

# Vaccination to prevent varicella: Goldman and King's response to Myers' interpretation of Varicella Active Surveillance Project data

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## Abstract

**Background:** There is increasing evidence that herpes zoster (HZ) incidence rates among children and adults (aged <60 years) with a history of natural varicella are influenced primarily by the frequency of exogenous exposures, while asymptomatic endogenous reactivations help to cap the rate at approximately 550 cases/100,000 person-years when exogenous boosting becomes rare. The Antelope Valley Varicella Active Surveillance Project was funded by the Centers for Disease Control and Prevention in 1995 to monitor the effects of varicella vaccination in one of the three representative regions of the United States. The stability in the data collection and number of reporting sites under varicella surveillance from 1995–2002 and HZ surveillance during 2000–2001 and 2006–2007 contributed to the robustness of the discerned trends. **Discussion:** Varicella vaccination may be useful for leukemic children; however, the target population in the United States is all children. Since the varicella vaccine inoculates its recipients with live, attenuated varicella–zoster virus (VZV), clinical varicella cases have dramatically declined. Declining exogenous exposures (boosts) from children shedding natural VZV have caused waning cell-mediated immunity. Thus, the protection provided by varicella vaccination is neither lifelong nor complete. Moreover, dramatic increases in the incidence of adult shingles cases have been observed since HZ was added to the surveillance in 2000. In 2013, this topic is still debated and remains controversial in the United States. **Summary:** When the costs of the booster dose for varicella and the increased shingles recurrences are included, the universal varicella vaccination program is neither effective nor cost-effective.

## Keywords

Cell-mediated immunity, varicella costs, exogenous boosting, herpes zoster, immunity, herpes zoster incidence, vaccination, varicella, varicella vaccine efficacy, varicella zoster virus

## Background

There are two major immune system processes that suppress the reactivation of the varicella–zoster virus (VZV) as herpes zoster (HZ; shingles): asymptomatic endogenous reactivations and periodic exogenous exposures to VZV being shed into the environment. Before the licensure of a varicella vaccine in 1995, and continuing thereafter, an ongoing debate has existed with respect to the significance of periodic exogenous exposures that serve to inhibit and postpone the reactivation of shingles.

Gregory A. Poland, Editor in Chief of journal *Vaccine*, (1) failed to notify Goldman and King in advance of the inclusion of a “discussion” article that challenged

their review article<sup>1</sup> and (2) subsequently refused the authors' response on the basis of its not “meeting *Vaccine's* current priorities.” Thus, to promote open dialogue and encourage the sharing of science-based findings, the following in-depth response to Dr Martin

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G. Myers' characterization of the Varicella Active Surveillance Project (VASP) is presented.

### **Authors' response to Dr Myers' "vaccination to prevent varicella"**

We agree with Dr Myers that varicella vaccination may be useful for leukemic children that experience serious complications from VZV infection.<sup>2</sup> But, the universal varicella vaccination initially targeted virtually all US children—the entire birth cohort of about 4 million.

If, as Dr Myers suggests, health care authorities were so concerned about the effects of varicella vaccination on the incidence of HZ, why did three Centers for Disease Control and Prevention (CDC)-funded active surveillance projects initially collect baseline data only for varicella and not HZ? Further, why, 18 years after licensure, are more definitive US studies on HZ incidence lacking?

In support of his views, Dr Myers highlights a VASP/CDC study of shingles incidence<sup>3</sup> among children aged <10 years and individuals aged from 10 to 19 years. Since the count of raw shingles reports was not ascertainment corrected, the computed incidence rates are simply project ascertainment rates that are not comparable to other historical studies that had higher percentages for reporting completeness. Focusing on this study ignores the reality that shingles incidence has dramatically increased among adults who harbor the wild-type (natural) VZV strain(s) because of their history of natural varicella (usually as a benign case acquired when they were children).

HZ incidence rates among both unvaccinated children and adults with a history of natural varicella were modulated by the frequency of exogenous exposures to children shedding VZV.

