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Assessment of Missed Opportunities for Hepatitis A Vaccination, National Immunization Survey Child

By

Shannon Cooney Casillas
Degree to be awarded: Master of Public Health

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Assessment of Missed Opportunities for Hepatitis A Vaccination, National Immunization Survey Child

By

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B.A., Seattle Pacific University, 2010

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An abstract of
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Abstract

Assessment of Missed Opportunities for Hepatitis A Vaccination, National Immunization Survey Child

By: Shannon Cooney Casillas

Objective: Quantify the number of missed opportunities for vaccination (MOV) with Hepatitis A vaccine (HAV) in children and assess the association of HAV MOV with covariates of interest.

Study Subjects: Weighted data from the 2013 National Immunization Survey of U.S. children aged 19-35 months, were used. Analysis was restricted to children with provider verified vaccination history (n=13,460).

Methods: MOV were quantified by determining the number of medical visits a child made when another vaccine was administered during eligibility for HAV vaccine, but HAV was not administered. Bivariate and multivariate polytomous logistic regression was used to assess the association of MOV with child and maternal demographic, socio-economic and geographic covariates.

Results: In 2013, 85% of children in our study population had initiated the HAV vaccine series, and 60% received two or more doses. Children with 2+ MOV initiated the vaccine series 6 months later than children with zero. Children who received zero doses of HAV vaccine had an average of 1.77 MOV compared to 0.43 MOV in those with two doses. Children who were younger, had younger mothers, had ever received WIC benefits, lived below the poverty line or lived in a state with childcare or school entry mandates were independently associated with a reduced odds for MOV; children with more educated mothers or married parents were at an increased odds.

Conclusions: MOV may contribute to the poor coverage for HAV vaccination in children, and it is important to understand why children are not having the vaccine administered when eligible.

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Chapter I.

Background

Hepatitis A virus

Hepatitis A virus (HAV) was first described in the 17th and 18th centuries as epidemic jaundice [1]. HAV is a "picornavirus that can produce symptomatic or asymptomatic infection in humans" [2], and it was first differentiated from other hepatitis viruses in the 1970's [1]. Humans are the only natural host of HAV, but the virus can be stable in the environment for months at a time, though it can be killed by heating to temperatures greater than 185 F for one minute, or through adequate water chlorination [1] [3]. The virus is shed in the stool, and infection often occurs with the ingestion of contaminated food or water [2]. Clinically, the incubation period till onset of symptoms is approximately 28 days (ranges from 15-50 days) [1]. However, the virus can be present in the blood and feces beginning 10-12 days after infection, and persist up to 3 weeks after symptom onset [1]. The biggest concern for transmission of infection is when the virus is present but clinical symptoms are not apparent [4]. The virus replicates in liver hepatocytes, and then is excreted from the liver to the bile where it enters the gastrointestinal tract [4].

Clinical symptoms of the virus include sudden onset of fever, fatigue, anorexia, nausea, abdominal discomfort and/or jaundice. These symptoms mirror those of other hepatitis viruses during their acute phase, making it difficult to distinguish clinically without serology testing. Most HAV infections are acute, with clinical symptoms lasting two months or less, but 10-15% of people are thought to have reoccurring symptoms that

can last up to six months [1]. Complications are rare, but can include "immunologic, neurologic, hematologic, pancreatic, and renal extrahepatic manifestations" [1]. Fulminant hepatitis is another rare complication of HAV infection, and prior to vaccine introduction, it was responsible for 100 deaths per year in the U.S. [1]. Pathogenesis of HAV increases with age, with 70% of young children having asymptomatic infection, while older children and adults present with symptoms more than 70% of the time [1]. However, asymptomatic individuals, who are predominantly children, still play a role in the propagation and spread of the virus. Persons at increased risk of infection include international travelers, men who have sex with men, intravenous drug users, those with occupational risks (i.e. health care or laboratory personnel), and those with clotting disorders or chronic liver disorders [2].

Since symptomatic infection is difficult to differentiate clinically from that of other types of acute viral hepatitis, laboratory serology testing is often performed. Diagnosis of HAV infection is most often through detection of serum immunoglobulin M (IgM) anti-HAV antibodies in the blood, which are usually detectable 5-10 days after infection [1]. This method of testing is highly effective, with sensitivity and specificity upwards of 95% [1]. Polymerase chain reaction (PCR) assays can also be used to compare genetic diversity of the virus, and are often helpful when investigating common-source outbreaks [1].

Importance in the U.S. and globally

In the U.S., HAV became a nationally notifiable disease in 1966. Prior to vaccine introduction, the pattern of HAV incidence was cyclic, with peaks every 10-15 years [5]. In 1971 the U.S. experienced the highest number of HAV cases on record, with estimates

of 59,606 infections [1]. However, HAV incidence in the U.S. is likely an underestimate, due to the asymptomatic nature of the illness, and because of the limitations of passive surveillance, and that there is "no regular national tally of all HAV outbreaks" [6].

Globally, in 2010, approximately 14 million cases of foodborne illness were attributed to HAV, resulting in 28,000 deaths [7]. Immunity and susceptibility levels vary across the world for HAV. The highest levels of HAV infection are found in developing countries due to poor sanitation and hygiene [8]. In these countries, about 90% of children are infected before age 10, and most present with minimal symptoms or are completely asymptomatic [8]. Since most children develop antibodies during their childhood infection, they are typically immune later in life. Therefore, outbreaks in endemic countries are more rare [8]. In developed countries with good sanitation and hygiene, infection rates are much lower. Therefore, there are lower levels of naturally acquired immunity and outbreaks are more common, especially in high risk groups [8]. Because of this, vaccination is important in countries with lower endemic levels of infection to increase population-level protection and reduce the risk of infection in vulnerable populations like adults and elderly.

In the U.S., from 2007 to 2011, the number of reported acute HAV cases declined steadily at an average rate of 17% over the four years period (range 13 to 23%), which was a total decline of 53% (from 2,979 in 2007 to 1,398 in 2011) [9]. In 2013, 1,781 HAV cases were reported to the Centers for Disease Control and Prevention (CDC), which was a 14% increase from the previous year, likely attributed to one significant outbreak [10]. However, due to the limitations that lead to under reporting mentioned previously, the CDC estimates that there were actually 3,474 cases of HAV in the U.S. in

2013 [10]. The rate of HAV infection during this same time period declined from 1.0 case per 100,000 in 2007 to 0.6 cases per 100,000 in 2013 [9]. Notably, HAV was one of only two vaccine preventable diseases that met the Healthy People 2010 target of less than 4.3 cases per 100,000, the other being meningococcal disease which declined from 1.3 to 0.4 cases per 100,000 from 1997 to 2008 (meeting the target of 1.0 case per 100,000) [11]. In 2013, of the cases reported with outcome information, 48% (n=519 of 1,081) were hospitalized and 0.9% (n=9 of 959) died from their infection [9]. Additionally, of the cases with information about linkage to an outbreak, 12.8% "indicated exposure that may have been linked to a common-source foodborne or waterborne outbreak" [10].

