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Assessing misclassification of vaccination status: Implications for studies of the safety of the childhood immunization schedule

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ABSTRACT

Background: To address public concern about the safety of the childhood immunization schedule, the Institute of Medicine recommended observational studies comparing adverse health outcomes of fully vaccinated children to children under-vaccinated due to parental choice. Misclassification of vaccination status could bias such studies.
Objective: To assess risk of misclassification of vaccination status within the Vaccine Safety Datalink (VSD).
Design/methods: A retrospective cohort study was conducted in three phases. In phase 1, electronic health record (EHR) data were used to identify patterns of under-vaccination during the first 24 months of life potentially due to parental choice. In phase 2, a random sample of records of under-vaccinated children was manually reviewed. In phase 3, a separate sample of parents were surveyed to assess whether EHR data accurately reflected their child's vaccination status. Phases 1 and 2 were conducted at 6 VSD sites, phase 3 at 1 site.
Results: The study cohort included 361,901 children born 2004 through 2012. By 24 months of age, 198,249 (54.8%) were fully vaccinated with no delays, 84,698 (23.4%) experienced delays but were fully vaccinated by 24 months of age, 4865 (1.3%) received no vaccines, 3789 (1.0%) delayed starting vaccination until ≥4 months of age, 4781 (1.3%) had consistent vaccine-limiting (≤2 vaccines per visit), and the remaining 65,519 (18.1%) were missing vaccine series or doses. When a diagnosis code for vaccine refusal was present in EHR data, encounter notes confirmed vaccine refusal as the reason for under-vaccination for nearly 100% of sampled records. Parent surveys confirmed these findings. Parents of under-vaccinated children were more likely to report visiting an alternative medical provider than parents of fully vaccinated children.
Conclusions: Specific groups of children, under-vaccinated due to parental choice, can be identified with relatively low likelihood of misclassification of vaccination status using EHR-based vaccine data and diagnosis codes.

1. Introduction

Vaccination is regarded as one of the greatest public health achievements of the past century [1], and vaccination coverage for young children in the U.S. remains high relative to historical benchmarks [2]. However, survey data indicate that more than 10% of parents have intentionally refused or delayed vaccines for

Abbreviations: ACIP, Advisory Committee on Immunization Practices; ADU, average days under-vaccinated; CI, confidence interval; IIS, immunization information system; KP, Kaiser Permanente; VSD, Vaccine Safety Datalink.

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their children, with vaccine safety reported as a primary concern [3–6]. Some parents have questioned the safety of the immunization schedule as a whole, expressing the opinion that children receive too many vaccines at too young an age, and that early childhood immunization "overwhelms" the immune system [7–9].

In response to these concerns, in 2012 an Institute of Medicine (IOM) committee reviewed scientific evidence regarding the safety of the recommended childhood immunization schedule, and concluded that available evidence strongly supported the safety of the schedule [10]. The committee also identified limitations with existing safety data, asserting that "most vaccine-related research focuses on the outcomes of single immunizations or combinations of vaccines administered at a single visit," and consequently "key elements of the entire schedule-the number, frequency, timing, order, and age at administration of vaccines-have not been systematically examined in research studies" [10]. The committee advocated for new observational studies of the safety of the schedule, and suggested that the Vaccine Safety Datalink (VSD) project [11,12] was an important resource for conducting such studies.

To evaluate the safety of the schedule, the IOM committee recommended comparing adverse health outcomes between fully vaccinated children, completely unvaccinated children, and those on a delayed or alternative schedule [10]. Using observational data to make these comparisons creates significant methodological challenges [10,13,14], in part because health- and health care-related behaviors may differ in systematic ways between parents of fully vaccinated children and those under-vaccinated due to parental choice [15,16]. In addition, vaccination status can be misclassified; in the VSD, this occurs when children who appear under-vaccinated within VSD data have actually received vaccines elsewhere. As detailed in a VSD White Paper, such misclassification could bias studies of the safety of the schedule [17].

The objective of the current investigation was to determine the degree of misclassification of vaccination status within the VSD, specifically in the context of designing future studies of the safety of the recommended childhood immunization schedule. This process included: (1) developing an algorithm to identify specific patterns of under-vaccination that were likely due to parental choice; (2) conducting a manual review of electronic health record (EHR) data to verify vaccination status and reasons for under-vaccination; and (3) surveying a sample of parents of under-vaccinated and fully vaccinated children to assess vaccination status, reasons for under-vaccination when present, and reported receipt of vaccines and health care elsewhere than at their VSD site.

