Assessment of the Excess Risk of *Salmonella dublin* Infection Associated with the Use of Certified Raw Milk

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Synopsis

The risk of serious illness attributable to infection with Salmonella dublin *associated with the consumption of certified raw milk in California was evaluated. Data were derived from case reports of* S. dublin *isolations from persons in the State of California during the period 1980–83 and from production figures for raw milk from the major supplier.*

It is estimated that more than one-third of reported S. dublin *infections in California in the first 4 years of this decade were attributable to raw milk consumption. Among raw milk consumers, it is estimated that more than 95 percent of reported* S. dublin *infections were acquired from raw milk; this proportion corresponds to a rate of reported* S. dublin *infections acquired from raw milk in the range of 8 to 35 cases per 100,000 users per year. It appears that immunocompromised persons are at exceptionally high risk of becoming seriously ill or dying from* S. dublin *exposure, and therefore raw milk is a particular health hazard for such persons.*

IN MOST STATES, RAW (unpasteurized) milk continues to be sold for human consumption, despite opposition by most public health organizations and authorities (*1*). California has the largest number and proportion of raw milk consumers, as well as the largest producer of raw milk for human consumption. *Salmonella dublin*, a gram-negative bacillus capable of producing serious typhoid-like illness, septicemia, and (occasionally) death, has in several instances been isolated from raw milk produced in California. A matter of considerable public health concern is to determine the number and proportion of serious illnesses due to *S. dublin* that are attributable to infection acquired from raw milk. This paper presents such a determination, based on those *S. dublin* cases reported to the State of California Department of Health Services in the period 1980–83, and production figures for raw milk from the major supplier of this product.

Materials and Methods

We obtained from the State of California Department of Health Services information on all laboratory identified cases of *S. dublin* from 1980 to 1983, the last year for which all reports were available during our data collection period, 1984–85. Complete data included the age, sex, and location of the person, diagnosis and culture outcome, complications (for example, septicemia), co-existing illnesses, and outcome of the *S. dublin* infection (recovery or death). A total of 241 out of 303 cases reported to the State had a complete response to a question concerning raw milk consumption.

Although *Salmonella* infections are reportable diseases in the State of California, it appears likely that the level of underreporting is extremely large (2). A diagnosis of salmonellosis can be made only through use of laboratory tests. Further, it is

probable that specimens are obtained and submitted to the laboratory primarily for more seriously ill patients. Therefore, our study necessarily refers only to laboratory identified cases of *S. dublin*, rather than all cases, and so our inferences may be limited to "serious" cases, and "serious" can be qualified as "serious enough to lead to testing for *Salmonella*." We will address issues of possible reporting bias in a later section.

Although exact figures are not available, it appears that Alta-Dena Dairy, a southern California company, supplies more than 80 percent of the raw milk distributed for human consumption in the State. The raw milk sold by Alta-Dena is labelled "Certified Raw Milk," an appellation given by the American Association of Medical Milk Commissions, and it is the only cow's milk so labelled in California. The California Depart ment of Food and Agriculture provided estimates of the distribution of Alta-Dena raw milk between 1980 and 1983. These estimates ranged from 12,000 to 13,500 gallons per day. We used 13,000 gallons per day as the best estimate of the mean distribution during the period 1980 to 1983.

Production figures were unavailable for non-Alta-Dena raw milk, which comes from a number of small dairies. Therefore we limited most of our assessments to the impact of certified raw milk by eliminating from our case series those of the 11 persons who indicated that they drank raw milk, but not certified raw milk, and 3 people who indicated that they used both certified and other raw milk. The remainder consisted of 79 persons who reported using only certified raw milk and 148 who reported no raw milk use.

To estimate the average number of persons per day exposed to raw milk in California during the 4 years, we estimated the average individual consumption, and in addition we took into account the small but unknown proportion of certified raw milk exported from the State. This step led us to consider two relatively extreme values for the number exposed per day: a low of 67,200 persons per day, based on distribution of 10,500 gallons of certified raw milk per day in California, a typical 8-ounce portion, and 2 1/2 portions per day; and a high of 320,000 persons per day, based on a distribution of 15,000 gallons of certified raw milk per day in California, a typical 6-ounce portion, and one portion per day. If one assumes a near-stable population of raw milk consumers over a year, these figures imply a population of 70,000 to 320,000 consuming certified raw milk. Given an approximate population for California of 24 million in 1980–83, these figures indicate that between 0.3 and 1.3 percent of the State's population regularly used certified raw milk during the study period.