In the U.S., outbreaks of HAV infection occur most frequently in restaurants, private homes, workplaces and schools, and contaminated fruits, vegetables and shellfish are the most commonly contaminated food items [12] [13]. In foodborne outbreak situations, food handlers who prepare the food at the point of sale or service are often implicated as the source of transmission of the virus [13]. However, contamination of food during growing, harvesting, processing or distribution does also occur, and in outbreak situations, these types of cases can be difficult to link because of widespread distribution of the products geographically [13]. In 2013, an outbreak of HAV occurred in several group homes that house adults with developmental disabilities in Michigan. In this outbreak, there were a total of 8 cases across 5 different group homes [14]. No single food source was implicated as the causative agent, but one unvaccinated health care worker was linked to six of the cases [14]. This outbreak highlights an at-risk population that would benefit from HAV vaccination. Simultaneously in 2013, an outbreak of HAV

occurred in the U.S., which was attributed to contaminated pomegranate seeds from Turkey [15]. There were 165 individuals with confirmed diagnosis of HAV infection in this outbreak. Of those identified, 69 were hospitalized, 2 developed fulminant hepatitis, and one required a liver transplant [15]. Fortunately, there were no deaths in this outbreak. These types of outbreaks highlight vulnerable populations, especially when individuals are unvaccinated.

In addition to direct morbidity and mortality, there are additional impacts of HAV outbreaks. Outbreak control measures put a strain on health departments and also on the food manufacturer that may have to recall its products and remove them from store shelves. A recent nationally representative study using NHANES data, analyzed the prevalence of anti-HAV in the U.S. adult population (adults 20 years and older) and found that it had decreased from 29.5% in 1996-2006 to 24.2% in 2007-2012 [16]. This is important to consider when those with the highest morbidity due to HAV infection tend to be the adult and elderly populations.

The economic burden of HAV outbreaks is important to consider when discussing vaccination policy. There have been several studies that have examined the average cost per HAV case. One study from an outbreak that infected 145 people in Spokane County, Washington, found that the average cost per case was $3,837, summing to $556,386 total for the outbreak [17]. Costs included direct, such as medical care, and indirect, such as lost productivity costs [17]. A similar study from a 1992 HAV outbreak in Denver, Colorado found that for 43 cases, the total costs were $809,706, which included medical costs and outbreak response costs of the health department [18]. One study modeled the cost-effectiveness of HAV vaccination in children using a single 2005 U.S. birth cohort

of approximately 4 million individuals from birth till age 95 [5]. The model estimated that "routine vaccination at age 1 year would result in 183,806 fewer infections and 32 fewer deaths in each cohort" and the cost-effectiveness ratio was estimated to be $173,000 per life year gained and $24,000 per quality adjusted life year gained [5]. The economic burden of HAV should be taken into account when considering the importance of vaccination in our country.

Vaccination development and recommendations

Vaccines are undoubtedly one of the greatest public health advances in history [19]. In 1995, the first HAV vaccine was licensed for use in the United States. Currently, there are three vaccines available in the U.S.; HAVRIX, manufactured by GlaxoSmithKline, and VAQTA, manufactured by Merck, which are both administered as a two-dose sequence, 6-12 months apart, and are approved for use in adult and pediatric populations (beginning at 12 months of age). Twinrix, also manufactured by GlaxoSmithKline, is a combination Hepatitis A & B vaccine administered as a three-dose sequence, and it is approved for use in adults 18 and older. Studies show protective antibodies develop in more than 95% of individuals after one dose of vaccine, and almost 100% of individuals after two doses [1]. Sustained protection from HAV after vaccination is still being assessed, though initial studies show that immunity could last up to 20 years in children, and 25 years or longer in adults [3].

The Advisory Committee on Immunization Practices (ACIP) develops recommendations for the use of vaccines in the U.S. In 1996, the ACIP recommended administration of HAV vaccine to at risk populations. Three years later in 1999, they revised this, and recommended routine vaccination for all children in the 17 states who

had the highest number of cases [5]. Then in 2006, the recommendation changed again, this time calling for all children be vaccinated beginning at one year of age [5]. However, even with this universal recommendation, state laws for childcare and school entry mandates vary across the United States. In 2013, only 16 states and the District of Columbia (D.C.) required children to be vaccinated against HAV for childcare entry, and 10 states and D.C. had kindergarten school entry requirements. Rates of HAV infection in adults have had greater declines in vaccinating states (states that recommend children to be routinely vaccinated or considered for routine vaccination) than in non-vaccinating states, suggesting that childhood vaccination plays a part in herd immunity for older individuals [20].

Despite current recommendations for HAV vaccination in all children, immunization rates for the second dose remain the lowest of all childhood vaccines [21]. Data from the 2014 National Immunization Survey showed that 85.1% of children 19-35 months old had received one dose of HAV vaccine, and only 57.5% had received two or more doses [21]. Children who receive their first dose late, and subsequently do not receive their second dose before 35 months of age, would be counted as one-dose recipients in this statistic, though they may still receive the vaccine before reaching kindergarten age. This is a promising increase from 2003, when HAV vaccination was first included on the National Immunization Survey. In 2003, vaccination among children 24-35 months old was "50% in the 11 states in which routine vaccination is recommended, and 25% in the 6 states where routine vaccination is to be considered" and coverage in the remaining 33 states was only 1% [20]. Annually, the CDC collects data

on vaccination coverage levels among children in kindergarten, but only DTaP, MMR and Varicella are currently evaluated [22].

Missed opportunities for vaccination & gaps in the current literature

A missed opportunity for vaccination (MOV) is typically defined as "any situation in which an eligible child has contact with a health facility and is not administered an indicated vaccine, despite not having contraindications" [23]. MOV are often assessed to find patterns in those who are and are not receiving necessary immunizations when they have an opportunity to receive one. Often it is necessary to consider follow-up studies to assess why people have MOV, which can be done using qualitative tools (like focus groups), clinical surveys, or patient surveys [23]. MOV data can show associations that are of cultural, political and economic importance both locally and globally, and point to where corrective action needs to be taken. Previous studies have indicated MOV as a primary reason for underimmunization [24].

