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Review

Review of the United States universal varicella vaccination program: Herpes zoster incidence rates, cost-effectiveness, and vaccine efficacy based primarily on the Antelope Valley Varicella Active Surveillance Project data

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ABSTRACT

In a cooperative agreement starting January 1995, prior to the FDA's licensure of the varicella vaccine on March 17, the Centers for Disease Control and Prevention (CDC) funded the Los Angeles Department of Health Services' Antelope Valley Varicella Active Surveillance Project (AV-VASP). Since only varicella case reports were gathered, baseline incidence data for herpes zoster (HZ) or shingles was lacking. Varicella case reports decreased 72%, from 2834 in 1995 to 836 in 2000 at which time approximately 50% of children under 10 years of age had been vaccinated. Starting in 2000, HZ surveillance was added to the project. By 2002, notable increases in HZ incidence rates were reported among both children and adults with a prior history of natural varicella. However, CDC authorities still claimed that no increase in HZ had occurred in any US surveillance site. The basic assumptions inherent to the varicella cost–benefit analysis ignored the significance of exogenous boosting caused by those shedding wild-type VZV. Also ignored was the morbidity associated with even rare serious events following varicella vaccination as well as the morbidity from increasing cases of HZ among adults. Vaccine efficacy declined below 80% in 2001. By 2006, because 20% of vaccinees were experiencing breakthrough varicella and vaccine-induced protection was waning, the CDC recommended a booster dose for children and, in 2007, a shingles vaccination was approved for adults aged 60 years and older. In the prelicensure era, 95% of adults experienced natural chickenpox (usually as children)—these cases were usually benign and resulted in long-term immunity. Varicella vaccination is less effective than the natural immunity that existed in prevaccine communities. Universal varicella vaccination has not proven to be cost-effective as increased HZ morbidity has disproportionately offset cost savings associated with reductions in varicella disease. Universal varicella vaccination has failed to provide long-term protection from VZV disease.

1. Introduction

The varicella-zoster virus (VZV) is a member of a family of viruses known as Alphaherpesvirinae [genus and species: *Varicellovirus human herpesvirus 3* (*HHV-3*)] that upon initial exposure causes varicella (chickenpox) as a primary infection. The initial infection is followed by a variable latency period, after which the lifelong VZV in the dorsal root ganglia can subsequently reactivate as herpes zoster (HZ), commonly known as shingles, a secondary infection. Following short-term safety and efficacy clinical trials in the US, the varicella vaccine, Merck's Varivax®, was licensed for use in children 12 months and older by the US Food and Drug Administration (FDA) on March 17, 1995. On July 12, 1996, the US Centers for Disease Control and Prevention (CDC) published the recommendations of its Advisory Committee on Immunization Practices (ACIP) for universal varicella vaccination of all healthy, susceptible children aged 12- to 18-months with a single 0.5-mL vaccine dose [1].

Prior to the initiation of the universal varicella vaccination program in the US, most public health officials assessing the cost–benefit of vaccination to protect against varicella were principally concerned with data pertaining to clinical chickenpox—largely ignoring the potential effects of this vaccine on the interrelated HZ epidemiology. In fact, three US project sites (Antelope Valley, California; Travis County, Texas; and West Philadelphia, Pennsylvania) were initially selected and funded by the CDC to only perform active surveillance for varicella in order to ascertain the effects of the varicella vaccine on the population. Unfortunately, this limiting decision meant

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that the important baseline incidence data for HZ would not be collected.

2. Methods

In 1995, The Los Angeles Department of Health Services (LADHS), Acute Communicable Disease Control (ACDC) unit entered into a cooperative agreement with the CDC to establish the Antelope Valley Varicella Active Surveillance Project (AV-VASP) which immediately began conducting surveillance for varicella. The Antelope Valley surveillance region consisted of approximately 35 communities, covering approximately 2000 square miles, located about 50 miles northeast of Los Angeles, California in the high-desert plains, with a stable community of 300,000 residents (60% of which were found in the two principal cities of Lancaster and Palmdale). Approximately 300 different reporting units, representing all the identifiable sources in the study region, submitted varicella case logs biweekly to the project. Each case log consisted of a listing of the varicella cases encountered by a given reporting unit. The reporting units comprised all known public and private schools and preschool/daycare centers with enrollments of 12 or more children and approximately 90% of the public health clinics, hospitals, private practice physicians, health maintenance organization (HMO) offices, correctional facilities, and large employers in the region.

With verbal permission of a parent/guardian, a structured telephone interview was conducted regarding each reported varicella case under the age of 20 years old. To minimize recall bias, these interviews were usually conducted with the caregiver within 4 weeks of the case report date. The interview provided detailed demographic (to assist in detecting duplicate case reports), clinical (e.g., temperature of high fever if applicable, list of any pre-existing conditions and/or medications, rating of severity of illness and characteristics of rash at the time of peak illness, duration of the rash, etc.), and health impact data (e.g., days the parent and/or student missed school or work). If other potential susceptible and exposed household members were identified, these were re-interviewed in another 4–6 weeks. The data from each interview was entered into a computer database designed by project staff and implemented by Gary S. Goldman, PhD (Goldman), the project's Research/Epidemiology Analyst from 1995 to November 2002.

