). Originally number of MOs ranged from 0 to 93 and the 95th percentile was 15 MOs.

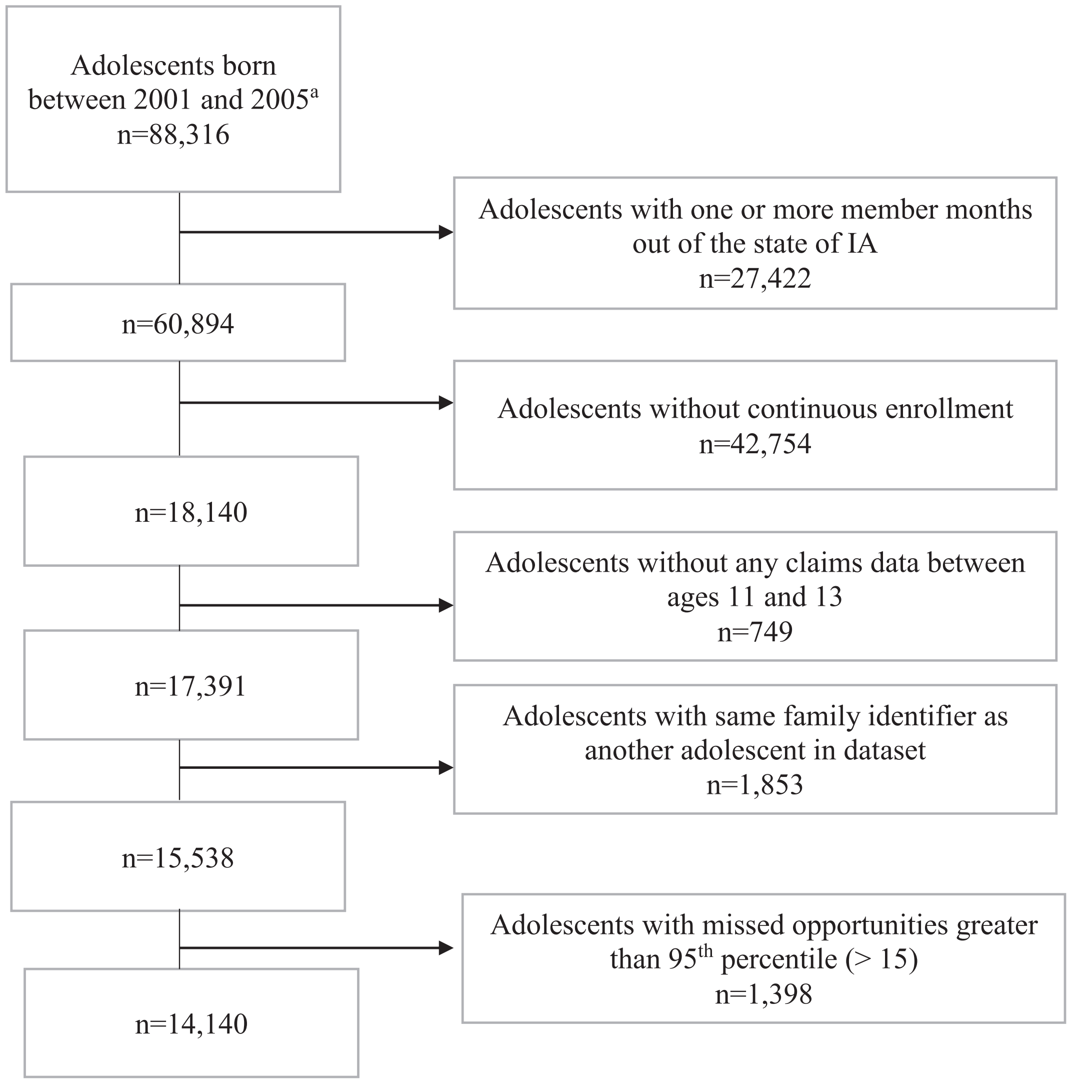

Fig. 1. Inclusion and exclusion criteria to create sample.