In the U.S., there have been numerous studies that have analyzed the number of MOV for various childhood and adolescent vaccines, including influenza, HPV and tetanus-diphtheria immunizations [25] [26] [27], though little information exists for HAV. One such 2013 study analyzed data for 7 childhood vaccines (not including HAV), across 42 pediatric practices (n=2,076). The results showed that 82.4% of the study population had at least one MOV from birth to the time of the assessment, and 37.8% had at least one MOV to administer an overdue vaccination [24]. Notably, was the finding that "providers missed an opportunity to administer at least 1 vaccine for which the child was eligible or overdue at 31.3% (95% CI 26.5-36.6) and 12.1% (95% CI 8.2-17.3) of all encounters, respectively" [24]. Another study published in 2015 assessed associations of

MOV for seasonal influenza, and found that factors that were independently associated included age, insurance type, number of visits, and type of medical practice [28].

Most of the current research about HAV immunization has focused on coverage levels, with little known about MOV for HAV vaccination. One recent observational study of health care claims databases of children born between 2005 and 2009 found that "one in every three to five children remained unvaccinated against hepatitis A" [29]. Additionally, "62.8–90.1% of the children who never initiated hepatitis A vaccine had at least one well visit from 1 year to three and a half years old," signifying that numerous missed opportunities occurred in this population [29]. Results suggested that year of birth, health plan type, primary provider type, number of doctor's office visits, number of well visits, receipt of MMR/Varicella vaccine, or residing in a state with universal vaccination recommendation or school/childcare requirements were associated with HAV vaccine series initiation [29]. However, the association of these covariates and the number of MOV was not specifically addressed [29]. Another study using data from the 2009 National Immunization Survey found that residing "in a state with hepatitis A vaccination recommendations prior to 2006, or in a metropolitan statistical area within such a state, or being a minority child" were independently associated with higher vaccination initiation [30]. Lastly, one other study went further to determine why the vaccine series was not being initiated in children, by surveying parents of children. The results of the study showed that lack of provider recommendation, not having heard of the vaccine, and parent's not perceiving their child as likely to get HAV as factors associated with not receiving the HAV vaccination [31].

MOV have been described in the literature for various vaccinations in both the adult and pediatric populations. However, there is little information available on missed opportunities for HAV vaccination and the association with demographic characteristics such as race/ethnicity, poverty status, mother's education, living in a state with vaccine mandates for HAV, etc. Through analysis of MOV for HAV, we can better understand where opportunities can be improved upon to vaccinate children, and subsequently increase coverage levels for this vaccine. The focus of this paper is to quantify the number of MOV and analyze the associations of MOV with demographic, socioeconomic and geographic variables.

Assessment of Missed Opportunities for Hepatitis A Vaccination, National Immunization Survey Child

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Short title: Missed opportunities for Hep A vaccination, NIS-Child

Abbreviations:
95% CI- 95% confidence interval; ACIP- Advisory Committee on Immunization Practice; aOR- Adjusted odds ratio; CDC- Centers for Disease Control and Prevention; HAV- Hepatitis A virus; IRB- Institutional Review Board; IQR- Interquartile range; MOV- Missed opportunities for vaccination; NIS-Child- National Immunization Survey Child; OR- Odds ratio; WIC- Women, Infants, and Children; U.S.- United States

Key Words: children, hepatitis A, immunization, missed opportunities, NIS-Child, National Immunization Survey Child, pediatrics, primary care, United States, vaccination

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What is known on this subject:
The Hepatitis A vaccine is universally recommended at one year of age, but the second dose of two has the lowest coverage of all childhood vaccines. Previous studies of missed opportunities for vaccination indicate that these may contribute to underimmunization.

What this study adds:
Studies have quantified missed opportunities for childhood vaccines, but Hepatitis A has not been addressed. Since hepatitis A vaccination is not required for childcare or school entry in all states, we can analyze how these covariates could impact missed opportunities.

Contributors' statement:

Shannon Cooney Casillas: Ms. Casillas conceptualized the design of the study, carried out the data analyses, drafted the initial manuscript, and approved the final manuscript as submitted.

Robert A. Bednarczyk: Dr. Bednarczyk conceptualized the design of the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Disclaimer

All analyses, interpretation and conclusions are those reached by the aforementioned authors, and not that of the NCHS, which is only responsible for the initial collection of the data used.

Chapter II.

Introduction

Vaccines are one of the most impactful public health advancements in history [19]. In 1996, Hepatitis A Virus (HAV) was added to the list of vaccine preventable diseases [1]. HAV is an acute illness, typically caused by the ingestion of food or water contaminated with fecal matter from an infected person. Historically, children were at a higher risk of acquiring the virus, but often were asymptomatic while still playing a role in transmission [1].

In 2013, the incidence rate of HAV infection in the United States (U.S.) was estimated to be 0.6 cases per 100,000, with a total of 1,781 cases reported to the Centers for Disease Control and Prevention (CDC), though this number is likely an underestimate of incidence due to the asymptomatic nature of the illness in many individuals [10]. Even though the overall population-level risk of HAV infection is quite low, HAV outbreaks can be large, and outbreak control measures are difficult and require rigorous public health efforts [3]. Fortunately, HAV is preventable through administration of a highly effective vaccine, which provides high levels of immunity for 20 years or longer [3].

There are three HAV vaccines licensed for use in the U.S.; two protect against HAV only and are administered as a two-dose sequence 6-18 months apart, and are approved for use in both pediatric and adult populations [1]. The third is a combination Hepatitis A & B vaccine administered as a three-dose sequence, and is approved for use in adults 18 and older. As of 2006, the Advisory Committee on Immunization Practice (ACIP) recommended routine vaccination for all children in the U.S., beginning at one year of age [1]. Despite ACIP vaccination recommendations, 2013 HAV vaccination

rates were the lowest of all childhood vaccines, with only 54.7% of children having obtained two doses [32]. Previous studies have indicated that high levels of missed opportunities for vaccination (MOV) may contribute to underimmunization [24]. Numerous studies have quantified MOV for various childhood vaccines, but little is known specifically about missed opportunities for HAV vaccination.

In this study, we assessed the number of MOV for HAV in children 19-35 months old, and examined the association between demographic, socioeconomic and geographic variables with MOV. We hypothesized that there are frequent MOV for HAV, and that these may contribute to the low childhood vaccination coverage for HAV.

Methods

Data Sources & Recruitment

We conducted a cross-sectional study using data from the 2013 National Immunization Survey Child (NIS-Child) public use dataset [33] [34]. The NIS-Child is a national survey that uses random digit dialing of both landlines and cell phones to identify households with children 19-35 months of age. Following a short screener survey, household information questionnaires are administered to gather details on the child's vaccination history, socioeconomic characteristics, and demographics. Additionally, the parent or guardian is asked whether they consent to having their child's health care provider contacted to verify their immunization history. If permission is given, an immunization history questionnaire was mailed to the child's provider to verify the child's vaccination dates [35].

