

Estimation of the basic reproduction ratio (R_0) for Shiga toxin-producing *Escherichia coli* O157:H7 (STEC O157) in beef calves

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SUMMARY

To understand the dynamics of transmission of Shiga toxin-producing *Escherichia coli* O157:H7 (STEC O157) in beef calves, serum samples were obtained from calves in a beef cow-calf herd approximately every 6 weeks from birth until weaning for three consecutive years. The presence of specific anti-O157 antibodies in these serum samples was detected using a blocking ELISA assay incorporating an anti-O157 monoclonal antibody. Using seroconversion data, the basic reproduction ratio (R_0) was estimated for each of the three years as well as in aggregate using both deterministic and Martingale methods. R_0 for STEC O157 infection in range beef calves by deterministic methods varied from 2·9–5·6, with an average of 4·3 (95% CI 2·8–5·9). Martingale estimates of R_0 ranged from 3·5–7·4, or 5·3 (95% CI 3·9–6·6), for data from all three years. Given the above estimate of R_0 , it is predicted that 65–86% of a herd of calves must be effectively vaccinated, or must be rendered non-susceptible through other means, to eliminate STEC O157 infection from a herd.

INTRODUCTION

Shiga toxin-producing *Escherichia coli* O157:H7/NM (STEC O157) may cause severe disease and death in humans [1, 2]. Cattle have been implicated as a reservoir of STEC O157 and as a primary source of beef contamination [3–6]. Recent studies using improved culture methods have indicated that the overall prevalence of STEC O157 infection in cattle, as estimated by faecal shedding, may be significantly higher than originally estimated [4, 5]. These studies found peak STEC O157 faecal shedding rates occur during summer and early autumn, with prevalence varying from 0% to as high as 61% on some farms. Several

studies have indicated that shedding of STEC O157 may be intermittent and thus, even with sensitive culture methods, prevalence estimates based on faecal shedding alone may not accurately reflect the infection status of a cattle population [7–9]. Previously, we developed a specific competitive ELISA (cELISA) for the detection of antibodies directed against the O157 antigen [10]. Using this method, we demonstrated high seroprevalence of anti-O157 antibodies in beef calves at weaning which, in addition to STEC O157 faecal culture data, demonstrated that most calves had been exposed to STEC O157 prior to weaning [5].

The basic reproduction ratio (R_0) is defined as the average number of secondary infections generated when an infectious individual is introduced into a population of susceptible individuals [11]. R_0 is dependent on the duration of the infectious period of infected individuals, the rate of contact between infected and susceptible individuals, and the probability that such contact results in a new infection. As such,

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R_0 describes the ease of transmission of an agent within a population. Implicit in the definition of R_0 is that if $R_0 < 1$, an infection will not propagate within the population and will ultimately disappear. Thus, the (usually unstated) goal of infection control programmes is to reduce R_0 to less than 1 in a given population. Estimates of R_0 can be used to predict the relative effort and extent of control efforts required to achieve this goal. In addition, changes in R_0 resulting from interventions may be used to evaluate their effectiveness. In this study, we determined the age of calves when anti-O157 antibodies were first detected in their serum (seroconversion), as well as the cumulative number of seroconversion events in the population, and utilized this data to estimate R_0 . This estimate of R_0 may be used to calculate the required effective vaccination or other prophylactic treatment coverage needed to eradicate STEC O157 from beef cattle herds.

MATERIALS AND METHODS

Herds and sampling

The study herd was composed of an average of 531 [1996 ($n=537$), 1997 ($n=583$), 1998 ($n=473$)] mixed-breed commercial beef cows on high-quality grass pasturage. Calves born to cows in this herd were sampled over three consecutive years (1996–1998). Blood samples were obtained from calves 48 h after birth and then approximately every 7 weeks through weaning. Samples were also obtained 6 weeks after entry into the feedlot and when cattle were shipped for slaughter, 38 weeks after entry into the feedlot. A random sample of 45 individual calves (46 in 1996) was selected for anti-O157 serology from each annual sample set, a total of 136 calves. A total of 796 serum samples were tested.

cELISA

Anti-O157 antibodies were detected by cELISA, performed as previously described [10]. Sera that inhibited the cELISA reaction by 50% or more at a dilution of 1:4 or greater were considered positive, as previously determined by receiver operating characteristic analysis [10]. Calves were considered to have seroconverted in the period immediately prior to their first positive sample. The birth date of the calf was subtracted from the first positive sampling date to estimate age at seroconversion.

Estimation of force of infection and R_0

Force of infection, the *per capita* rate at which susceptibles are infected, was estimated as previously described [5, 12, 13]. R_0 was estimated from average age at seroconversion by the method of Dietz et al. [14], using Excel. The deterministic formula used was:

$$R_0 = 1 + e_0/A,$$

where e_0 is the average lifespan of calves (e_0 was assumed to equal 1.5 years for this analysis) and A is the average age at seroconversion. An estimate of R_0 was also determined by the Martingale method of Becker using the final size of the infected population according to the formula below, using Excel [15].

$$R_0 = [N/(X-Z)] * \sum_{j=S_T+1}^{S_0} 1/j,$$

where N =total no. of animals included in study; X =no. of cattle that seroconverted during approximately 1.5 years of follow-up; S_0 =no. of seronegative animals at time 0 (=susceptible calves); S_T =no. of cattle seronegative through the end of feeding period (approximately 1.5 years); Z =no. of infectious cattle still present after the last generation of susceptibles became infected during follow-up.