Cogently, by 2000/2001, 50% of children aged <10 years had been administered the varicella vaccine in the Antelope Valley (AV) community (California, USA). Contrary to the initial cost-benefit assumption that varicella vaccination would have no deleterious impact on HZ epidemiology,<sup>4</sup> the cohort of unvaccinated children having a history of natural varicella demonstrated HZ incidence rates that approached those previously reported in adults.<sup>5</sup> Concomitantly, adult HZ case reports dramatically increased—while the number of reporting sites under active surveillance remained stable.<sup>6</sup> Thus, active surveillance data (1) validated Hope-Simpson's 1965 hypothesis that exogenous exposures (or boosts) suppress the

reactivation of VZV as HZ<sup>7</sup> and (2) demonstrated that asymptomatic endogenous reactivations helped to limit the HZ incidence rate at 550 cases/100,000 person-years (p-y) among adults aged <60 years in the near absence of exogenous exposures. In support of the VASP trends, Guzzetta et al., in their more recent 2013 study, suggest that each episode of exposure to VZV increases protection against HZ and that "this mechanism may be critical in shaping HZ patterns".<sup>8</sup> The high HZ incidence rate among unvaccinated children computed by Goldman in 2001/2002,<sup>5</sup> where the relatively lower HZ rate among vaccinated children served as a control, was finally confirmed by a 2009 CDC publication.<sup>3</sup>

Additionally, from 2000 to 2001, during a stable period of active surveillance with no changes in leadership, the 28.5% increase in HZ reports among adults aged 20–69 years, yielded a statistically significant difference when considering each 10-year age category (Table 1). Moreover, the 2007 VASP annual summary to the CDC<sup>6</sup> presents data (not ascertainment corrected) demonstrating a statistically significant increase in HZ incidence rates, from 390/100,000 p-y in 2006 to 470/100,000 p-y in 2007 among adults aged 50 years and older (Table 2), during a period when data collection methods and the number of reporting sites under active surveillance (Table 3) in the AV remained stable.

Therefore, Myers' depiction of HZ case ascertainment as unreliable and confounded through "extrapolations" is unfounded. His argument that "there was no laboratory confirmation of HZ" is also baseless since health-care providers were responsible for 98.5% of the adult (aged 50 years and older) HZ reports to the AV-VASP during 2006–2007,<sup>6</sup> and HZ symptoms are so distinctive that a study by Schmader et al. found 98.9% agreement of self-reports to a physician diagnosis.<sup>9</sup>

### **A fundamental trend explains the "inconsistencies" in HZ incidence**

Dr Myers writes, "... there have been no consistent trends in reports of HZ incidence." Without in-depth analysis, this apparent conclusion likely considered the CDC study<sup>10</sup> that found no increases in HZ. However, further investigation reveals that this study was conducted in a community prior to widespread varicella vaccination.<sup>11</sup> Also, to be excluded from a consideration of HZ trends is an unpublished 1999–2000 CDC-promoted phone survey by the Massachusetts

**Table 1.** Adult HZ case reports stratified by 10-year age categories, VASP, 2000–2001.

Year of surveillance	Adult age category <sup>a</sup> (years)					Total
	20–29	30–39	40–49	50–59	60–69	
2000	10	20	50	43	35	158
2001	19	27	50	62	45	203 <sup>b</sup>

HZ: herpes zoster; VASP: Varicella Active Surveillance Project; *df*: degree of freedom.

<sup>a</sup>Elderly adults, aged 70 years and older, both prior to and following varicella vaccine licensure, had few opportunities for periodic exogenous boosting, and therefore, the HZ incidence rate among elderly adults is less sensitive to effects of widespread varicella vaccine coverage. The sedentary lifestyle of aged adults is in contrast to younger adults who are (1) more active in the community and (2) may engage frequently in activities involving school-age children.

<sup>b</sup>There was 28.5% increase in HZ case reports in 2001 compared with 2000 reports among adults aged from 20 to 69 years. Using the paired *t* test, the increase in HZ case reports among the five age categories was statistically significant ( $p < 0.042$ ;  $t = 2.95$ ;  $df = 4$ ).

**Table 2.** HZ incidence among adults aged 50 years and older, VASP, 2006 and 2007.<sup>6</sup>

Description	2006	2007
Verified HZ case reports from active surveillance <sup>a</sup>	316 <sup>b</sup>	404 <sup>b,c</sup>
Population aged 50 years and over	81,000 <sup>d</sup>	86,000 <sup>d</sup>
HZ incidence rate	390/100,000 p-y	470/100,000 p-y
2007 to 2006 incidence RR		1.2 (95% CI: 1.04–1.40)
Pearson $\chi^2$ statistic (statistically significant)		$\chi^2 = 6.1$ , $p = 0.013$

HZ: herpes zoster; VASP: Varicella Active Surveillance Project; p-y: person-years; RR: rate ratio; CI: confidence interval; CDC: Centers for Disease Control and Prevention.