Study Subjects

The study population for this analysis was U.S. children 19-35 months of age, for whom provider verification of vaccination history was obtained. The analysis was limited to children with provider verified immunizations to improve the accuracy of MOV measurements and determination of vaccination coverage. Of the 22,462 age eligible children for whom a household interview was completed, 13,904 were deemed to have adequate provider data (which includes those with no immunization history), and 13,460 (59.9%) had a provider verified vaccination history, and were retained for analysis.

Study variable measurements

Study variables were selected prior to analysis, based on previous research findings and availability of data from the NIS-Child survey. Covariates included child demographic variables (sex, age, race/ethnicity, and first born status), maternal variables (age, education, and marital status), socioeconomic variables (previous history of being uninsured or receiving Women, Infants and Children (WIC) benefits and poverty status), and geographic variables (census region, and whether the child lived in a state with childcare or school entry mandates for HAV vaccination). Only the child's age and vaccination history were physician confirmed. Variables for whether or not a child lives in a state with childcare or school entry mandates were derived using 2013 Immunization Action Coalition data on implementation of mandates compiled from state health departments [36]. All other information was obtained from the child's parent or guardian during the telephone household information questionnaire.

Data analysis

Data analysis was conducted using SAS v9.4 (The SAS Institute, Cary NC). Appropriate survey weights were used to account for the sampling methods in data collection. The sample weighting methods used are described in full detail in the 2013 NIS-Child Data Users Guide [35].

Eligibility for vaccination was determined based on 2013 ACIP dosing guidelines, which recommend children receive their first dose of HAV vaccine beginning at 12 months of age, and a second dose 6-18 months later [37]. MOV were quantified by determining the number of visits a child made to receive another vaccine while eligible to receive a HAV vaccine, without administration of HAV vaccine. Each of these unique visits was counted as one MOV. If more than one vaccine was administered at that visit, it was counted as one MOV. MOV were tallied, and categorized into three groups: zero, one, and two or more.

The weighted frequency of each covariate of interest was determined and presented for the restricted study population using PROC SURVEYFREQ. Cross-sectional associations of MOV with covariates were conducted using bivariate and multivariate polytomous logistic regression, as the MOV outcome variable did not meet the assumptions needed for ordinal logistic regression. We ran collinearity diagnostics and found no problems among variables in the multivariate model. Odds ratios (OR), adjusted odds ratios (aOR) and 95% Confidence Intervals (95% CI) were calculated using PROC SURVEYLOGISTIC.

Ethics

Data used in this analysis are publically available and contain no protected health information. The Emory Institutional Review Board (IRB) determined that it does not meet the definitions of research with "human subjects" or "clinical investigation" as set forth in Emory policies and procedures, and therefore does not require IRB review.

Results

Study population

We used data from 13,460 children with provider verified vaccination history for analysis. The weighted frequency and 95% CI for selected demographic, socio-economic and geographic variables for the total study population, and stratified by number of MOV are summarized in Table 1. Cumulatively, on average, there were 0.77 (weighted) MOV per child (95% CI: 0.74, 0.80). The weighted frequency of children with zero MOV was 56.2%, one MOV was 22.6%, and two or more MOV was 21.2%.

Administration of vaccine

Overall, 84.6% (95% CI: 83.4%, 85.7%) of children aged 19-35 months initiated the HAV vaccination series, and 59.9% (95% CI: 58.3%, 61.5%) completed both doses [Figure 1]. The median age for the receipt of first dose of HAV vaccine was 387 days (IQR: 370, 477) and the median age for receipt of the second dose was 617 days (IQR: 565, 739) [Table 2]. When stratified by the number of MOV, children with zero MOV initiated the vaccine series at a median age of 375 days (IQR: 368, 394), children with one MOV initiated the vaccine series at a median age of 463 days (IQR: 396, 544), and children with two or more MOV initiated the vaccine series at a median age of 565 days

(IQR: 546, 662). The difference in median age of initiation was 87 days higher in children with one MOV and 190 days higher in children with two or more MOV compared to those with zero. We found similar results for receipt of the second dose, with the median age of administration 156 days later for children with one MOV and 174 days later for those with two or more MOV compared to those with zero MOV. The mean difference in age of vaccine administration was found to be significantly different between the three-levels of MOV for both the first and second dose of vaccine ($p<.001$).

Missed opportunities for vaccination

Among children who had received zero doses of HAV vaccine, 75.1% had at least one MOV for administration of the vaccine, with an average of 1.77 MOV per child [Figure 1]; MOV distribution as an absolute percent is presented in Figure 2. Among those who had received one dose of vaccine, 48.4% had at least one MOV for administration of their first dose, and 15.0% had already had one MOV for administration of the second dose; overall children who had received one dose of HAV vaccine had an average of 0.97 MOV. Among those who had received at least two doses of HAV vaccine, 23.2% had at least one MOV for administration of their first dose, while 7.1% had at least one MOV for administration of the second dose; overall children who had received two or more doses of HAV vaccine had an average of 0.43 MOV.

Through bivariate regression analysis of each variable of interest, we found that younger children, children with younger mothers, children who had ever received WIC benefits, children living below the poverty line, children living in the southern census region or children living in a state with childcare or school entry mandates were at a reduced odds of MOV. Children with more educated mothers or children with married

parents were found to have increased odds for MOV. No bivariate association was found for child's gender or first-born status [Table 3].

When adjusting for all covariates of interest, several variables were significantly associated with a change in odds for one and two or more MOV [Table 3]. Children living in the Midwest, South or West census regions were at a reduced odds for two or more MOV compared to children in the Northeast census region; this relationship was also significant for the Midwest region with one MOV. Children living in a state with childcare entry mandates for HAV were at a reduced odds for one MOV (aOR: 0.69, 95% CI: 0.56, 0.86) and two or more MOV (aOR: 0.43, 95% CI: 0.33, 0.55), compared to those living in states without these mandates. Overall in the fully adjusted model, most associations remained similar to the bivariate model, except younger maternal age which was no longer associated with a reduced odds of MOV, and living in a state with school entry mandates which became null.

