1989

*Haemophilus influenzae* Type b Polysaccharide Vaccine: An Efficacy Study

Lee H. Harrison  
*Center for Infectious Diseases, Centers for Disease Control, Public Health Service, United States Department of Health and Human Services*

Claire V. Broome  
*Center for Infectious Diseases, Centers for Disease Control, Public Health Service, United States Department of Health and Human Services*

Allen W. Hightower  
*Center for Infectious Diseases, Centers for Disease Control, Public Health Service, United States Department of Health and Human Services*

Follow this and additional works at: [http://digitalcommons.unl.edu/publichealthresources](http://digitalcommons.unl.edu/publichealthresources)
Haemophilus influenzae Type b Polysaccharide Vaccine: An Efficacy Study

Lee H. Harrison, MD, Claire V. Broome, MD, Allen W. Hightower, MS, and the Haemophilus Vaccine Efficacy Study Group

From the Meningitis and Special Pathogens Branch and the Statistical Service Activity, Division of Bacterial Diseases, Center for Infectious Diseases, Centers for Disease Control, Public Health Service, United States Department of Health and Human Services, Atlanta, Georgia

ABSTRACT. The Haemophilus influenzae type b polysaccharide vaccine was licensed for use in the United States in April 1985. Postlicensure case-control efficacy studies have yielded markedly different estimates of efficacy, leading to contradictory recommendations to practicing physicians. To obtain additional information about the efficacy of the vaccine, we studied cases of invasive Haemophilus influenzae type b disease ascertained through active surveillance in areas with a total population of 34 million. We enrolled children 24 to 59 months of age who did not attend day-care centers. (Data from our day-care study have been published elsewhere.) For each case child, as many as three 24- to 59-month-old control children were chosen from a roster of acquaintances supplied by the child’s parent. Conditional logistic regression was used, and vaccine efficacy was estimated to be 62% (95% confidence interval = 0%, 85%), which did not change significantly after adjusting for age and parental smoking, variables that were significantly different for case and control children. Results of this study support our previous finding of a positive protective efficacy, albeit lower than the efficacy of 90% found in children 18 to 71 months of age in the Finnish prelicensure trial.

METHODS

Active surveillance for invasive H influenzae type b disease. Active surveillance for several infectious diseases was established on January 1, 1986 in Los Angeles County and in Missouri, New Jersey, Oklahoma, Tennessee, and Washington, areas with a combined population of approximately 34 million. Details of this surveillance system have been described elsewhere.5 Briefly, after a promotional period, all acute-care hospitals were requested to participate. Beginning in January 1986, biweekly telephone calls were placed to each hospital to solicit reports of all patients with sterile-site cultures positive for H influenzae, type b.
Data collected on each patient with *H influenzae* type b isolated from a normally sterile site included name, address, age, date of admission, clinical syndrome (eg, meningitis, epiglottitis), the sterile site from which the organism was isolated, and serotype. Directors of hospital laboratories were requested to submit to the Centers for Disease Control isolates of *H influenzae* type b collected from sterile sites in patients with clinical findings consistent with *H influenzae* type b infection. Serotype data came from three sources: hospital, state, and the Centers for Disease Control laboratories.

Estimates of total population and population <5 years of age were obtained from the US Census Bureau for July 1, 1986, with the exception of Los Angeles County, for which the population <5 was not available. This was estimated by applying the proportion of the total population that was <5 years of age for the last year that age-specific data were available (1984) to the total population of the county in 1986.

**Evaluation of Completeness of Surveillance.**

To assess the sensitivity of active surveillance, we reviewed *International Classification of Diseases*, revision 9 (ICD-9) discharge diagnoses for *H influenzae*. Except for several hospitals that declined to participate, this was done for all hospitals in Los Angeles County, Missouri, Tennessee, and Washington; a systematic sample of one half of all hospitals in Oklahoma; and for no hospitals in New Jersey. The sensitivity of surveillance for New Jersey is currently being determined directly by review of hospital laboratory records. Codes reviewed were 038.41 (*H influenzae* septicemia) and 320.0 (*H influenzae* meningoitis). Patients identified through ICD-9 information had their medical records reviewed to determine whether *H influenzae* type b had been isolated from a normally sterile body fluid. Sterile-site positive cases were then compared with cases reported through active surveillance. The sensitivity of surveillance was estimated as the proportion of cases identified by ICD-9 review that had also been reported through active surveillance.