<sup>a</sup>A verified HZ case met the case definition of HZ and had a completed case report or a medical chart review that validated the diagnosis of HZ and resided inside the surveillance area. A total of 91.5% of cases were localized to a single dermatome; main dermatomes affected included thoracic (51.5%), cervical (30%), and lumbosacral (16%).<sup>6</sup>

<sup>b</sup>None of the HZ cases reported history of vaccination with Zostavax<sup>®</sup> by Merck and Co. Inc (Whitehouse Station, New Jersey, USA).

<sup>c</sup>The 27.8% increase in reported HZ cases is a conservative, likely minimum figure since the VASP annual summary to the CDC<sup>6</sup> cautions that in 2007 there were “many staffing vacancies and decreased reporting should be considered.”

<sup>d</sup>Population census estimates were obtained through the Los Angeles County Department of Public Health for each corresponding year.<sup>6</sup>

Department of Public Health with insufficient statistical power to detect HZ increases. More recently, a French study<sup>12</sup> found HZ incidence among the general adult population to be similar to that of monastic adults having no recent contact with children—a finding that seemingly minimized the role of exogenous boosting. However, the study ignored, among other factors, the fact that the cell-mediated immunity (CMI) of these monastic nuns and monks was boosted by cases of HZ occurring among themselves.

The seemingly inconsistent outcomes of the various HZ incidence studies, however, are supportive of a fundamental trend that manifests when vaccination coverage in a community reaches 50% of the children aged <10 years: as the rate/coverage of varicella vaccination increases, the opportunity for exogenous exposures decreases and HZ incidence increases among both children and adults (aged <60 years) with a prior history of natural varicella, approaching an upper limit of 550 cases/100,000 p-y.

### Prior to licensure of the varicella vaccine, more than 95% of adults were protected

By 2001, 6 years after licensure, <80% efficacy (Table 4) of the one-dose program among household contacts in the AV<sup>13</sup> was evidenced, in part, by increases in cases of breakthrough varicella. The annual rate of breakthrough varicella significantly increased with the time since vaccination, from 1.6 cases/1000 p-y (95% confidence interval (CI): 1.2–2.0) within 1 year after to 58.2/1000 p-y (95% CI: 36.0–94.0) at 9 years (in 2004).<sup>23</sup> Waning immunity, especially prior to adoption of the two-dose protocol in 2006, resulted in 15 to 20% of vaccinees experiencing breakthrough varicella,<sup>24</sup> with many individuals remaining unprotected as adults. Relative to children, adults who contract varicella have a 25 times greater risk of dying and 13 times greater risk of hospitalization.<sup>25</sup>

**Table 3.** Number of sites under active surveillance during years of increasing adult HZ reports, VASP.<sup>6</sup>

Reporting site type	Year of surveillance <sup>a</sup>			
	2000	2001	2006	2007
Preschools/day care centers, elementary and high schools <sup>b</sup>	177	183	171	163
HMO offices, private practices, and public health clinics	111	104	118	115
Hospitals	3	3	2	2
Long-term care, adult day care, dermatology and pain management facilities	0	0	7	7
Correctional facilities	3	3	4	4
Large employers	10	10	10	10
Miscellaneous, households, and outside normal sampling	5	6	5	5
Total	309	309	317	306

HZ: herpes zoster; VASP: Varicella Active Surveillance Project; HMO: health maintenance organization.

<sup>a</sup>Improved data collection from Kaiser HMO (using ICD-9 codes for HZ) contributed to increases in reported HZ cases and incidence rates from 2002 onward. Results summarized in the review<sup>1</sup> were reported during stable surveillance periods and were either prior to the addition of the Kaiser HMO or independent of the 2002–2004 problematic surveillance project data.

<sup>b</sup>The contribution of reported adult HZ cases by school reporting sites was negligible because only the teachers and staff were generally aged 20 years and older.