Analysis

We used multivariable regression models stratified by non-initiators (adolescents with no HPV vaccines) and initiators (adolescents with at least one HPV vaccine) to assess relationships between covariates and our outcome variable, number of MOs between ages 11 and 13. Prior research suggests that characteristics of initiators compared to non-initiators may be different which supports the stratification of models [29,30]. We performed all analyses using SAS version 9.4.

Given support in the literature for the association between hypothesized covariates and HPV vaccination, and the descriptive, rather than predictive nature of this analysis, we employed a theory-driven approach to model building. Variable selection was informed by current research on individual, interpersonal/provider, and community factors associated with HPV vaccination uptake. We considered inclusion of all hypothesized covariates in the models, but to avoid issues related to overspecification and multicollinearity, we examined statistical relationships between all potential covariates using either Spearman correlation coefficients or t-tests. If there was a significant relationship between two covariates, we determined whether that relationship was just clinically or statistically significant [31], and whether it was warranted to remove one of these variables. While the relationships between most covariates were statistically significant, only the association between well-child visits and number of influenza vaccines was determined to be of concern. Both variables represent utilization of preventive care services; however, influenza vaccines are not mandated and can be given at alternative locations (other than primary care provider offices). Therefore, in the interest of not over-specifying models, only the variable for well-child visits was ultimately included.

We first generated descriptive statistics and used either chi-square or t-tests to explore differences in covariates between initiators and non-initiators. We then looked at bivariate relationships between each of the covariates and the number of MOs using either t-tests or Spearman correlation coefficients. We estimated regression models with the PROC GLIMMIX procedure for generalized linear mixed models. We first estimated models under the Poisson distribution and assessed the fit statistics for a conditional distribution looking at the chi-square statistic, which indicated the presence of overdispersion in the outcome variable. To account for this, we used a negative binomial distribution for final models. We included a random intercept in the models to account for clustering of adolescents at the provider level.

Table 1
Variable definitions used in creation of cohort and regression modeling.

Variable name	Variable Definition
Family identifier	Unique number tied to the contract holder used to identify adolescents who have coverage under the same plan member
Non-initiators	Adolescents who have claims data but have no record of an HPV vaccination using CPT codes: 90649, 90650, 90,651
Initiators	Adolescents with at least one dose of the HPV vaccine using CPT codes: 90649, 90650, 90,651
Total MOs	Sum of MOs for HPV vaccination occurring between ages 11 and 13
Adolescent birth year	Birth year associated with adolescent
Adolescent gender	Male or female
Tdap/MenACWY vaccines received	CPT Codes: 90714, 90715; CPT codes for MenACWY: 90619, 90734
Total number of adolescent vaccines	Value of zero (no Tdap or MenACWY), one (Tdap or MenACWY), or two (both Tdap and MenACWY)
Total influenza vaccines received	Sum of influenza vaccines calculated using CPT Codes: 90630, 90653, 90654, 90655, 90656, 90657, 90658, 90659, 90660, 90661, 90662, 90672, 90673, 90674, 90682, 90685, 90686, 90687, 90688, 90694, 90,724
Number of well-child Visits	Total of encounters for the following ICD 9/10 codes for: routine child health examination (Z00.12/V.202), with abnormal findings (Z00.121/ V.202), without abnormal findings (Z00.129/V.202)
Provider type	Dichotomous indicator for pediatrician vs. all other types of specialties
Provider birth decade	Birth year of primary physician, categorized into decades: 1930–1939, 1940–1949, 1950–1959, 1960–1969, 1970–1979, 1980–1989, 1990–1999
Rurality	Dichotomous definition of RUCA ZCTA-codes using the assigned primary care provider's city Urban codes: 1.0, 1.1, 2.0, 2.1, 3.0. 3.1, 4.1, 5.1, 7.1, 8.1, 10.1 Rural codes: 4.0, 4.2, 5.0. 5.2, 6.0, 6.1, 7.0, 7.2, 7.3, 7.4, 8.0, 8.2, 8.3, 8.4, 9.0, 9.1, 9.2, 10.0. 10.2, 10.3, 10.4, 10.5, 10.6