**Selection of Case Children**

A child was considered eligible if he or she was 24 to 59 months of age, had *H influenzae* type b isolated from any site normally considered to be sterile in conjunction with clinical signs of infection, did not attend day-care (defined as any supervised care of at least two unrelated children for at least 4 h/wk) in the week before the positive *H influenzae* type b culture, and lived in a surveillance area. Eligibility also required that the date of positive culture for *H influenzae* type b be between January 1 and December 31, 1986. The lower age limit was chosen because children <24 months of age who are not in day care are generally not eligible for HBVP. The upper cutoff (<60 months of age) is consistent with the Immunization Practices Advisory Committee recommendations for HBVP usage.10

A consent statement was obtained from and a screening questionnaire was administered to parents of all children who met the age criteria to determine day-care status and willingness to participate. Children not in day care were enrolled. A questionnaire was completed for each eligible patient by interviewing one of the child's parents or guardians.

Data collected for each case child included demographic and socioeconomic variables, type of health care provider (private vs public), and HBVP status. Vaccination status was verified for all case children by interviewing each child's health care provider while the provider had the child's medical record in hand. Only children who had been vaccinated ≥14 days before the date of hospital admission or date of positive culture result were considered to be vaccinated. Additional data obtained for each vaccinated child included date of vaccination, brand of HBVP administered, lot number, concurrent diphtheria-tetanus-pertussis vaccine administration, and reported adverse reactions to HBVP. In addition, physicians were asked about any underlying disease that might predispose the child to serious infection, regardless of vaccination status.

**Selection of Control Children**

Control children were selected from a roster of acquaintances obtained from the case child's parent. Parents were asked to provide a list of all acquaintances living in the study area on the case date of admission who might have children aged 24 to 59 months. Parents were unaware of the study hypothesis, and HBVP was not mentioned until the list of potential control children had been obtained. Parents of potential control children were contacted to determine whether their children were eligible, using the same age and day-care criteria applied to case children. As many as three control children were chosen for each case child; control children were matched to case children based on closeness in age. Control children were not permitted to be siblings of each other; if siblings were listed as potential control children, only the sibling closest in age to the case child was selected. The same information collected for the case child was collected for each eligible control child. The verifi-
cation of vaccination status form was completed for each control child while the health care provider had the child's medical record in hand.

**Laboratory Methods**

All sterile-site isolates of *H. influenzae* type b received by the Centers for Disease Control were characterized serologically by slide agglutination with the use of *H. influenzae* polyvalent capsular antiserum and type-specific antiserum prepared at the Centers for Disease Control for capsule types a through f.

**Statistical Methods**

Conditional logistic regression was used for statistical analysis. This method, which is designed for matched studies, can be used to adjust for multiple confounding variables, as well as to evaluate effect modification. In our study, age was a potential confounder because it is related to both the disease and the likelihood of vaccination. Because we did not closely match children's ages, cases children were younger than control children. To handle this potential problem, vaccine efficacy estimates were age adjusted by including a linear term for age in months in all models. This corrects for age differences of ≥1 month between case and control children. Estimates of vaccine efficacy were calculated using the formula $VE = 1 - \text{matched odds ratio}$. Differences in vaccine efficacy were evaluated with a likelihood ratio test.

**RESULTS**

**Rates of Invasive *H. influenzae* Type b Disease**

A total of 1444 cases of invasive *H. influenzae* type b disease in children <5 years of age were reported from the six surveillance areas during 1986 (Table 1). The overall rate of invasive *H. influenzae* type b disease was 58/100 000 per year in children <5 years of age. Rates by area ranged from 40/100 000 for New Jersey to 80/100 000 for Oklahoma.

