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Cumulative and episodic vaccine aluminum exposure in a population-based cohort of young children

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ABSTRACT

Background: In addition to antigens, vaccines contain small amounts of preservatives, adjuvants, and residual substances from the manufacturing process. Some parents have concerns about the safety of these ingredients, yet no large epidemiological studies have specifically examined associations between health outcomes and vaccine ingredients, other than thimerosal. This study examined the extent to which the Vaccine Safety Datalink (VSD) could be used to study vaccine ingredient safety in children.
Methods: Children born 2004–2011 were identified in VSD data. Using immunization records, two cohorts were identified: children who were up-to-date and children who were undervaccinated before age 2 years. A database was also created linking vaccine type and manufacturer with ingredient amounts documented in vaccine package inserts. Thirty-four ingredients in two or more infant vaccines were identified. However, only amounts (in mg) for aluminum were consistently documented and commonly contained in infant vaccines. Analyses compared vaccine aluminum exposure across cohorts and determined the statistical power for studying associations between aluminum exposure and hypothetical vaccine adverse events.
Results: Among 408,608 children, mean cumulative vaccine aluminum exposure increased from 1.11 to 4.00 mg between ages 92–730 days. Up-to-date children were exposed to 11–26% more aluminum from vaccines than undervaccinated children. Power analyses demonstrated that safety studies of aluminum could detect relative risks ranging from 1.1 to 5.8 for a range of adverse event incidence.
Conclusions: The safety of vaccine aluminum exposure can be feasibly studied in the VSD. However, possible biological mechanisms and confounding variables would need to be considered before conducting any studies.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; ADU, average number of days undervaccinated; ICD-9-CM, International Classification of Diseases, 9th edition, Clinical Modification; EHR, electronic health record; MCO, managed care organization; VSD, Vaccine Safety Datalink.

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1. Introduction

Along with immunogens, vaccines contain small amounts of preservatives, adjuvants, additives and residual substances from the manufacturing process [1]. Examples of these additional non-antigen vaccine ingredients include formaldehyde, antibiotics, aluminum, squalene, and monosodium L-glutamate. Although evidence from animal studies, pharmacokinetic modeling, observational studies, and clinical investigations support the safety of ingredients in currently licensed vaccines [2–5], some parents cite vaccine ingredients as a safety concern. These concerns may be contributing to increased rates of undervaccination and adoption of alternative immunizations schedules across the United States [6–10]. To date, there have been no population-based studies specifically designed to evaluate associations between clinically meaningful outcomes and non-antigen vaccine ingredients, other than thimerosal [11–13].

Concerns about the safety non-antigen vaccine ingredients may also contribute to more general concern of some parents that the current immunization schedule exposes young children to "too many vaccines too soon". As recognized by the Institute of Medicine in a review of the feasibility of studying the safety of the immunization schedule, large epidemiological studies represent a logical first step in evaluating these concerns [14]. In addition, a 2009 report by the National Vaccine Advisory Committee (NVAC) recommended a comprehensive safety evaluation of cumulative levels of non-antigen vaccine ingredients as it relates to the recommened schedule [15]. It is possible that such studies could be conducted in the Vaccine Safety Datalink (VSD), an established collaboration of nine managed care organizations (MCOs) where electronic health record (EHR) data are used to conduct observational studies of vaccine safety [16]. In the VSD, large cohorts of children can be assembled to examine potential associations between vaccines and rare adverse events.

In this feasibility study, we conducted an evaluation of the extent to which VSD could be used to conduct a population-based evaluation of the safety of non-antigen vaccine ingredients. We first identified the main non-antigen ingredients in vaccines and determined how well exposure to specific ingredients could be quantified. As an example of how exposure levels could be quantified and categorized, we assessed vaccine-specific aluminum contents among cohorts of children that had been vaccinated according to different schedules. Finally, we assessed the statistical power to evaluate relative risks by level of aluminum exposure over a range of incidence rates.

2. Methods

2.1. Setting and study population

Using VSD databases, we identified a study population of children born between 1/1/2004 and 12/31/2011. Children were included if they were continuously enrolled for 12 months and had at least one outpatient visit in the MCO by one year of age. Follow-up for each child stopped at either their second birthday, end of MCO enrollment, or end of the study period (12/31/2012). Cohort exclusion criteria are listed in Fig. 1.

Vaccination data were collected from the VSD files from birth up to age two years. Data collected on each child included birthdate, sex, all recorded weight measurements and vaccines received. For vaccines received, data were collected on vaccine type, administration date, manufacturer, lot, and injection site. We only considered vaccines recommended by the Advisory Committee on Immunization Practices (ACIP) for children under age two years [17]. During the study period, ACIP's universal immunization recommendations for children under age two years included the following 10 vaccines: hepatitis B (Hep B), diphtheria-tetanus-acellular pertussis (DTaP), inactiviated polio (IPV), Haemophilus influenzae type b (Hib), pneumococcal conjugate (PCV), rotavirus, measles-mumps-rubella (MMR), varicella, Hepatitis A (HepA), and inactivated influenza vaccines. Children are recommended to receive Hep B vaccination at birth, and to start the DTaP, IPV, Hib, PCV, and rotavirus vaccine series at age two months. Medically stable preterm and low birth weight infants are also recommended to start these series at the same chronological ages, though modifications may be necessary for Hep B vaccination in infants less than 2000 g [18].

This study was approved by the Kaiser Permanente Colorado (KPCO) Institutional Review Board (IRB). Participating MCOs either ceded IRB oversight to the KPCO IRB or obtained approval from their site's local IRB.

2.2. Study cohort, undervaccination and alternative Schedules

After the study population was assembled, we calculated the average number of days undervaccinated (ADU) to determine which children were age-appropriately vaccinated according to the recommended ACIP schedule. ADU is a continuous metric that quantifies immunization status over the first two years of life. The details of how ADU is calculated have been reported previously [10,19]. In brief, for each recommended vaccine, days undervaccinated is calculated by comparing the day the child received the vaccine to the recommended age (in days) of receipt, allowing for a 30 day grace period. To calculate ADU, the days undervaccinated from each vaccine are summed and then divided by the total number of recommended vaccine series, representing the average number of days undervaccinated across all series. A detailed table showing ACIP's age recommendations for vaccination and the parameters used to calculate undervaccination for each vaccine dose before age two years in available in Glanz et al. [10].

The study population was first divided into two cohorts: children who were up-to-date and children who were undervaccinated at any point before age 2 years. Within the undervaccinated cohort, a sub-cohort of children with an International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM) code for vaccine refusal (V64.05 and V64.06) or on a specific documented alternative schedule was also identified. Previous work has shown that the V64.05 and V64.06 ICD-9-CM codes are highly specific for intentional parental delay or refusal of childhood vaccination [10]. Children identified as being on a known alternative schedule had a vaccination pattern consistent with the alternative and selective schedules described in *The Vaccine Book* [20], were consistent shot-limiters [6], delayed starting all vaccinations until past four months, or were completely unvaccinated. Vaccination status was assessed at the end of follow-up for children whose follow-up ended between ages 12 and 23 months.

2.3. Vaccine ingredient content

In parallel with the study population and cohort database, we created a database linking vaccine type and vaccine manufacturer with specific ingredient amounts documented in vaccine package inserts and other sources [21,22]. We identified 34 different ingredients that were contained in at least two infant vaccines (Table 1). When available, we documented the concentration of these ingredients in different infant vaccines.

There was considerable variability in documentation of the specific amounts across the various manufacturers; amounts for several ingredients were documented as a combination of "trace",