The data just presented were analyzed using standard epidemiologic statistical methods for estimation of rates, rate ratios, and attributable ("etiologic") fractions (*3,4*).

Results

Relative and absolute rates. We first estimated the ratio of the rate of reported *S. dublin* infection among certified raw milk users only to the same rate among persons not using raw milk. This rate ratio (or relative risk) can be estimated as the ratio of the certified raw milk exposure odds among cases to the exposure odds in the general population (see for example reference *3*, chapter 4). The exposure odds among our cases was $79 \div 148 = 0.534$, while our estimated exposure odds for the general population varied from $0.3 \div 99.7 = 0.003$ (a 0.3 percent use rate) to $1.3 \div 98.3 = 0.0135$ (a 1.3 percent use rate). These last two calculations ignore users of noncertified raw milk and users of both certified and noncertified raw milk, since they are a small proportion of the population. Thus our rate-ratio estimate ranged from $0.534 \div 0.0135 = 40$ to $0.534 \div 0.003 = 178$.

A standard error estimate for the natural log of the case exposure odds is $(1 \div 79 + 1 \div 148)^{1/2} = 0.1393$ (*3,4*); this yields a 95 percent confidence interval for the case exposure odds of $0.534 \exp(\pm 1.96\ (0.1393)) = 0.406, 0.702$. These yield a lower confidence limit for the lower rate ratio estimate of $0.406 \div 0.0135 = 30$, and an upper confidence limit for the upper rate ratio estimate of $0.701 \div 0.003 = 234$. Although this represents an eightfold possible range for the rate ratio, either figure indicates that the rate of reported *S. dublin* infection is far higher among raw milk users than among nonusers.

If we assume the $303 - 241 = 62$ cases in which the person's milk use status was unknown can be distributed in the same proportions as in the remaining 241 cases, we may estimate the absolute rates of reported *S. dublin* infection among users and nonusers. Users of only certified raw milk represent $79 \div 241 = 0.328$ of those with known status, indicating that $0.328(303) = 99$ of all those with reported cases used certified raw milk alone; this yields a rate estimate between $99 \div 4(320{,}000) = 8$ and $99 \div 4(70{,}000) = 35$

infections per 100,000 users per year. Similarly, nonusers of raw milk represent 148 ÷ 241 = 0.614 of those with known status, indicating that 0.614(303) = 186 of all those with reported cases did not use raw milk; this yields a rate estimate of 186 ÷ 4(24 million) = 0.19 cases per 100,000 nonusers per year. The estimated excess of reported *S. dublin* infections in California for 1980–83 is thus between 8 and 35 cases per 100,000 users per year.

Fraction of cases attributable to raw milk. In our study, the excess fraction of cases among users attributable to *S. dublin* in certified raw milk, denoted AF_e, may be estimated using the formula $AF_e = (RR - 1) \div RR$, where RR is the rate ratio (*3,4*). Employing the above rate ratio estimates in the formula yields (30 − 1) ÷ 30 = 0.97 and (234 − 1) ÷ 234 = 0.996. Thus, it appears that more than 96 percent of reported *S. dublin* infections among certified raw milk users in California during the study period were acquired from the milk. These results were essentially unchanged upon control of other variables, such as year of case.

Among the 241 cases with complete information, there were 79 + 11 + 3 = 93 or 38.6 percent in which some use of certified or noncertified raw milk was reported (table 1). Assuming that the attributable fraction of cases among noncertified milk users is the same as among certified raw milk users, it appears that between 0.96 (38.6 percent) = 37 percent and 0.996 (38.6 percent) = 38 percent (or more than one-third) of all reported cases of *S. dublin* infections in California, 1980–83, were acquired from raw milk.

Death rates. We repeated the preceding analyses using only the reported deaths from *S. dublin*: these represent a proper subset of the reported cases. Whether the person eventually recovered or died was known for 205 of the 241 cases in which the person's milk use status was reported. Table 1 shows the distribution of deaths and raw milk use among these persons. As can be seen, there appears to be no difference in case fatalities between raw milk users and nonusers.