Table 1. Invasive *Haemophilus influenzae* Type b Disease in Children Less Than 5 Years of Age, by Study Area, 1986

<table>
<thead>
<tr>
<th>Area</th>
<th>Total No. of Children With Disease</th>
<th>Population &lt;5 y of Age</th>
<th>Rate per 100 000 Children &lt;5 y of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Jersey</td>
<td>198</td>
<td>499 000</td>
<td>40</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>311</td>
<td>676 000</td>
<td>46</td>
</tr>
<tr>
<td>Tennessee</td>
<td>203</td>
<td>327 000</td>
<td>62</td>
</tr>
<tr>
<td>Missouri</td>
<td>255</td>
<td>370 000</td>
<td>69</td>
</tr>
<tr>
<td>Washington</td>
<td>263</td>
<td>339 000</td>
<td>78</td>
</tr>
<tr>
<td>Oklahoma</td>
<td>214</td>
<td>267 000</td>
<td>80</td>
</tr>
<tr>
<td>All areas</td>
<td>1444</td>
<td>2 478 000</td>
<td>58</td>
</tr>
</tbody>
</table>

Of the 74 case children identified through active surveillance, 24 met our age criteria. Day-care status was known for 239 children, or 98%. Of these, 128 (54%) were not in day care. For 109 (85%) of these children, parents were contacted and interviewed and vaccination status verified. Enrollment was higher for case children with dates of culture during the last 6 months of 1986 (62 of 65 eligible case children enrolled [95%]) than during the first 6 months (47 of 63 case children [75%]) ($P = .002$). This was because the study was initiated in October 1986, and many of the children with cases of disease that had occurred during the first 6 months of the year had moved by that time. Of the 109 children for whom parents could be contacted, 74 (68%) had age-matched control children and thus were included in the matched analysis. Reasons why control children could not be identified for 35 case children included failure of case parents to identify acquaintances with children eligible for the study, refusal of case parents to provide a list of acquaintances, and inability to locate acquaintances provided by case parents. There were a total of 129 control children; vaccination status was available for 127. Thirty-seven case children (50%) had 1 control child, 19 (26%) had 2 control children, and 18 (24%) had 3 control children.

**Vaccination Status and Analysis of Questionnaire Variables**

Of the 74 case children with control children, 9 (12%) had received HBPV compared with 28 of 127 (22%) control children.

Variables that were associated with vaccination...
in the control children included total family income ≥$20,000/y (69% for vaccinated control children vs 39% for unvaccinated control children, P = .08, Fisher's exact test, two-tailed) and mean years of maternal education, P = .02, Wilcoxon rank-sum test, two-tailed). However, when case and control children were compared by these and other potentially confounding variables (Table 2), only age (average 33.9 months for case children vs 37.2 months for control children (matched odds ratio = 0.96, 95% confidence interval = 0.92, 0.99, conditional logistic regression) and parental smoking (more common in case children, matched odds ratio = 2.37, 95% confidence interval = 1.17, 4.82) were significantly different.

An unmatched comparison of vaccinated case children and control children by injection site, concurrent administration of diphtheria-tetanus-pertussis vaccine, and type of vial (single vs multidose) showed no significant differences between the two groups.

**Vaccine Efficacy**

Before the data were adjusted for differences in age and parental smoking, vaccine efficacy (crude vaccine efficacy) was 64%. After adjusting for age and parental smoking, vaccine efficacy was estimated to be 62% (95% confidence interval = 0%, 85%).

Three of 33 (9%) case children without control children had been vaccinated, which was not significantly different from the rate of vaccination of case children with control children (12%). However, because both the rate of vaccination of case children and control children determines the estimate of vaccine efficacy, we compared the case children with control children to those without control children for six socioeconomic variables (Table 3). Although several differences were found, none was of substantial magnitude, and none was statistically significant.

There was not a statistically significant difference in efficacy between children 24 to 35 months of age (50 case children with control children) and 36 to 59 months of age (24 case children with control children), although the statistical power to detect a difference was limited. Sample sizes for the six study areas were inadequate to estimate efficacy by area.