### Exogenous boosts and negative PCR test results cause overestimation of vaccine effectiveness

While vaccine efficacy (VE) of the one- and two-dose protocols has been reported as high as 94.4 and 98.3%, respectively, these figures are derived from a study of children aged 1–12 years who were vaccinated in late 1991 to early 1993,<sup>26</sup> prior to licensure of the varicella vaccine in 1995, such that 80% of the 10-year follow-up period was during a time when the CMI of these vaccinees was additionally boosted annually by outbreaks of children shedding wild-type varicella. In a later study by Shapiro et al., there is again a high two-dose vaccine effectiveness of 98.3% reported based on a limited number of 71 subjects enrolled over a 2.5-year period.<sup>27</sup> Of 247 initially enrolled case subjects, however, 176 (71.3%) were excluded since 135 (54.7%) had negative polymerase chain reaction (PCR) assay results, and 41 (16.6%) had inadequate samples for PCR.<sup>27</sup> Shapiro et al.<sup>27</sup> explain that failure to detect VZV was due to less ideal specimen collection technique used for macules. CDC authors noted that VE can be overestimated and confounded when there is reliance on PCR laboratory testing since a negative test result would exclude varicella cases.<sup>28</sup> This issue was demonstrated in a CDC outbreak investigation of 82 varicella cases where all 10 clinical samples and 48 environmental samples tested negative.<sup>29</sup> Thus, PCR assay could not confirm varicella as the etiology of this outbreak.

A comprehensive meta-analysis, based on 14 studies of outbreaks in day care centers/elementary schools,

reports a lower overall VE of 72.5% (95% CI: 68.5–76.0) for the one-dose program.<sup>30</sup> A CDC outbreak investigation team in 2000/2001<sup>31</sup> reported the lowest VE of 44% in a day care center.

Finally, another CDC outbreak investigation conducted in 2006,<sup>32</sup> well after exogenous boosting became rare, reported no significant difference in vaccine effectiveness between one- and two-dose vaccine recipients (83.4 and 88.1%, respectively) attending an Arkansas school. The elementary school children that experienced breakthrough disease may have been exposed to a genetically distinct VZV strain that is heterologous relative to the Oka strain (or vaccine strain). Additionally, those children who “appeared” protected by not manifesting a clinical varicella rash could have experienced asymptomatic reinfection of a second VZV strain. Under both scenarios, one or both VZV strains that have established latency can reactivate in the future as HZ.<sup>1</sup>

### Factors that contributed to the robustness of the observed trends

Unlike the other two VASPs located in Travis County (Texas, USA) and West Philadelphia (Pennsylvania, USA), the AV region, consisting of 300,000 residents principally located in Palmdale and Lancaster, California, USA, (1) was geographically isolated (i.e. few individuals traveled outside the area to attend school or seek health care treatment) and (2) virtually all school and health-care provider sites in the region were under active varicella surveillance (i.e. there was no survey sampling of the available sites). Furthermore,