Discussion

The results of this study indicate that there are numerous opportunities for Hepatitis A vaccination that are not being capitalized upon. Children with two or more MOV start the vaccination series approximately 6 months later than children with zero MOV, which highlights a gap in the ability to fully protect these children. HAV vaccination coverage in U.S. children is lagging behind that for other recommended vaccines, especially for the second dose, which has the lowest coverage of all childhood vaccines. We found that HAV vaccination coverage in children 19-35 months of age is 84.6% for the first dose and 59.9% for the second. Healthy People 2020 targets are for 85% coverage for both doses [38]. If providers are unable to decrease the number of

MOV, this goal will likely be unattainable. When children are seen clinically, it is important for providers to verify whether they are up to date on all recommended vaccines. Further studies of methods and systems used by providers to ensure children's immunizations are up to date are needed. Additionally, more research is needed to identify why these MOV are occurring specifically for HAV, as there is evidence that children are having other vaccines administered.

It is important to understand why overall HAV vaccination coverage is less than optimal. In recent years, levels of vaccine hesitancy have increased [39] and as many as 25% of parents in one New York study were found to choose alternative vaccine schedules for their children [40]. Both of these factors, among numerous others, could contribute to underimmunization and also explain the high number of MOV for immunizations not required by that state. One community health study found that MOV significantly decreased after educating practitioners and tagging charts for children with vaccine opportunities. Of the remaining MOV identified in that study, parental refusal, child illness, and incorrect up-to-date documentation were the leading causes of MOV [41]. A second study supports these same conclusions, and found that one of the primary reasons for MOV was failure to review patient's charts completely and recognize opportunities for vaccination [30]. To improve vaccination rates, an understanding of what is contributing to MOV is needed to make meaningful changes. Since the data in our analysis did not control for parental refusal or how providers verified that children were up to date on vaccines, it is impossible to know how each of these possible confounders contributes to MOV.

Furthermore, it will be important for states to research best practices for increasing immunization coverage, including childcare and school entry mandates. In our analysis, we found that children living in states that had implemented childcare and/or kindergarten entry mandates prior to the data collection year, had a reduced odds of MOV. Increased utilization of Hepatitis A vaccine mandates for childcare and school entry may increase national-level Hepatitis A vaccine coverage.

There are few published data that quantify MOV for HAV, though previous studies quantified MOV for other vaccines, such as influenza, human papillomavirus, and tetanus-diphtheria [25] [26] [27]. One recent observational study by Weiss et al., found that HAV vaccination initiation improved in children born between 2005-2009 from 63.8%, to 74.3% to 79.4% during a three and a half year follow-up (n=503,793), however, it still failed to meet Healthy People 2020 goals for 85% coverage [29] [38]. Weiss also found that vaccination completion rates for HAV were higher for younger birth cohorts, in states that had HAV recommendations prior to the 2006 ACIP recommendation, and in states with childcare and school entry mandates [29]. Childcare and school entry mandates may play a role in this, as states are slowly beginning to implement policies for HAV vaccination requirements, immunization coverage levels are likely to rise. An earlier study by Byrd et al., yielded similar conclusions, though they found an association of being a minority child with a higher number of MOV [30].

Further, a recent case-control study found that for each one-unit increase in mean clinical encounters a child makes per month, the risk of being underimmunized decreased by 54% [24]. Many of the children in our analysis were seen numerous times for vaccination visits, but they still did not receive a HAV vaccine. A 2003 study attempted

to determine why HAV vaccination coverage was so low, and found that children who did not receive a provider recommendation for the vaccine or whose parents had not heard of the vaccine or did not perceive that their child was at risk for HAV were less likely to actually receive the vaccine [31]. More current research can be used to compare to those findings to identify specific parental barriers to HAV vaccination, and determine additional informational and recommendation-based needs to improve HAV coverage.

Strengths & limitations

One strength of our study was the large sample size, and because of the sampling methods used, it can be considered representative of the entire U.S. cohort of children in this age group. Additionally, the NIS-Child is the only data source that provides vaccination data at the state and local level, though the estimates using these variables are less precise than the national data due to smaller sample sizes. Therefore, we were able to analyze the effects of childcare and school entry mandates by state recommendation types.

There are several limitations to this study. First, the MOV calculations may underestimate health care system encounters, as they only accounted for visits a child made to a health care provider and received another vaccination, but not for other visits to a health care facility. We were also limited to the variables in the dataset to assess associations, when there are likely other factors that may confound the associations we found. For example, parental perceptions of vaccination may lead to missed opportunities if vaccines are refused. Parental refusal may be a variable of interest, and future research is needed to focus on this important aspect, specifically in regards to its association with MOV. Furthermore, our study population was restricted to children who had provider

verified vaccination history. The omission of children without provider information may create bias in the data, as these children may have different distributions of MOV than the rest of the population. Last, the NIS-Child population was limited to children whose parents have a landline or cell phone. This could also produce bias in that not all parents have access to personal telephones, and those who do not may have more or less MOV and differences in coverage. Sampling weights were used to attempt to adjust for this, though the true association between owning a telephone and the outcome is difficult to quantify without additionally collecting data from this cohort.

Conclusions

In conclusion, our findings indicate that there are many opportunities to improve vaccination coverage for HAV. By quantifying the number of MOV in this study, we have shown that there are numerous occasions when children are seen in a health care setting but do not receive needed preventive care, like HAV vaccination. Health care providers need to take advantage of all encounters they have and make sure that children receive all recommended vaccinations.

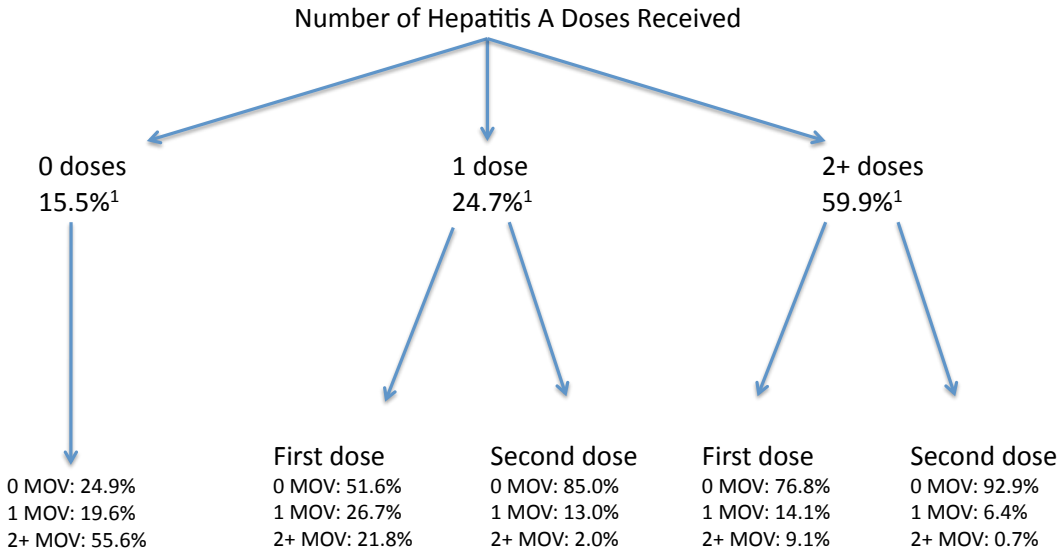
Tables and Figures

Table 1. Weighted frequency of selected population characteristics, by total and stratified by number of missed opportunities for HAV vaccination, among 19-35 month olds with provider verified vaccination history, National Immunization Survey Child, 2013.