Results

Adolescent demographics

Table 2 contains descriptive statistics for the cohort included in this analysis along with a statistical comparison of initiators and non-initiators. There were significant differences (p <.001) between the two groups in comparisons on all covariates. Notably, non-initiators had more MOs (*M* = 5.67) compared to initiators (*M* = 4.62). They also had significantly fewer well-child visits (*M* = 1.28) compared to initiators (*M* = 1.61) and over one-third (34%) had no other adolescent vaccinations compared to less than ten percent of initiators.

Stratified multivariable regression models

Table 3 presents results for each model as well as the raw and exponentiated regression coefficients. Statistically significant covariates differed between initiators and non-initiators. All interpretations that follow assume other variables in the model are held constant. Among initiators, some variables at the individual, provider and community level were significant. Birth year, having more well-child visits and having either of the other adolescent vaccines were significantly associated with increased numbers of MOs. Adolescents born later (e.g. 2002 compared to 2001) had 2% more MOs per year. For every additional well-child visit, initiators had 21% more MOs, those with either vaccine (Tdap/MenAWCY) had 18% more MOs, and those with both had 14% more MOs. Additionally, initiators whose primary care provider was a pediatrician had 7% fewer MOs and those that had a provider practicing in a rural area had 6% more MOs.

Among non-initiators, only adolescent characteristics, birth year, well-child visits, and receipt of other vaccines, were significantly associated with MOs. For non-initiators, birth year was negatively associated with MOs, which adolescents having a 1.7% decrease in MOs per year. Similar to initiators, non-initiators had 17% more MOs per additional well-child visit, and non-initiators with either other vaccine (Tdap or Meningococcal) had 18% more MOs and those with both had 16% more MOs. None of the other covariates were significantly associated with MOs for non-initiators.

Discussion

In this study we explored associations between adolescent and provider characteristics and number of MOs for HPV vaccination, with results finding that factors driving increased numbers of MOs differ by initiation status. Our results echo those from prior research that identified significant relationships between variables from levels of the Social Ecological Model and HPV vaccination uptake [15,29]. In our models, both adolescent and provider characteristics were significant for initiators, but only adolescent characteristics were significant for non-initiators. For initiators, significant relationships were observed between number of MOs and later birth year, number of well-child visits, receipt of the other ACIP-recommended vaccines (Tdap and MenACWY), and whether the adolescent's assigned primary care provider was a pediatrician and whether that provider practiced in a rural area. Relationships between birth year, well-child visits and receipt of other vaccines were also observed among non-initiators, however provider characteristics were not significantly associated. An important thing to note in the interpretation of these results is the difference between statistical and clinical significance [31]; while birth year was significantly associated with MOs in both groups, in reality this was only a difference of about one-tenth of a visit between birth years. The most unexpected finding from this analysis was the relationship between more healthcare utilization and increased number of MOs.

There are several potential explanations for this finding. In the first place, preventive care visits, or well-child visits, were low in both groups, meaning that most MOs occurred at acute care visits. Previous research has found that adolescents are more likely to be vaccinated at well-child visits [11,12], thus while acute care visits are opportunities to vaccinate, providers are not taking advantage of them. The second explanation may be related to a factor that was not captured in this data: the impact of provider recommendation on MOs. Provider recommendation is one the strongest predictors of an adolescent being vaccinated [17,32,33]. Providers report making these recommendations primarily at well-child visits, and to a far lesser extent at sports physicals and acute care visits [34]. Therefore, related to the first point, these adolescents with few well-child visits are likely not receiving provider recommendations for the vaccine and may have more MOs as a result. Additionally, barriers such as time constraints at acute care visits and the need to address potential contraindications of vaccination at acute care visits may prevent providers from using these types of encounters as opportunities to vaccinate [35], thus resulting in higher numbers of MOs.