**Table 4.** Mounting evidence from the AV-VASP<sup>a</sup> in support of Hope-Simpson's hypothesis.

Evidence description	Quantified result
<ul style="list-style-type: none"> <li>• True ascertainment-corrected HZ incidence rate among children aged &lt;10 years with a history of natural varicella is threefold higher relative to prior historical studies (approximately 145/100,000 p-y); however, the HZ incidence rate among varicella-vaccinated children was low as expected, serving as a control.</li> </ul>	VASP used two-source capture–recapture methods <sup>b</sup> to estimate the true HZ incidence rate of 446/100,000 p-y among children aged <10 years with history of natural varicella. <sup>c,1,13</sup>
<ul style="list-style-type: none"> <li>• Ascertainment-corrected varicella incidence rates approximated those rates reported by the NHIS gold standard. When the same capture–recapture methods<sup>b</sup> are applied to HZ reports, the VASP ascertainment-corrected HZ incidence rate among varicella-vaccinated children closely agrees with the rate of 27.4/100,000 p-y (95% CI: 22.7 to 32.7) based on follow-up of 446,027 p-y reported by Tseng et al.<sup>14</sup></li> </ul>	VASP estimates an ascertainment-corrected HZ incidence rate of 28 per 100,000 p-y among varicella-vaccinated children aged <10 years based on VASP reporting completeness of 50%. <sup>b,1,13</sup>
<ul style="list-style-type: none"> <li>• From 2000 to 2001, HZ cases (not ascertainment corrected) reported to VASP either maintained or increased in every adult 10-year age category (20–29, 30–39, . . . , 60–69 years), yielding a statistically significant difference (Table 1).<sup>1</sup></li> </ul>	Reported HZ cases among adults aged 20–69 years increased 28.5%—from 158 in 2000 to 203 in 2001 ( $p < 0.042$ ; $t = 2.95$ , $df = 4$ ) (Table 1). <sup>1</sup>
<ul style="list-style-type: none"> <li>• From January 2000 through April 2002 (28 months), the VASP recurrent HZ incidence rate was 3.3-fold higher than that reported in a 2-year Harvard Community Health Plan study by Donahue et al. based on four recurrences during an observation time of 538 p-y.<sup>15</sup></li> </ul>	High VASP recurrent HZ rate of 2440 (95% CI, 1220 to 4374)/100,000 p-y <sup>1,5</sup> based on 11 HZ recurrences during an observation time of 450 p-y.
<ul style="list-style-type: none"> <li>• VASP adult HZ case reports during 2006 and 2007 demonstrated a statistically significant increase in the HZ incidence rate.</li> </ul>	HZ incidence rates among adults aged 50 years and older increased from 390 to 470 per 100,000 p-y (Table 2). <sup>1</sup>
<ul style="list-style-type: none"> <li>• Initial studies of (VE were biased high during 1995–1999—the “honeymoon” period when VZV was still circulating and boosting vaccinees. VE sharply declined in subsequent years<sup>13</sup> under the one-dose protocol.</li> </ul>	Decreasing VE <sup>1,13</sup> : 96% (95% CI, 83 to 99%) in 1999 86% (95% CI, 74 to 92%) in 2000 74% (95% CI, 58 to 84%) in 2001

AV: Antelope Valley; VASP: Varicella Active Surveillance Project; HZ: herpes zoster; p-y: person-years; NHIS: National Health Interview Survey; CI: confidence interval; *df*: degree of freedom; VE: vaccine efficacy; CDC: Centers for Disease Control and Prevention.

<sup>a</sup>The review<sup>1</sup> discusses seven additional studies that support the significance of exogenous boosting by authors Arvin et al.<sup>16</sup>, Gershon et al.<sup>17</sup>, Salleras et al.<sup>18</sup>, Solomon et al.<sup>19</sup>, Terada et al.<sup>20</sup>, Thomas et al.<sup>21</sup>, and Yih et al.<sup>22</sup>

<sup>b</sup>During 2000–2001, schools and health-care providers reported 54 and 91 HZ cases, respectively, among unvaccinated children and adolescents aged 5–19 years. Of these 145 case reports, 19 were duplicates. Thus, capture–recapture methods estimated VASP reporting completeness of 50% (95% CI: 34 to 65%).

<sup>c</sup>VASP/CDC authors' raw (i.e. unadjusted) cumulative 2000–2006 true HZ incidence rate of 239/100,000 p-y (95% CI: 193 to 295)<sup>3</sup> closely agrees with Goldman's unadjusted cumulative 2000–2003 rate of 223/100,000 p-y (95% CI: 180 to 273).<sup>5</sup> VASP reporting completeness was estimated at 50% for both varicella and HZ; thus, the ascertainment-corrected incidence rates are double the unadjusted rates.

two different sources of case reports allowed the use of capture–recapture statistical methods to estimate reporting completeness and compute the ascertainment-corrected number of cases and rates.<sup>33</sup>

Despite limitations in accuracy of two-source capture–recapture estimates, both the close agreement between the AV-VASP ascertainment-corrected (a) age-specific varicella incidence rates (in 1995) and the 1990–1994 National Health Interview Survey “gold

standard” and (b) cumulative 2000–2003 HZ incidence rate among varicella-vaccinated children and the cumulative 2007/2008 rate reported by an independent study with a large observation time (Table 4), imply that the underlying capture–recapture assumptions were reasonably satisfied and the ascertainment-corrected rates represent better estimates of the true rates than raw or uncorrected rates that ignore reporting completeness.