	Total Study Population, Weighted Frequency (95% CI)	0 MOV, Weighted Frequency, (95% CI)	1 MOV, Weighted Frequency, (95% CI)	2+ MOV, Weighted Frequency, (95% CI)	Pr>Chisq[1]
Child Demographics					
Gender					
Female	48.8 (47.2, 50.4)	57.1 (54.8, 59.3)	21.4 (19.6, 23.1)	21.6 (19.7, 23.5)	0.24
Male	51.2 (49.6, 52.8)	55.4 (53.1, 57.7)	23.7 (21.7, 25.7)	20.9 (19.2, 22.7)	
Age category					
19-23 months	30.0 (28.5, 31.5)	60.1 (57.2, 63.1)	21.1 (18.8, 23.4)	18.8 (16.4, 21.3)	0.04
24-39 months	34.0 (32.4, 35.5)	54.8 (51.9, 57.7)	23.2 (20.8, 25.6)	22.0 (19.6, 24.3)	
30-35 months	36.0 (34.5, 37.6)	54.3 (51.7, 56.8)	23.2 (20.9, 25.5)	22.6 (20.6, 24.6)	
Race/Ethnicity					
Hispanic	27.2 (25.5, 28.9)	63.1 (59.2, 66.9)	21.2 (18.0, 24.4)	15.8 (12.9, 18.6)	<.001
Non-Hispanic white only	47.9 (46.3, 49.4)	52.5 (50.6, 54.5)	21.5 (20.0, 23.1)	26.0 (24.2, 27.7)	
Non-Hispanic black only	12.7 (11.7, 13.7)	56.3 (51.9, 60.7)	26.9 (23.1, 30.8)	16.8 (13.2, 20.4)	
Non-Hispanic other + multiple race	12.2 (11.2, 13.3)	55.2 (50.9, 59.6)	25.1 (21.0, 29.2)	19.7 (16.3, 23.0)	
First born status					
Yes	40.0 (38.4, 41.6)	54.8 (52.3, 57.4)	22.8 (20.6, 25.1)	22.3 (20.2, 24.5)	0.31
No	60.0 (58.4, 61.6)	57.1 (55.1, 59.2)	22.4 (20.7, 24.1)	20.5 (18.9, 22.2)	
Maternal Demographics					
Age of Mother					
≤ 19 years	1.9 (1.4, 2.4)	64.1 (54.2, 74.0)	20.0 (13.4, 26.6)	15.9 (7.8, 24.0)	<.001
20-29 years	42.6 (41.0, 44.3)	59.2 (56.5, 61.8)	23.9 (21.6, 26.2)	17.0 (15.1, 18.8)	
≥ 30 years	55.5 (53.8, 57.1)	53.7 (51.6, 55.7)	21.6 (20.0, 23.2)	24.7 (22.9, 26.5)	
Education of Mother					
<12 years	18.4 (16.9, 19.8)	66.8 (63.0, 70.5)	19.5 (16.5, 22.5)	13.8 (10.9, 16.7)	<.001
12 years	25.7 (24.1, 27.2)	57.6 (54.1, 61.2)	24.3 (21.1, 27.4)	18.1 (15.4, 20.9)	
>12 years, non-college grad	22.2 (20.9, 23.4)	55.6 (52.4, 58.7)	24.6 (21.8, 27.4)	19.9 (17.3, 22.4)	
College grad	33.8 (32.4, 35.3)	49.8 (47.5, 52.1)	21.6 (19.6, 23.6)	28.6 (26.4, 30.8)	
Marital Status of Mother					
Married	62.4 (60.8, 64.1)	52.8 (50.9, 54.8)	23.1 (21.5, 24.8)	24.0 (22.4, 25.7)	<.001
Never Married/Widowed/Divorced/ Separated/Deceased	37.6 (36.0, 39.3)	61.8 (59.0, 64.6)	21.6 (19.2, 24.0)	16.6 (14.5, 18.7)	
Socio-economic Variables					
Child ever received WIC benefits[2]					
Yes	58.1 (56.5, 59.6)	61.5 (59.3, 63.7)	23.1 (21.1, 25.0)	15.4 (13.8, 17.1)	<.001
No	41.6 (40.1, 43.2)	48.9 (46.6, 51.1)	21.8 (20.0, 23.6)	29.4 (27.3, 31.4)	
Never heard of WIC/Don't Know	0.3 (0.2, 0.5)	51.1 (38.1, 64.2)	28.3 (22.2, 34.5)	20.5 (10.2, 30.9)	
Poverty Status					
Above poverty, >75k	27.4 (26.1, 28.8)	48.3 (45.6, 51.0)	21.7 (19.4, 24.0)	30.0 (27.4, 32.6)	<.001
Above poverty, ≤ 75k	33.9 (32.3, 35.4)	54.2 (51.5, 56.9)	24.4 (21.9, 26.8)	21.5 (19.3, 23.7)	
Below poverty	33.4 (31.8, 35.0)	64.4 (61.6, 67.2)	21.9 (19.6, 24.3)	13.7 (11.8, 15.5)	
Unknown	5.3 (4.3, 6.3)	58.2 (50.1, 66.2)	19.4 (14.2, 24.5)	22.5 (15.2, 29.8)	
Geographic Variables					
Census Region					
Northeast	16.3 (15.7, 16.9)	48.1 (45.1, 51.0)	21.6 (19.2, 24.0)	30.4 (27.7, 33.1)	<.001
Midwest	20.8 (20.2, 21.5)	55.8 (53.4, 58.3)	22.1 (20.0, 24.1)	22.1 (20.1, 24.2)	
South	38.4 (37.3, 39.4)	58.4 (55.9, 60.9)	23.2 (21.0, 25.4)	18.4 (16.5, 20.4)	
West	24.5 (23.3, 25.8)	58.6 (54.1, 63.0)	22.6 (19.0, 26.3)	18.8 (15.2, 22.4)	
Lives in state with childcare entry mandate[3]					
Yes	28.1 (27.2, 29.0)	65.5 (63.0, 68.1)	20.5 (18.3, 22.6)	14.0 (12.2, 15.9)	<.001
No	71.9 (71.0, 72.8)	52.6 (50.5, 54.6)	23.4 (21.7, 25.1)	24.1 (22.4, 25.7)	
Lives in state with school entry mandate[4]					
Yes	21.8 (20.9, 22.6)	66.5 (63.5, 69.6)	20.5 (17.9, 23.1)	13.0 (10.8, 15.2)	<.001
No	78.3 (77.4, 79.1)	53.3 (51.5, 55.2)	23.1 (21.6, 24.7)	23.5 (22.0, 25.1)	