Disparities in provider recommendation may also explain why, among initiators, having an assigned primary care provider who was a pediatrician was associated with fewer MOs and having a provider in a rural area was associated with more MOs. Pediatricians, compared to other types of providers, are far more likely to make a recommendation for the HPV vaccine [18]. Additionally,

Table 2
Adolescent and Provider Characteristics of Initiators (n = 6,123) and Non-initiators (n = 8,017).

		Initiators (n = 6,123)		Non-initiators (n = 8,017)		
		n/mean	**%/ SD**	**n/mean**	**%/SD**	**p-value**
Adolescent Characteristics						
	Male	2820	46.06	4453	44.46	<0.001
	Female	3303	53.94	3564	55.54	
	Birth year 2001	1093	17.85	2457	31.77	<0.001
	Birth year 2002	1251	20.43	2124	26.49	
	Birth year 2003	1144	18.68	1437	17.92	
	Birth year 2004	1235	20.17	970	12.10	
	Birth year 2005	1400	22.86	939	11.71	
	No other adolescent vaccines	578	9.44	2721	33.94	<0.001
	Tdap *or* MenACWY	789	12.89	1803	22.49	
	Tdap *and* MenACWY	4756	77.67	3493	43.57	
	Influenza vaccines	0.81	0.98	0.46	0.87	<0.001
	Well-child visits	1.61	0.90	1.28	0.99	<0.001
	Total MOs	4.622	3.42	5.67	3.52	<0.001
Provider Characteristics	Pediatrician	1412	23.06	1579	19.70	<0.001
	Other type of provider	4711	76.94	6438	80.30	
	Birth year	1966.89	8.09	1965.97	7.68	<0.001
	Rural	2577	42.09	4144	51.69	<0.001
	Urban	3456	57.91	3873	48.31	

Table 3
Relationship between Adolescent and Provider Characteristics and Missed Opportunities for HPV vaccination, Results from Multivariable Stratified Regression Models.

		Initiators (n = 6,123)				Non-initiators (n = 8,017)			
		B	**Standard Error**	**Exponentiated *B***	**p-value**	***B***	**Standard Error**	**Exponentiated *B***	**p-value**
Adolescent characteristics	Male[a]	0.023	0.019	1.02	0.22	-0.024	0.013	0.9763	0.07
	Birth Year	0.017	0.008	1.02	0.04	-0.017	0.006	0.9831	0.003
	Well-child visits	0.193	0.011	1.21	<0.001	0.159	0.007	1.172	<0.001
	Tdap or MenACWY[b]	0.165	0.042	1.18	<0.001	0.166	0.019	1.181	<0.001
	Both Tdap and MenACWY[b]	0.127	0.034	1.14	<0.001	0.152	0.017	1.164	<0.001
Provider characteristics	Pediatrician[c]	-0.070	0.025	0.93	0.01	0.019	0.019	1.019	0.29
	Birth decade	0.005	0.011	1.00	0.64	0.004	0.008	1.004	0.60
	Rural	0.055	0.023	1.06	0.02	0.016	0.0153	1.016	0.31

[a]Referent category: Female.
[b]Referent category: Neither Tdap or MenACWY vaccines.
[c]Referent category: Any other provider type.

research shows that rural adolescents are less likely to receive a provider recommendation for HPV vaccination, compared to their urban counterparts [36]. Future studies could address this by exploring whether there are differences in what types of visits providers consider vaccination opportunities.