When vaccine efficacy was analyzed by clinical syndrome, efficacy for meningitis (38 cases), epiglottitis (16 cases), and all other infections (20 cases) was 91% (95% confidence interval = −21%, 99%), 57% (95% confidence interval = −352%, 96%), and −14% (95% confidence interval = −466%, 77%), respectively. The “other” category included primary bacteremia (15 cases), pneumonia (2 cases), cellulitis (2 cases), and both cellulitis and arthritis (1 case). The differences in vaccine efficacy by syndrome were not statistically significant (P = .19). In addition, there were no significant

---

**TABLE 3.** Case Children With Controls Compared With Case Children Without Controls in the Case-Control Study of Vaccine Efficacy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case Children With Controls (n=74)</th>
<th>Without Controls (n=35)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (boys)</td>
<td>55</td>
<td>29</td>
<td>0.15*</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71</td>
<td>64</td>
<td>0.50*</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>29</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Income &gt;$20 000 (%)</td>
<td>52</td>
<td>38</td>
<td>0.27*</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>33.9</td>
<td>36.7</td>
<td>0.07†</td>
</tr>
<tr>
<td>Maternal education (y)</td>
<td>12.0</td>
<td>11.1</td>
<td>0.13†</td>
</tr>
<tr>
<td>Rooms in house (No.)</td>
<td>5.5</td>
<td>5.1</td>
<td>0.22†</td>
</tr>
</tbody>
</table>

* Fisher's exact test.
† Wilcoxon rank-sum test.

---

**TABLE 2.** Possible Confounding Variables in the Case-Control Study of Vaccine Efficacy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case Children (n=74)</th>
<th>Control Children (n=127)</th>
<th>Matched Odds Ratio</th>
<th>95% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (boys)</td>
<td>55</td>
<td>52</td>
<td>1.24</td>
<td>0.67, 2.33</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71</td>
<td>78</td>
<td>0.71</td>
<td>0.14, 3.59</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>29</td>
<td>22</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Income &gt;$20 000 (%)</td>
<td>52</td>
<td>46</td>
<td>1.35</td>
<td>0.68, 2.69</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>33.9</td>
<td>37.2</td>
<td>0.96</td>
<td>0.92, 0.99</td>
</tr>
<tr>
<td>Maternal education (y)</td>
<td>12.0</td>
<td>12.2</td>
<td>1.02</td>
<td>0.86, 1.20</td>
</tr>
<tr>
<td>Rooms in house (No.)</td>
<td>5.5</td>
<td>5.7</td>
<td>0.96</td>
<td>0.76, 1.21</td>
</tr>
<tr>
<td>Parental smoking (%)</td>
<td>50</td>
<td>35</td>
<td>2.37</td>
<td>1.17, 4.82</td>
</tr>
<tr>
<td>Breast-feeding (%)</td>
<td>47</td>
<td>61</td>
<td>0.56</td>
<td>0.27, 1.15</td>
</tr>
</tbody>
</table>
differences in the distribution of cases by syndrome among case children with control children, case children contacted but without control children, and case children who could not be contacted.

To determine whether the inclusion of case children with positive culture results during months of low enrollment biased our estimate of efficacy, we estimated vaccine efficacy for the first 6 months of the year (enrollment of 75%) and for the last 6 months (enrollment of 95%). The resulting estimates were 74% and 55%, respectively; the difference was not statistically significant (P = .58).

To measure the potential bias of the approximately 10% underreporting in our active surveillance system, we recalculated vaccine efficacy after increasing the number of case children by 10%; we assumed that all of these children were unvaccinated, because reporting bias, if any, would most likely favor the identification of vaccinated children. Unmatched vaccine efficacy in this hypothetical example was estimated to be 62%. Because the sensitivity of active surveillance is unknown for New Jersey, we reanalyzed the data excluding case children and control children from this state and estimated efficacy to be 56% (95% confidence interval = -4%, 83%).

We assessed the effectiveness of the age adjustment by calculating vaccine efficacy for case children with tightly age-matched control children. An age-matched control child is within the same predetermined age stratum (24 to 35 and 36 to 59 months of age) as a case child. Vaccine efficacy in this analysis was 58% (95% confidence interval = -37%, 87%), suggesting that our model did not change the point estimate of efficacy but did increase the statistical power.