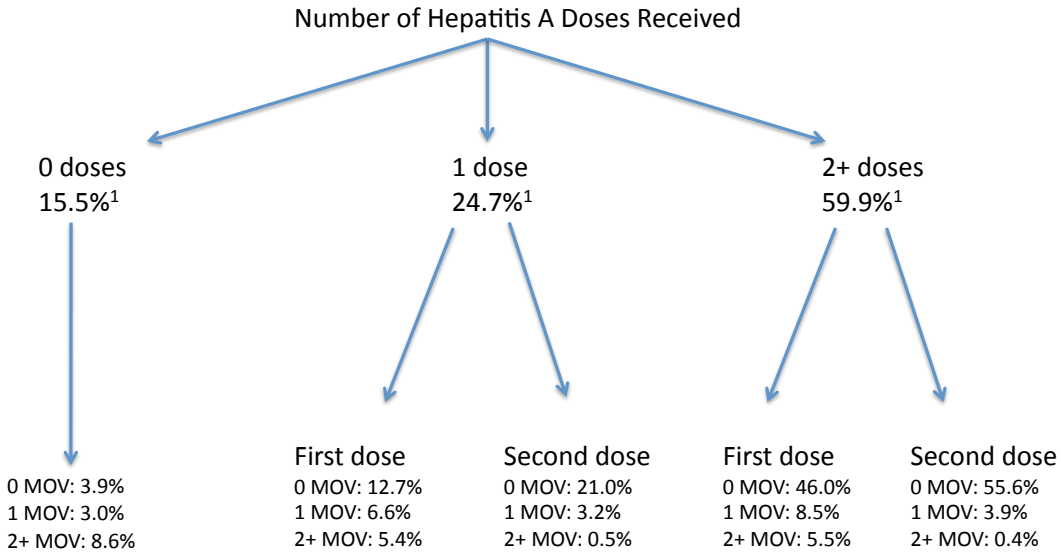
1. Chi-square test for difference in distribution of MOV by the selected characteristic.
2. Special Supplemental Nutrition Program for Women, Infants and Children (WIC)
3. States with childcare entry mandates for HAV in 2013 included: Alaska, Connecticut, District of Columbia, Georgia, Idaho, Kansas,
4. States with school entry mandates for HAV in 2013 included: Alaska, Connecticut, District of Columbia, Georgia, Idaho, Nevada,

Figure 1. Frequency of MOV stratified by number of Hepatitis A doses received, National Immunization Survey Child, 2013.



1. Weighted frequency of children who receive zero, one or two doses of Hepatitis A vaccine.

Figure 2. Absolute frequency of MOV stratified by number of Hepatitis A doses received, National Immunization Survey Child, 2013.



1. Weighted frequency of children who receive zero, one or two doses of Hepatitis A vaccine.

Table 2. Age in days at administration of first and second dose of HAV vaccine, stratified by number of MOV, National Immunization Survey Child, 2013.

Dose	Number of MOV	% of Population (95% CI) (Weighted)	Median age in days (IQR)	Mean age in days (95% CI)	Pr>F[1]
First					
	0	40.4 (37.2, 43.6)	375.1 (368.4, 393.7)	395.4 (392.9, 397.9)	<.001
	1	33.9 (30.9, 37.0)	462.6 (396.2, 543.9)	487.8 (477.4, 498.2)	
	2+	25.7 (23.1, 28.4)	565.4 (546.5, 661.9)	588.3 (575.3, 601.3)	
	Overall		387.4 (370.2, 477.4)	445.6 (441.5, 449.8)	
Second					
	0	70.8 (68.9, 72.8)	582.3 (558.2, 660.3)	621.4 (617.1, 625.7)	<.001
	1	18.7 (17.0, 20.3)	738.2 (729.3, 764.7)	745.1 (734.2, 756.0)	
	2+	10.6 (9.2, 11.9)	756.1 (735.7, 817.5)	799.2 (783.6, 814.7)	
	Overall		617.3 (564.6, 738.5)	663.2 (658.5, 667.9)	

1. Difference of means for each exposure category (MOV); found using PROC SURVEYREG, and modeling each outcome (age in days of vaccination compared to the MOV3 category)

Table 3. Bivariate and multivariate polytomous logistic regression, odds ratios for 1 vs 0 MOV, and 2+ vs 0 MOV, among 19-35 month olds with provider verified vaccination history, National Immunization Survey Child, 2013.

