Heterogeneous shedding of *Escherichia coli* O157 in cattle and its implications for control

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Identification of the relative importance of within- and between-host variability in infectiousness and the impact of these heterogeneities on the transmission dynamics of infectious agents can enable efficient targeting of control measures. Cattle, a major reservoir host for the zoonotic pathogen *Escherichia coli* O157, are known to exhibit a high degree of heterogeneity in bacterial shedding densities. By relating bacterial count to infectiousness and fitting dynamic epidemiological models to prevalence data from a cross-sectional survey of cattle farms in Scotland, we identify a robust pattern: ≈80% of the transmission arises from the 20% most infectious individuals. We examine potential control options under a range of assumptions about within- and between-host variability in infection dynamics. Our results show that the within-herd basic reproduction ratio, R_0, could be reduced to <1 with targeted measures aimed at preventing infection in the 5% of individuals with the highest overall infectiousness. Alternatively, interventions such as vaccination or the use of probiotics that aim to reduce bacterial carriage could produce dramatic reductions in R_0 by preventing carriage at concentrations corresponding to the top few percent of the observed range of counts. We conclude that a greater understanding of the cause of the heterogeneity in bacterial carriage could lead to highly efficient control measures to reduce the prevalence of *E. coli* O157.

bacterial count | core groups | super shedder | superspreading | targeted control

The role of heterogeneous infectiousness on the course of disease outbreaks was highlighted during the recent severe acute respiratory syndrome outbreak (1), in which a few individuals were responsible for a disproportionate number of transmission events. Awareness of heterogeneities in transmission dynamics can be important for the effective implementation of disease control measures and can lead to efficient targeting of interventions at a subset of the population (2–5). Factors that might lead to such heterogeneities include variability in infectiousness, exposure, genetic susceptibility, contact rates, and behavior (6–10). Quantifying their impact on the transmission dynamics can be achieved through direct methods, such as contact tracing and outbreak reconstruction (1, 11), or indirectly through their effect on the distribution of infected cases (12).

Escherichia coli O157 is an important zoonosis with a known reservoir in cattle (13, 14). Prevalences of infection are generally low, usually reported to be <10% of animals carrying the pathogen (14). Typically, however, the distribution of prevalences is highly skewed (15); at any one time, shedding is not detected in the majority of cattle groups, but a small proportion of groups contains high numbers of individuals shedding bacteria in their feces.

The range of prevalences of an infectious agent in a small population is expected to be influenced both by stochasticity and underlying heterogeneities in the transmission dynamics. In a recent analysis of prevalence data from Scottish cattle farms (12), it was shown that the observed distribution of prevalences across cattle groups could not arise through the inherent stochasticity in infection dynamics alone but that the highly skewed distribution is best explained when a small proportion of cattle is assumed to have much higher transmission rates than the others.

Accumulating evidence suggests that some cattle may harbor and shed *E. coli* O157 at higher concentrations than others. Several recent studies of slaughterhouse cattle have identified a proportion of animals as being high shedders of *E. coli* O157 (16–19). A recent longitudinal study of naturally infected calves (20) found that although in the majority of calves the pathogen was isolated intermittently, a small number of individuals appeared to be persistent high shedders.

Although considerable variation in shedding concentrations is observed (16–22), many of these studies do not reveal the relative extent of within- and between-host variability in carriage during the course of a natural infection with the organism. However, the success of previous modeling work (12) in describing the *E. coli* O157 prevalence data suggests that between-host variation in shedding concentrations is epidemiologically important.

In the present study, we consider a cross-sectional study of cattle groups from 474 cattle farms (see Fig. 1*a*) for which bacterial counts (see Fig. 2) were obtained for the majority of positive samples. These two data sets provide a unique opportunity to examine the role of heterogeneities in shedding concentrations on the transmission dynamics of *E. coli* O157 in the field.