To exclude the potential bias of selective vaccination of children with illnesses that predispose to invasive H influenzae type b disease, we excluded from the analysis three case children (one each with a bone marrow transplant, a renal transplant, and thalassemia) and one control child (with an unspecified malignancy) reported by their physicians as having an underlying disease. Vaccine efficacy was 70% (95% confidence interval = 17%, 89%).

The Centers for Disease Control received and serotyped H influenzae type b strains for 49 (66%) of the 74 patients with matched control children. All of the strains were serotype b. An additional 15 case children (20%) either had serotyping done by hospital or state laboratories or had positive antigen detection for H influenzae type b. Serotype information was not available for 10 (14%) case children. Although >95% of invasive H influenzae type b strains in children are serotype b, we analyzed our data excluding the children for whom serotype information was not available. Vaccine efficacy was 62% (95% confidence interval = -4%, 87%), identical with our original point estimate.

**Risk of Invasive H influenzae Type b Disease During Week Following Vaccination**

To address the issue of the risk of H influenzae type b disease in the 7-day period following immunization, we determined the number of case children and control children who had received HBPV within 7 days before the case date of admission. Only one case child and no control children fit this criterion.

**DISCUSSION**

The decision to license HBPV in the United States in April 1985 was based on one randomized clinical trial that demonstrated an efficacy of 90% (95% confidence interval = 55%, 98%) in children 18 to 71 months of age. Because randomized, controlled trials were no longer ethically feasible after licensure, it became necessary to develop alternative methods for monitoring HBPV efficacy. A number of investigators resorted to case control studies.

All studies to date, except one, have demonstrated positive efficacy, with individual point estimates ranging from 41% to 88%. The one study with a negative point estimate (-69%) had a small sample size and had broad 95% confidence limits (-415%, 33%). Several possible explanations for the wide range in efficacy estimates have been raised, including regional differences in efficacy; until the biologic plausibility of this hypothesis is demonstrated, it must be considered speculative.

A computer simulation of the range of efficacy estimates expected from studies of a similar size to those conducted showed that, if the true efficacy were 50%, a wide range of study results similar to that observed would be expected. This points out the problem of limited statistical precision in small case-control studies for vaccines of low efficacy. For example, even though 126 case children and 291 control children were enrolled in our day-care-based HBPV efficacy study (the larger of our two studies) that estimated an efficacy of 45%, our 95% confidence limits were relatively wide (-1%, 70%). Had the true efficacy been 75% to 90%, which is the range of efficacies we used to calculate the expected sample size for that as well as the present study, our confidence limits would have been much narrower.

The finding of parental smoking as a risk factor for primary H influenzae type b disease (matched odds ratio = 2.37; 95% confidence interval = 1.17%, 2.37; 95% confidence interval = 1.17%, 5.8); 95% confidence interval = 1.17%, 2.37; 95% confidence interval = 1.17%, 5.8).
4.82%) is difficult to interpret, given that our previous study of risk factors for *H influenzae* type b disease did not find this association, nor did a review of unpublished data from our earlier HBPV efficacy study. However, several studies have indicated a link between passive exposure to cigarette smoke and upper respiratory tract infections in children. Whether such exposure is truly a risk factor for invasive *H influenzae* type b disease will need to be evaluated in future studies.

Like all case-control studies, our study might have biases that could affect our results. For example, because we began this study 9 months into 1986, we could not contact some of the children who had had disease that occurred earlier in the year. However, the fact that efficacy was not significantly different for months with incomplete enrollment compared with months with good enrollment suggests that incomplete enrollment did not bias our estimate of efficacy.

In addition, exclusion from the matched analysis of the 35 case children without control children could have affected our estimate. Two facts, however, suggest that this is not the case. First, the rate of vaccination of the 35 case children who were contacted but did not have controls (9%) was not significantly different from the 74 case children with control children (12%). Second, the case children without control children did not differ significantly from the case children with control children when compared for variables that affect the likelihood of vaccination (Table 3). This suggests that, had we been able to obtain matched acquaintance control children for these case children, their rate of vaccination would not have differed from the rate of vaccination of our 129 actual matched acquaintance control children. This is important, because both the rate of vaccination of case children and control children is used to calculate vaccine efficacy.