From table 1, we see that the odds for exposure to certified raw milk only versus no raw milk among the deaths was 15 ÷ 31 = 0.484, yielding a rate-ratio estimate ranging from 0.484 ÷ 0.0135 = 36 to 0.484 ÷ 0.003 = 161. A standard-error estimate for the natural log of the exposure odds among the deaths is $(1 \div 15 + 1 \div 31)^{1/2} =$ 0.315. This yields a 95 percent confidence interval for these odds of 0.484 exp(± 1.96(0.314)) = 0.261, 0.897, which in turn yield a lower confidence limit for the lower estimate of 19, and an upper confidence limit for the upper estimate of 299. Thus it appears that in California 1980–83, at least (19 − 1) ÷ 19 = 95 percent of fatal *S. dublin* infections among certified raw milk users were acquired from the milk, and that at least (15 ÷ 48) 95 percent = 30 percent of fatal *S. dublin* infections among all California residents were acquired from certified raw milk.

Table 1. Case fatality among *Salmonella dublin* cases according to raw milk usage and vital outcome of cases, California 1980–83

Possible source	Deaths		Known outcomes	Unknown outcomes	Total number
	Number	Rate[1] (percent)			
Certified raw milk	15	22	69	10	79
Other raw milk	1	10	10	1	11
Certified and other raw milk	1	100	1	2	3
No raw milk	31	25	125	23	148
Unknown	21	68	31	31	62
Total	69	29	236	67	303

[1] Case fatality rate based on cases with known outcomes.

Table 2. Joint distribution of compromised health status and raw milk use among persons with *S. dublin* cases reporting milk use, California, 1980–83

Exposure status	Compromised[1]		Not compromised	
	Number	Percent	Number	Percent
Certified raw milk user	55	33	24	32
Other raw milk user	7	4	4	5
Both certified and other raw milk users	2	1	1	1
No raw milk use	103	62	45	61
Total	167	100	74	100

[1] See text for definition.

Compromised health status. We examined the associations of raw milk use and *S. dublin* infection with compromised immune status, because raw milk has been promoted as a health food, and persons with compromised immune status are more likely to contract serious or fatal illness from *S. dublin* infection. We classified persons with *S. dublin* cases as "compromised" if in the case report they were noted to have one or more of a

list of potentially immunocompromising conditions or exposures, including cancer, chemotherapy, radiation therapy, corticosteroid therapy, diabetes, hematologic condition (including AIDS), liver disease, alcoholism, rheumatoid arthritis, collagen disease, kidney disease, or were under 1 or older than 74 years. Table 2 presents the joint distribution of the host person's immune status with raw milk use. There is no apparent association of altered immune status with raw milk use: 64 ÷ 167 = 38 percent of compromised hosts used raw milk, versus 29 ÷ 74 = 39 percent of the remainder.

On the other hand, the prevalence of immunocompromised hosts in the entire case series is 167 ÷ 241 = 69 percent, which must be far higher than their prevalence in the general population. This finding indicates that immunocompromised individuals must be at greatly elevated risk of acquiring reportable *S. dublin* infection. For example, even if the prevalence of immunocompromised hosts in the 1980–83 California population was as high as 10 percent, the prevalence observed in our cases indicates that immunocompromised persons have a rate of serious *S. dublin* infection that is (69 ÷ 31) ÷ (10 ÷ 90) = 20 times higher than other persons. Because raw milk is promoted as a health food, it is not unlikely that immunocompromised individuals have a somewhat high prevalence of raw milk use, which would partially account for their higher infection rate. Nevertheless, we find it extremely implausible that immunocompromised individuals have a 20-fold higher prevalence of raw milk use, especially since a large proportion of the persons classified as immunocompromised were so classified only because of their age. Thus, we would argue that the elevated rate among immunocompromised persons must primarily represent their greater risk of serious illness upon exposure to *S. dublin* (rather than greater exposure to *S. dublin*), and so the rate indicates a greater absolute risk associated with raw milk use among those who are immunocompromised. As evidence favoring this explanation, we note that the fatality rate among immunocompromised hosts was 36 percent, almost threefold the 13 percent rate seen among immunocompetent persons.