2. Methods

2.1. Study setting

A retrospective cohort study was conducted in the VSD, a collaboration between the Centers for Disease Control and Prevention (CDC) and 9 large medical care organizations (referred to as "sites") from across the U.S [11,12,18]. Six VSD sites participated: Group Health Cooperative; Marshfield Clinic; Kaiser Permanente (KP) Northwest; KP Northern California; KP Southern California; and KP Colorado.

This investigation was accomplished in three phases. In phase 1, vaccination and diagnosis data from the EHR were used to identify patterns of under-vaccination potentially due to parental choice. In phase 2, manual medical record review was performed on a sample of records within each pattern of under-vaccination. In phase 3, a survey was conducted among a separate sample of parents to assess whether vaccine data in the EHR accurately reflected a child's true vaccination status. Phases 1 and 2 were conducted at six VSD sites; phase 3 was conducted at KP Colorado. The study was approved by institutional review boards at all study sites. Written consent was not required for survey administration, and parents could opt out of the survey verbally or in writing.

2.2. Study population

We identified all children within participating VSD sites born January 1, 2004 through December 31, 2012. Within this cohort, we evaluated all vaccines received in the first 24 months of life. We required children to have continuous health insurance enrollment in their respective VSD site from 6 weeks of age through their second birthday. We excluded 91 children (0.02%) with contraindications to vaccination, 288 (0.08%) with obvious vaccine data errors (e.g. vaccine dates prior to date of birth), 2305 (0.63%) with an uncertain vaccine type, and 1150 (0.31%) with vaccines not routinely given under 2 years of age. Four VSD sites (Group Health Cooperative, Marshfield Clinic, KP Northwest, KP Colorado) had access to vaccine data from their statewide immunization information system (IIS) [19], while two VSD sites (KP Northern California, KP Southern California) did not. For VSD sites with IIS linkages, an estimated 1% or less of all vaccines were identified in IIS but not internal site data.

2.3. Phase 1: Identifying under-vaccination due to parental choice

In this phase, EHR vaccination and diagnosis data were used to identify specific patterns of under-vaccination likely due to parental choice. First, an algorithm developed by Luman [20] and modified by Glanz [15] was used to calculate the average days under-vaccinated (ADU) for each child in the study population. The algorithm assesses all vaccines routinely recommended during the first 24 months of life by the Advisory Committee on Immunization Practices (ACIP) [21–23] except influenza and hepatitis A vaccines, and incorporates information on minimum ages, minimum intervals between doses, different dose requirements based on different vaccine products, national vaccine shortages, and changes in vaccination recommendations over time (all historical U.S. immunization schedules are available at https://www.cdc.gov/vaccines/schedules/past.html). Children with ADU = 0 had received all recommended vaccines with no delays.

Next, we examined vaccination patterns for all children with ADU $\geq$ 1 day. Based upon prior work [15,24] as well as published "alternative" vaccination schedules [25], we grouped the observed vaccination patterns into one of six hierarchical, mutually exclusive categories of under-vaccination: (1) no vaccines (completely unvaccinated); (2) first vaccine at $\geq$4 months of age; (3) consistent vaccine-limiting, defined as 2 or fewer vaccines per visit at 2 or more vaccine visits within the first year of life [24]; (4) any vaccine series not received, including not receiving measles-mumps-rubella vaccine or varicella vaccine; (5) vaccine doses not received; and (6) fully vaccinated by 24 months of age, but with some vaccines delayed prior to 24 months. In this context, delay was defined as receiving one or more vaccines $\geq$30 days after the recommended age of administration [21,22,26].

We also assessed the use, at any time between 3 days and 24 months of age, of diagnosis codes indicating "vaccination not carried out because of caregiver/patient refusal" (International Classification of Diseases, 9th Revision, Clinical Modification codes V64.05 and V64.06). In earlier work these codes had high specificity but poor sensitivity as a marker for under-vaccination due to parental choice [15]. We also examined codes for preventive pediatric health care (i.e. well-child care) visits (V20.1, V20.2, V70.x), under the hypothesis that parents of children receiving well-child care but limited or no vaccines were more likely declining vaccination as opposed to encountering barriers to care.

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