Z was assumed to be zero when $S_T > 0$. When $S_T = 0$ (years 1996 and 1998), Z was set equal to the no. of cattle that seroconverted during the time interval in which in the seroprevalence reached 100% (=the size of the last generation of cases) [16].

The following assumptions were applied: (1) the calf population was homogeneously mixed and contacts between individuals were random; (2) the dams represented a homogenous background upon which calf infections proceeded; (3) duration of infectious period had an exponential distribution and (4) force of infection is not age-related for STEC O157 in calves. The percent coverage (P_c) for effective vaccination was calculated using the formula below, described in Anderson and May [11].

$$P_c = 1 - R_0^{-1}.$$

Descriptive and other statistics were derived using Systat 9.01 (SPSS Inc., Chicago, IL, USA).

RESULTS

The time-course of seroconversion to the O157 antigen by year, and the mean of all years, is shown in the Figure. Approximately 70% of calves were

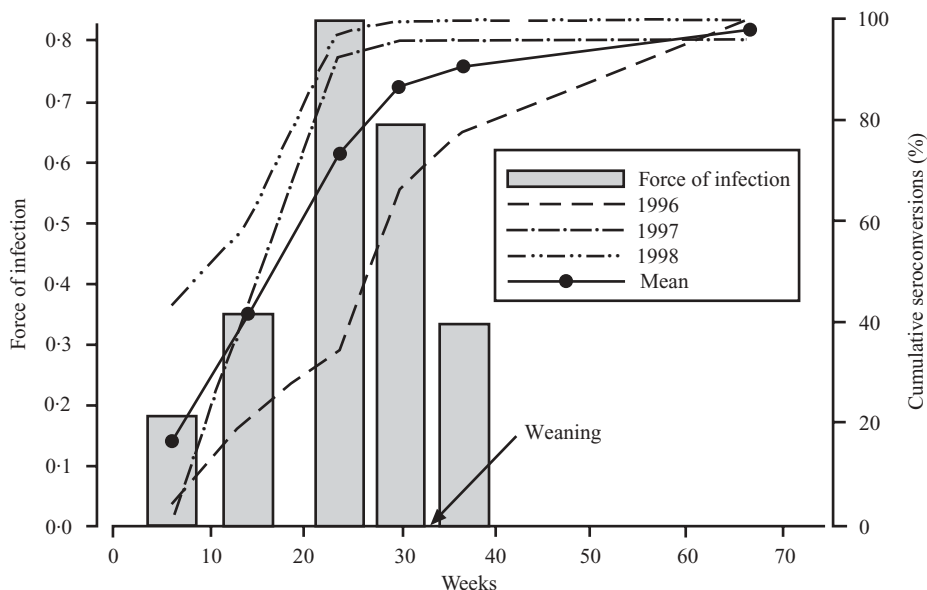


Fig. Cumulative seroconversions and force of infection for STEC O157 in beef calves, 1996–1998.

seropositive at 48 h of age due to antibodies passively acquired from their dams (data not shown). Most were seronegative on the next sampling (Fig.). Force of infection for STEC O157 infection, as estimated by seroconversion, is shown for each sampling interval (Fig.). While there is year-to-year variation in the time-course of seroconversion, the majority of calves were seropositive prior to weaning in each year (87.5%; 95% CI 80.5–92.3). Accordingly, force of infection was highest in the two sampling intervals prior to weaning at 210.4 days of age (95% CI 208.7–212.2). Average age at seroconversion was similar in 1997 and 1998, but was significantly higher in 1996 ($P < 0.0001$, Table). Thus, deterministic estimates of R_0 were lower in 1996 than in the other years (Table). Estimates of R_0 derived through deterministic and Martingale techniques for each of the three years, as well as those based on data pooled for the three years, were similar (Table).

DISCUSSION

Both deterministic and Martingale methods gave similar estimates of R_0 for STEC O157 in beef cattle, 3.9 and 5.3 respectively, indicating that 4 to 5 secondary STEC O157 infections result from each primary infection in beef calves. Considerable year-to-year variation in R_0 estimates was observed, however (Table). One year in particular, 1996, had a significantly higher age at seroconversion than the other two

years, although ultimately all calves seroconverted (Table, Fig.). Some of this variation is probably due to unrecognized STEC O157 strain and/or environmental variation but it also reflects the stochastic nature of these outbreaks. Since seropositive calves may be reinfected by STEC O157, the value of R_0 derived in this study should be considered a minimum estimate [8]. With an R_0 of 4, it might be expected that minor outbreaks of STEC O157 infection would occur in which far fewer individuals seroconvert. The failure to observe any indication of such minor outbreaks suggests that an R_0 value of 4 may be an underestimate for STEC O157.