**Table 5.** Initial cost-benefit assumptions<sup>4</sup> and subsequent updated realities.

Initial cost-benefit assumptions	Updated realities
<ul style="list-style-type: none"> <li>• Vaccination cost is US\$35 per dose with only a US\$5 administration fee.</li> </ul>	After FDA approval, the vaccine pricing increased to nearly double the modeled cost. As of 1 July 2013, CDC and private sector cost/dose is US\$75.36 and US\$90.55, respectively. <sup>36</sup>
<ul style="list-style-type: none"> <li>• A single vaccine dose confers lifelong immunity.</li> </ul>	In 2006, updated recommendation specified two doses: one at age 12–15 months and a booster dose at age 4–6 years.
<ul style="list-style-type: none"> <li>• VE is high (85–95%) using the one-dose vaccine protocol, with negligible adverse reactions.</li> </ul>	Single-dose VE among household contacts was high during 1995–1999 (the “honeymoon” period) when exogenous exposures to children shedding natural VZV were still prevalent. <sup>13</sup> When exogenous exposures became rare, VE declined to below 80%, and 15–20% of vaccinees experienced breakthrough varicella. <sup>24</sup>
<ul style="list-style-type: none"> <li>• Universal varicella vaccination has no adverse effect on the closely related HZ incidence among adults.</li> </ul>	Statistically significant increases in adult HZ cases reported to VASP occurred in 2000–2001, when 50% of children aged <10 years had been vaccinated. <sup>1</sup>
<ul style="list-style-type: none"> <li>• Annual vaccination costs of US\$162 million exceeded the annual medical cost savings of US\$80 million (i.e. from the health payer perspective, US\$2 was spent for each US\$1 saved). However, by considering the cost of a parent’s absence from work to care for a child with varicella at US\$392 million annually, one-dose varicella vaccination is cost-effective from a societal perspective.</li> </ul>	A 2005 economic evaluation of the universal varicella vaccination program <sup>29,37</sup> concluded, “compared to the one-dose program, the two-dose program may not be cost effective.” While the CDC analysis included HZ in vaccinees and outbreak management costs, it excluded both (a) increasing HZ among those with a history of natural varicella <sup>1,4,8</sup> and (b) “potentially higher future post-vaccination incidence due to further accumulation of susceptible persons and future outbreaks.”

FDA: Food and Drug Administration; VASP: Varicella Active Surveillance Project; HZ: herpes zoster; p-y: person-years; VE: vaccine efficacy; CDC: Centers for Disease Control and Prevention; VZV: varicella-zoster virus.

## Summary

Unfortunately, costs associated with increases in adult HZ far outweigh any medical and societal savings associated with varicella epidemiology, especially considering the additional costs associated with (1) the adoption of the two-dose childhood varicella vaccination protocol, (2) the increased hospitalizations due to increased shingles recurrences, and (3) the necessary addition of a shingles vaccine to boost protection in adults who previously received natural exogenous boosts at no cost from children shedding VZV in the community.<sup>1</sup>

Myers does not believe that Goldman and King’s “inferences are justified” despite the mounting qualitative and quantitative evidence from AV-VASP data summarized in Table 4. However, some health care policymakers in the United Kingdom and European countries (except Germany and France) have recognized the validity of these inferences and, to date, have declined to implement universal varicella vaccination programs.<sup>34</sup>

When will US health care policymakers admit that routine vaccination against varicella has proven extremely costly<sup>35</sup> with initial cost-benefit analyses

based on overly optimistic (i.e. false) initial assumptions?<sup>4</sup> (Table 5) Rigorous epidemiological studies of HZ incidence have already corroborated,<sup>1</sup> and additional studies will continue to validate,<sup>8</sup> those trends observed in the AV region. As longitudinal study results are gleaned from various populations under universal varicella vaccination, refinements in understanding age-related incidence trends associated with the interrelated varicella and HZ epidemiology will be further elucidated. Presently, the United States has traded a dramatic reduction in varicella disease which in the prevaccine era accounted for only 25% of the VZV medical costs (i.e. 75% of VZV medical costs were attributed to cases of HZ) for a disproportional increase in HZ costs associated with increasing HZ incidence among adults with a history of wild-type varicella.<sup>1</sup> Based on a 2009 cost-effectiveness model,<sup>38</sup> the Joint Committee on Vaccination and Immunisation, an independent expert advisory committee to the UK Department of Health, “indicates that a two-dose childhood vaccination programme ... could be cost effective but only after 80–100+ years of vaccination ...”

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