	Bivariate polytomous		Multivariate polytomous (Full Model)		Multivariate polytomous (Reduced Model)[1]	
	OR for 1 vs 0	OR for 2+ vs 0	OR for 1 vs 0	OR for 2+ vs 0	OR for 1 vs 0	OR for 2+ vs 0
Child Demographics						
Gender						
Female	0.88 (0.75, 1.03)	1.00 (0.85, 1.18)	0.89 (0.76, 1.04)	1.03 (0.87, 1.21)		
Male	ref	ref	ref	ref		
Age category						
19-23 months	0.82 (0.69, 0.98)	0.77 (0.63, 0.93)	0.82 (0.68, 1.00)	0.75 (0.61, 0.93)	0.82 (0.68, 1.00)	0.74 (0.60, 0.91)
24-39 months	1.09 (0.91, 1.29)	1.09 (0.92, 1.31)	0.98 (0.81, 1.19)	0.93 (0.77, 1.13)	0.99 (0.82, 1.20)	0.92 (0.76, 1.12)
30-35 months	ref	ref	ref	ref	ref	ref
Race/Ethnicity						
Hispanic	ref	ref	ref	ref		
Non-Hispanic white only	1.04 (0.89, 1.22)	1.74 (1.46, 2.06)	1.02 (0.81, 1.30)	1.20 (0.91, 1.57)		
Non-Hispanic black only	1.23 (0.98, 1.54)	0.77 (0.58, 1.01)	1.35 (1.01, 1.82)	1.05 (0.73, 1.52)		
Non-Hispanic other + multiple race	1.16 (0.91, 1.47)	0.94 (0.74, 1.19)	1.16 (0.86, 1.57)	0.92 (0.66, 1.28)		
First born status						
Yes	ref	ref	ref	ref		
No	1.07 (0.90, 1.26)	1.14 (0.96, 1.34)	1.03 (0.87, 1.21)	1.06 (0.89, 1.28)		
Maternal Demographics						
Age of Mother						
≤ 19 years	0.77 (0.41, 1.45)	0.65 (0.26, 1.63)	1.04 (0.54, 2.01)	1.02 (0.41, 2.56)		
20-29 years	1.01 (0.86, 1.20)	0.63 (0.53, 0.75)	1.12 (0.93, 1.35)	0.87 (0.72, 1.07)		
≥ 30 years	ref	ref	ref	ref		
Education of Mother						
<12 years	ref	ref	ref	ref	ref	ref
12 years	1.07 (0.88, 1.30)	0.78 (0.63, 0.97)	1.35 (1.02, 1.78)	1.32 (0.95, 1.84)	1.39 (1.05, 1.83)	1.34 (0.96, 1.86)
>12 years, non-college grad	1.14 (0.95, 1.37)	0.93 (0.77, 1.13)	1.32 (0.99 1.75)	1.27 (0.90, 1.78)	1.39 (1.05, 1.83)	1.30 (0.93, 1.81)
College grad	1.12 (0.95, 1.31)	1.95 (1.66, 2.30)	1.17 (0.86, 1.59)	1.26 (0.88 1.81)	1.24 (0.92, 1.68)	1.34 (0.95, 1.90)
Marital Status of Mother						
Married	ref	ref	ref	ref		
Never Married/Widowed/Divorced/ Separated/Deceased	0.80 (0.67, 0.95)	0.59 (0.49, 0.71)	0.78 (0.64, 0.97)	0.97 (0.77, 1.23)		
Socio-economic Variables						
Child ever received WIC benefits[2]						
Yes	0.84 (0.72, 0.98)	0.42 (0.36, 0.50)	0.95 (0.75, 1.20)	0.59 (0.45, 0.77)	0.93 (0.73, 1.17)	0.56 (0.43, 0.72)
No	ref	ref	ref	ref	ref	ref
Never heard of WIC/Don't Know	1.38 (0.60, 3.17)	1.06 (0.33, 3.41)	1.25 (0.52, 2.99)	0.67 (0.17, 2.58)	1.24 (0.53, 2.92)	0.62 (0.17, 2.33)
Poverty Status						
Above poverty, >75k	ref	ref	ref	ref	ref	ref
Above poverty, ≤ 75k	1.19 (1.00, 1.41)	1.07 (0.91, 1.27)	1.02 (0.82, 1.27)	0.97 (0.78, 1.22)	1.04 (0.83, 1.29)	0.95 (0.76, 1.19)
Below poverty	0.78 (0.65, 0.92)	0.44 (0.36, 0.53)	0.85 (0.62, 1.15)	0.69 (0.50, 0.96)	0.84 (0.63, 1.13)	0.65 (0.47 0.90)
Unknown	0.82 (0.54, 1.25)	1.03 (0.64, 1.65)	0.80 (0.50, 1.29)	1.08 (0.63, 1.85)	0.80 (0.50, 1.29)	1.03 (0.60, 1.76)
Geographic Variables						
Census Region						
Northeast	ref	ref	ref	ref	ref	ref
Midwest	0.98 (0.84, 1.15)	1.06 (0.91, 1.25)	0.80 (0.65, 0.98)	0.52 (0.42, 0.63)	0.78 (0.64, 0.96)	0.52 (0.43, 0.64)
South	0.99 (0.84, 1.16)	0.75 (0.64, 0.89)	0.96 (0.78, 1.19)	0.62 (0.51, 0.76)	0.95 (0.78, 1.16)	0.62 (0.51, 0.75)
West	0.95 (0.75, 1.20)	0.81 (0.63, 1.05)	0.87 (0.67, 1.12)	0.51 (0.38, 0.68)	0.83 (0.64, 1.08)	0.49 (0.37, 0.65)
Lives in state with childcare entry mandate[3]						
Yes	0.70 (0.59, 0.83)	0.47 (0.39, 0.56)	0.69 (0.56, 0.86)	0.43 (0.33, 0.55)	0.65 (0.55, 0.77)	0.43 (0.36, 0.52)
No	ref	ref	ref	ref	ref	ref
Lives in state with school entry mandate[4]						
Yes	0.71 (0.59, 0.86)	0.44 (0.36, 0.55)	0.94 (0.72, 1.23)	1.02 (0.74, 1.42)		
No	ref	ref	ref	ref		

1.Reduced model was found through backward elimination, at alpha=0.05. Elimination order (first to last): lives in state with school entry mandates, first born status of child, sex, race/ethnicity, mother's age, marital status,
2. Special Supplemental Nutrition Program for Women, Infants and Children (WIC)
3. States with childcare entry mandates for HAV in 2013 included: Alaska, Connecticut, District of Columbia, Georgia, Idaho, Kansas, Nevada, New Mexico, North Dakota, Oklahoma, Oregon, Pennsylvania, Rhode Island, Tennessee, Texas, Utah, West Virginia
4. States with school entry mandates for HAV in 2013 included: Alaska, Connecticut, District of Columbia, Georgia, Idaho, Nevada, Oklahoma, Oregon, Tennessee, Texas, Utah

Chapter III.

Summary

We found that there are numerous missed opportunities to vaccinate children for HAV. Children who have a higher number of MOV are more likely to be underimmunized, and to start their vaccination series significantly later than those with fewer missed opportunities. Additionally, we found that children living in states with child care or school entry mandates for HAV vaccination are likely to have a fewer number of missed opportunities, which may signify that providers are more likely to be aware of this vaccination recommendation or parents are more willing to vaccinate their children in states where there is a requirement in place.

Public Health Implications

It is important for health care providers to verify each child's up to date status at every visit they make to a health care facility. In our study we only quantified missed opportunities at other vaccinating visits, so our results are likely to be an underestimate of the true number of MOV. By reducing MOV, providers can ensure that children obtain their vaccines as soon as they are eligible, and possibly prevent the child from being underimmunized, especially before they reach school age.

Possible Future Directions

In this study, we quantified MOV for HAV vaccination and analyzed possible predictors of missed opportunities. However, from the data used in this analysis, we are unable to fully understand what factors may be leading to missed opportunities. For example, in recent years, many parents have begun to refuse vaccinating their children,

and/or have chosen alternative vaccine schedules for their children [39] [40]. This could explain why during eligibility for HAV vaccination, often children are not actually having this vaccine administered. It is important to further understand why MOV occur, specifically for HAV vaccination in children. Future research should be done to survey providers and/or parents to determine what could be contributing to the high numbers of MOV.

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