Our previous HBPV efficacy study permitted us to examine the hypothesis that there may be a slightly increased risk of invasive *H influenzae* type b disease in the 7 days following immunization, and we found no significant association. Unfortunately, we do not have enough data in the present study to evaluate this hypothesis.

The true efficacy of HBPV has been actively debated. Nevertheless, four of five studies suggest that the vaccine is effective, albeit less so than anticipated. It should be kept in mind, however, that HBPV was introduced as an interim vaccine. In fact, the next-generation vaccine, a polysaccharide-diphtheria toxoid conjugate, has just been licensed for use in children ≥18 months of age. Hopefully it will be more efficacious than HBPV in children ≥18 months old; it may eventually be licensed for use in infants, who are at highest risk for invasive *H influenzae* type b disease.

Because licensure of the conjugate vaccine for use in children ≥18 months of age is based on immunogenicity data and comparisons with the recent Finnish trial, postlicensure case-control efficacy studies of the conjugate vaccine are warranted. In addition, the unproven hypothesis that there may be a slight increase in the risk of invasive *H influenzae* type b disease following vaccination with HBPV should be evaluated. However, the current controversy concerning the efficacy of HBPV points out the limitations of individual postlicensure case-control vaccine efficacy studies and the need for caution in their interpretation.

**ACKNOWLEDGMENTS**

This study was funded, in part, through an interagency agreement among the National Institute of Child Health and Development, Bethesda, MD, the Food and Drug Administration, Washington, DC, and the Centers for Disease Control, Atlanta, GA.

The *Haemophilus* Vaccine Efficacy Study Group consisted of Sandra L. Sitze and Margaret Spurrier (Missouri Department of Health, Jefferson City); Ellen Chahanovich, Gregory R. Istre, Sue Makintubee, and Jan White (Oklahoma State Department of Health, Oklahoma City); Robert C. McCready, David R. Cundiff, and Mau- reen C. Farrell (New Jersey Department of Health, Trenton); Janice D. Harwell (Washington State Department of Social and Health Services, Seattle); Lori Chronis, Betty Grimes, Carolyn C. Hoppe, and Stephen H. Water- man (Los Angeles County Department of Health Serv- ices, Los Angeles); Brenda K. Boner, Rose A. Kelley, Lewis B. Lefkowitz, Jr, and Jo A. Taylor (Department of Health and Environment, State of Tennessee; Depart- ment of Preventive Medicine, Vanderbilt University School of Medicine, Nashville); and Richard R. Facklam, Suzanne Gaventa, Arthur L. Reingold, and Jay D. Wen- ger (Centers for Disease Control).

We thank the physicians, parents, and hospital personnel who participated in this study; Lorrie Gavin, Linnette Jackson-Hunt, Ravi Alaghappan, and Joel Fine for the telephone interviewing; and Rose M. Horsley and Ray L. Ransom for the data processing.

**REFERENCES**

LISTERIOSIS

Listeria monocytogenes—an uncommon human pathogen of animal origin—has some unusual properties. The organism is widespread in the environment and many animals, and has the ability to grow over a temperature range (2–42°C) that includes refrigerator temperatures. The bacterium itself becomes intracellular and has an outstanding predilection for pregnant women, in whom it causes very slight or inapparent illness but may cross the placenta to kill the fetus or give rise to perinatal septicaemia or meningitis in the newborn baby. The infective dose is also unknown, but presumably it is lower for pregnant and immunologically compromised individuals than for the normal population.

What is very clear is that as produced, processed, and finally cross-contaminated in chicken packing plants, very nearly all chicken carcasses are contaminated with listeria, as well as with Campylobacter jejuni and salmonellae. In the past two or three years infections due to these microbes have increased almost exponentially; they are all sporadic in distribution, and all three organisms are frequently introduced into the environment of the domestic kitchen via chicken meat.

There is always complacency in the livestock industry when infective agents do not cause significant economic losses in flocks or herds—listeria, salmonellae, and campylobacters all fail to do this. Surely it is time to think of the effect on human beings.

Noted by J.F.L., MD