In 2000, HZ was added to the surveillance and data was collected in the same manner as previously described for varicella. For HZ cases aged 20 years and over, only demographic information was collected. In 2003, Goldman transported the AV-VASP database, consisting of several hundred demographic and clinical variables for each case, to the CDC for their continued processing and analyses. Because of (a) minor differences in algorithms, and (b) slight differences and/or changes in handling verified and probable cases, varicella and HZ case counts reported in this review may differ slightly from those presented in AV-VASP published studies and annual project summaries to the CDC.

A case of varicella was defined as illness with acute onset of a diffuse papulovesicular rash without other known cause that was diagnosed and/or reported by a licensed health care provider, school nurse, or parent. A case of HZ was defined as a unilateral vesicular rash in a dermatomal distribution, diagnosed by a licensed healthcare provider. In 2004, verified HZ cases included all cases validated by medical record review in addition to the case interview.

Initially, varicella case reports decreased 80%, from 2934 in 1995 to 587 in 1999. Since varicella typically displays a 5-year annual cycle in the Antelope Valley with a peak seasonal trend occurring during early winter and late spring, the reductions in varicella in 1996 and 1997 occurred during a natural decline, following the 1995 peak in this cycle, and were not the result of any early impact of varicella vaccination on the study region. The reality was that during the six surveillance years, 1995–2000, varicella vaccination likely had begun to significantly impact the otherwise naturally decreasing incidence trend only during the latter 2 or 3 years. In 2000 the number of varicella case reports increased to 836, which was still a 72% decrease relative to a naturally occurring cyclical peak in wild-type varicella cases reported in 1995.

Prior to the start of surveillance year 2000, Goldman recommended that HZ-case data be added to the surveillance based on anecdotal reports from long-time public school nurses who reported observing cases of childhood HZ that they had previously rarely, if ever, encountered. The CDC accepted the renewal grant application that included the HZ proposal. Thus, starting in 2000, VASP performed active surveillance for both varicella and HZ. The largest HMO (Kaiser—serving an estimated 30% of the study population) began regularly reporting HZ cases in 2002 based on filtering International Classification of Disease, Ninth Revision (ICD-9) codes for HZ-associated patient visits. Increased surveillance for adult HZ with the inclusion of skilled nursing facilities, dermatology practices, and internal medicine practices was proposed starting in 2005. Thus, HZ counts were significantly under-reported in years prior to 2005.

The study results presented in this review are primarily from this Antelope Valley population, which experienced relatively high levels of varicella vaccine uptake/coverage. Because the surveillance was active (and not passive), AV-VASP managed to collect 100% of the varicella case logs biweekly from all of the reporting units participating in the AV-VASP [2]. Moreover, the surveillance was able to detect sensitive trends early in the universal varicella vaccination program because of four contributing factors: (1) the survey region was relatively isolated geographically with few residents seeking healthcare or attending schools outside the region, (2) the population was relatively stable, (3) there was no sampling (whereas, some sampling occurred in the other two CDC-funded sites), and (4) the existence of two ascertainment sources (schools and healthcare providers) allowed the use of capture–recapture statistical methods to derive ascertainment-corrected counts of varicella and HZ case reports.

The AV-VASP data collection was uninterrupted and surveillance activities remained relatively stable through 2002. However, the 302 adult HZ cases reported to AV-VASP in 2003, representing an 18% decrease from the 368 cases reported in 2002, was an artifact associated with the lack of the AV-VASPs sending a reminder via fax to each surveillance unit failing to submit a timely biweekly report (as had been previously done by an automated fax system implemented by the Research Analyst from 1995 through 2002). AV-VASP operations and reporting patterns were again temporarily affected when a new Project Director was installed in 2004 following the resignation of the initial Project Director.

3. Early-determined HZ incidence rates were censored

By 2000, exogenous exposures to natural varicella (producing immunologic boosts) were dramatically reduced, especially after a marked decline in varicella incidence beginning in 1999 [2]. After 2 years of active HZ surveillance (2000 and 2001), Goldman noted that the number of HZ case reports had maintained or increased in every adult age category except elderly adults aged 70 years and older (Fig. 1) [3]. Using the paired t-test, the 28.5% increase in HZ case reports from 158 in 2000 to 203 in 2001 for ages 20–69 years was statistically significant ($p < 0.042$; $t = 2.95$, dF = 4) (Fig. 1). Also, the HZ incidence rate was low among vaccinated children under 10 years of age. However, the ascertainment-corrected, true HZ incidence rate of 307/100,000 person-years (p-y) during 2000–2001 [3] and 446/100,000 p-y during 2000–2003 [4] among