Another notable finding, that was not originally the focus of our analysis, was the differences in healthcare utilization between initiators and non-initiators. Our results suggest that there may be a need to target these groups differently to promote vaccine uptake. Non-initiators tended to have less healthcare utilization overall, with fewer well-child visits and less uptake of other ACIP recommended vaccines. It should be noted that the American Academy of Pediatrics advises that adolescents ages 11 to 13 have a well-child visit every year [37], but all adolescents, both initiators and non-initiators, had considerably fewer than that. Additionally, over 33% of non-initiators had neither the Tdap nor MenACWY vaccine, compared to just under 10% of initiators. Considering these two vaccines are required for entry into seventh grade in Iowa, which generally occurs around age 11 to 13 [38], it is surprising that so many adolescents in the non-initiator group had not received these vaccines. In 2017 (the year in which adolescents included in this study and born in 2004 would have been 13), 86% of 13-year-olds nationally had received the Tdap vaccine and 84% had received the MenACWY vaccine [39]. It is possible that adolescents in this group have vaccine-refusing parents, a factor which could not be accounted for in this study. However, literature suggests that the group of overall vaccine-refusers is very low, one study estimated only 2% of all parents to be refusers [40], and it is therefore unlikely to be the reason for such low vaccination rates in the study population. Future research could delve deeper into factors driving these low vaccination rates. Finally, in addition to underutilization of healthcare, non-initiators more frequently had a provider type other than a pediatrician and a provider located in a rural area, compared to initiators. These differences between the two groups suggest that approaches to reduce MOs may need to be tailored for initiators compared to non-initiators. For example, non-initiators may not attend well-child visits as frequently. In practice, this might mean that providers need to especially focus on acute care visits as opportunities to recommend and vaccinate adolescents and that the use of alternative settings (e.g. pharmacies [41] or school-based clinics [42] should be promoted.

Strengths and limitations

There are several key strengths to this study. The use of medical claims data provides a comprehensive view of healthcare utilization that is not seen in analyses of MOs using other types of data (e.g., EHR data). Additionally, limiting the sample to adolescents with continuous enrollment ensured that all interactions that were billed for with during this five-year period of adolescence were captured. There are also several primary limitations to note. First, there is the possibility of misclassification of an adolescent's primary care provider. This would result in the provider variables (provider type, birth decade, and rurality) being incorrectly attributed. Although literature identified the plurality method to assign a primary care provider as among the most accurate ways to do so, studies have found that misclassification can occur up to 75% of the time [26]. Secondly, generalizability is limited by three factors. Only adolescents with continuous enrollment, living in Iowa, and with insurance underwritten by this specific insurer were included in analyses, therefore results cannot be generalized beyond these populations. Despite these limitations, these results make it clear that there are widespread MOs for HPV vaccination occurring in Iowa, especially among adolescents who have higher utilization of preventive care services (well-child visits and other vaccinations). Finally, while the continuous enrollment criteria meant that all encounters billed to insurance were captured, it is possible that some adolescents in this sample received vaccines elsewhere that would not be captured in this data.

Conclusions

In this study we identified several provider and adolescent characteristics related to higher numbers of MOs, as well as some important differences between initiators and non-initiators. Adolescent and provider characteristics were significantly different between initiators and non-initiators. These findings may be particularly useful in identifying which populations may be more at risk for not initiating the HPV vaccine series by age 13. Results from regression models showed significant associations between number of MOs and birth year, receipt of Tdap and MenACWY vaccines, and number of well-child visits. Given that adolescents with more MOs also have greater vaccine adherence and higher numbers of well-child visits, this indicates that providers are not taking advantage of routine care appointments as opportunities to provide HPV vaccinations. Future research needs to build towards understanding what happens at clinic visits that result in a MO, as well as implementing known strategies to reduce them.

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CRediT authorship contribution statement

Grace W. Ryan: Conceptualization, Formal Analysis, Investigation, Project administration, Methodology, Writing-original draft, Writing-review & editing. **Sarah S. Perry:** Formal analysis, Writing-review & editing. **Aaron Scherer:** Supervision, Conceptualization, Writing-review & editing. **Mary E. Charlton:** Supervision, Conceptualization, Writing-review & editing. **Sato Ashida:** Supervision, Conceptualization, Writing-review & editing. **Paul A. Gilbert:** Supervision, Validation, Writing-review & editing. **Natoshia Askelson:** Funding acquisition, Supervision, Conceptualization, Writing-review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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