There are limitations to generalization of this estimate of R_0 for STEC O157 in other cattle populations. In this study, the calves were commingled for their entire lifespan, approximating a homogenously mixed population. While representative of a beef cattle herd in the plains of the central United States, this production environment is quite different from that of a typical United States dairy or a British beef operation. For example, the effective contact rate is likely to differ between penned and free-ranging calves, affecting estimates of R_0 . Other factors, such as strain(s) of STEC O157, genetics of the herd, climate and population density may also affect R_0 . Thus, R_0 for STEC O157 may vary from the present estimates in other cattle populations and environments. Furthermore, only spring-born calves were included in the present study. Given the known seasonality of

Table. Estimation of R_0 for *E. coli* O157 infection of beef calves

Year	<i>n</i>	Age (years; 95% CI)	R_0	<i>Pc</i> (%)
(a) Based on age at seroconversion				
1996	46	0.69 (0.58–0.79)	2.9	65.5
1997	44	0.38 (0.34–0.42)	4.5	77.8
1998	45	0.28 (0.23–0.34)	5.6	82.1
Mean (95% CI)		0.46 (0.41–0.51)	4.3 (2.8–5.9)	75.1 (65.4–84.9)
Pooled 1996–1998			3.9	74.3
Year	<i>n</i>	R_0 (95% CI)		<i>Pc</i> (%)
(b) Based on final size of seropositive population				
1996	46	5.29 (2.52–8.06)		81.1
1997	44	3.53 (2.30–4.75)		71.7
1998	45	7.37 (4.98–9.76)		86.4
Pooled 1996–1998		5.25 (3.87–6.64)		81.0

STEC O157 prevalence in cattle, it is likely that R_0 will differ for calves born at other times of the year.

The proportion of calves that seroconverted to STEC O157 in this study was nearly 100%. This result is consistent with data from our laboratory and others that indicate high prevalence of faecal shedding of STEC O157 in beef cattle, especially in late summer and autumn where up to 100% of cattle in a group may be culture positive for STEC O157 [17]. Prevalence of STEC O157 shedding in beef cattle faeces is estimated to peak at around 15–30%, but shedding of STEC O157 by cattle is intermittent and the actual proportion of cattle infected is likely to be higher than point-prevalence estimates indicate [4, 5, 18–21]. Estimates of prevalence of STEC O157 infection in cattle are further complicated by the relatively high limit of detection of current culture methods, approximately 10^3 – 10^4 c.f.u./g faeces [18, 22]. Thus cattle could be infected but shedding non-detectable levels of STEC O157, resulting in an underestimate of actual prevalence. Serology, in general, is a more sensitive and stable indicator of having been infected by a given infectious agent. In a previous study, we have shown a significant positive correlation between prevalence of anti-O157 serum antibodies in cattle and prevalence of STEC O157 faecal culture-positive cattle within herds [5]. Therefore, it is likely that essentially all cattle in this study experienced STEC O157 infection. It is possible, however, that some anti-O157 antibodies result from response to non-STEC O157 *E. coli* or other bacterial species that bear the O157 antigen such as *Salmonella* O30 [23].

An R_0 of 4 predicts that 65–85% of calves would have to be vaccinated with a 100% efficacious vaccine

to reduce R_0 to less than 1 (Table, [11]). If, as stated above, we believe that R_0 is underestimated, the per cent vaccine coverage is also underestimated and would need to be increased for effective control of STEC O157. For an imperfect vaccine or for other interventions, such as competitive exclusion, that are unlikely to be completely efficacious, effective coverage would probably have to approach 100%. The situation is further complicated by the capability for prolonged survival of STEC O157 in the production environment under certain conditions, providing a potential source for re-infection of cattle. Thus, while some interventions may reduce the number of infected cattle, achieving eradication of STEC O157 from a herd will require significant effort and development of highly effective intervention tools.

Estimates of force of infection from this study indicate that the rate of primary STEC O157 infection in beef calves is highest prior to weaning, consistent with previous studies [5]. This result does not indicate that transmission does not occur between cattle at later stages of the production cycle, only that the majority of calves experience their first infection prior to weaning. This implies that, in the relatively clean environment of calves grazing on pasture, transmission of STEC O157 occurs readily. The so-called industrial environment of the feedlot is not required for efficient transmission of these bacteria. Furthermore, interventions applied after weaning should be considered therapeutic, rather than prophylactic as most calves will have experienced STEC O157 infection.

Both deterministic and Martingale methods give similar estimates of R_0 for STEC O157 infection in

beef calves, 3.9 and 5.3 respectively. These estimates of R₀ for STEC O157 indicate that eradication of STEC O157 in a population will require development of highly effective control strategies. These estimates are based on simplified assumptions about the behaviour of STEC O157 in beef cattle populations. Further refinement of the estimates to include other variables (seasonality, environmental contamination, contribution of the dam population, etc.), as well as estimation of R₀ in other beef cattle production settings will be required to determine the general applicability of these estimates.

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