Discussion

Our results are in broad agreement with the findings of the case-control study of the same cases by the California State Department of Health (*5*); these researchers estimated a rate ratio of 158 for the association of *S. dublin* infection and raw milk use. We note, however, that cases in this study were from the same source as the 1983 cases in our study, and therefore much agreement is to be expected.

Various forms of bias may have operated in reporting of cases and the ascertainment of the milk consumption by the study group. For example, it has been suggested that persons who admitted drinking raw milk may have been more likely to have been tested for *Salmonella* because of pre-existing suspicions regarding the association of *Salmonella* and raw milk. This would upwardly bias our estimates of raw milk's effect. It is apparent, however, that for such a bias to account completely for our estimated rate ratios, *S. dublin* victims would have to be at least 30 times and possibly more than 200 times as likely to be diagnosed and reported if they drank raw milk than if they did not. These numbers strike us as implausibly high for differential testing and reporting, especially given the severity of the presenting illness of the reported patients (as indicated by the high case-fatality rate).

We are unaware of any evidence that our case series suffers from bias in diagnosis or reporting. In fact, we have some evidence against such bias. If bias exists, it is extremely implausible that it would be large for deaths due to *S. dublin*, since death and cause of death must be reported in all cases. Thus, we would expect diagnostic or reporting bias to produce a stronger association of raw milk with nonfatal infections than with fatal infections. As shown previously, however, the association with raw milk use was the same whether considering all infections or fatal infections only. Nevertheless, if persons ill with *S. dublin* infection were, say, six times more likely to be diagnosed and reported if they drank raw milk, our rate ratio estimates would have to be divided by a factor of six to correct for the bias. In this case their range would now be 5 to 39, corresponding to estimates of (5 − 1) ÷ 5 = 80 percent to (39 − 1) ÷ 39 = 97 percent for the fraction of serious *S. dublin* infections among raw milk users contracted from raw milk. Thus, even postulating a sixfold bias in reporting leaves an impression that raw milk is responsible for an overwhelming majority of serious *S. dublin* infections among users.

Other possible biases include confounding by uncontrolled factors and misclassification of users as nonusers, or vice-versa. Calculations similar to

those in the preceding paragraph reveal that it is highly implausible such biases account for much, if any, of the association of reported *S. dublin* and raw milk seen in this study. Because the association appears far stronger than values commonly taken as definitive evidence of a causation, we are not concerned about any downward biases that may exist in our estimate.

We think it important to note that persons with compromised host defenses appear particularly vulnerable to severe and even fatal outcomes of *S. dublin* exposure. Thus we would recommend that such persons, especially those with HIV infection, be warned to avoid raw milk consumption, and that raw milk carry a label warning of the possible hazard to such persons.

In this paper we have not considered the issue of transmission of other hazardous bacteria (such as *Campylobacter*), through raw milk, in part because the case fatality rate associated with such infections is much lower than for overt *S. dublin* infection. However, other diseases associated with milk products, such as listeriosis infection, may have equally high case fatality rates. As a result, regulators may also wish to consider these diseases when evaluating the hazards of raw milk.

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NIDR—40 Years of Research Advances in Dental Health

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Synopsis

The National Institute of Dental Research (NIDR) was created by President Harry S Truman on June 24, 1948, as the third of the National Institutes of Health. NIDR's legislation contained the mandate to conduct research and research training to improve oral health. An impetus for federally funded dental research was the finding in World War II that the major cause of rejection for military service was missing teeth. Because of the population's widespread tooth decay problems, early NIDR research focused on eliminating dental caries. NIDR scientists confirmed the safety and effectiveness of the use of fluoride in tooth decay prevention, leading to one of the nation's most successful public health efforts, community water fluoridation.

During the past 40 years, NIDR scientists have provided research advances and fostered technologies which changed the philosophy and practice of dentistry and brought dental sciences into the mainstream of biomedical research. Dental researchers contribute to studies of such diseases and problems as AIDS, cancer, arthritis, cystic fibrosis, diabetes, herpes, craniofacial anomalies, pain, and bone and joint disorders.

NIDR's 40th anniversary in 1988 recognizes its continuing commitment to oral disease prevention and health research, and to achieving the goal of people maintaining their natural dentition for a lifetime.