As a consequence of the fact that most studies report farm level prevalences of *E. coli* O157 infection to be highly variable, typically comprising sporadic outbreaks, occasional high prevalences, and periods of apparent absence (23–28), we view the prevalence data as a snapshot of a dynamic process. Additionally, we take a previously undescribed approach in which we underpin the transmission dynamics with a model incorporating within-host variability based on the bacterial count data, which allows infectiousness to be related to the level of pathogen excretion. Specifically, by fitting a stochastic susceptible-infected-susceptible model incorporating within-host variability in infectiousness to the prevalence data, we aim to (*i*) relate infectious-

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Abbreviation: cfu, colony-forming unit.

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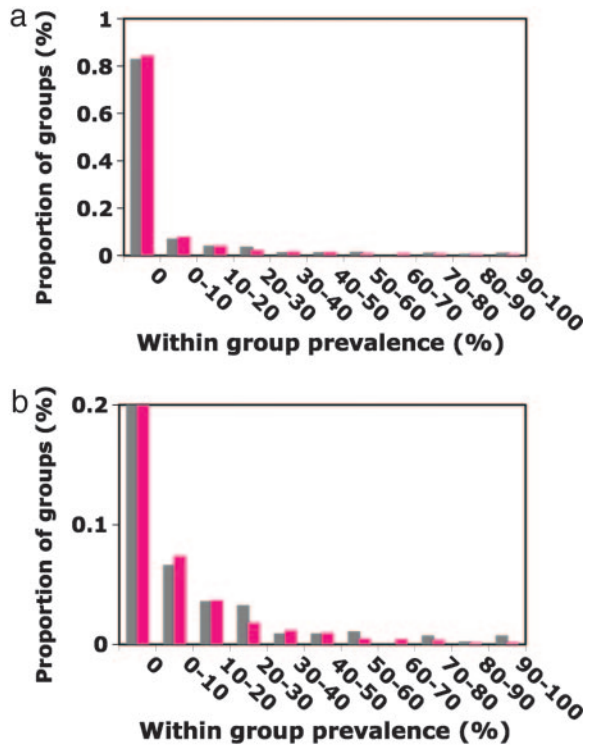

Fig. 1. The distribution of prevalences of *E. coli* O157. (*a*) Gray bars represent observed prevalences in fecal pats sampled from cattle groups on 474 Scottish cattle farms. Pink bars show output from a stochastic simulation of the model with infection profiles for infected individuals such that 20% of the observed variance in counts arises from host-to-host variability in bacterial carriage. Best fit parameters for this model are $R_0 = 1.5$, $\lambda = 0.01$, and $\alpha = 0.9$. (*b*) As in *a* but with a restricted vertical axis to expose the tail of the distribution.

ness to bacterial count under a range of assumptions about the relative extent of within- and between-host variability in bacterial carriage, (*ii*) determine how mean infectiousness varies between hosts, and (*iii*) evaluate the efficacy of potential control options.

Model Formulation

Within-Host Variability in Infectiousness. The infectiousness of an individual is assumed to be related to its bacterial count. We explore different possible relationships between infectiousness, *Inf*, and bacterial count, *C*, by relating the two quantities via an infectiousness parameter, α, in the following way:

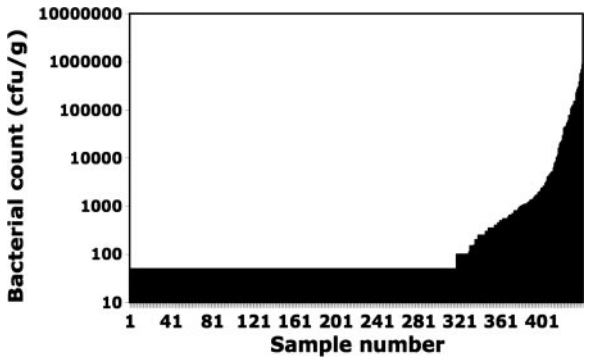

Fig. 2. The distribution of bacterial counts (cfu per gram of fecal matter) taken from 440 positive fecal pats. The limit of accurate enumeration is 100 cfu/g, and below this threshold, all counts have been set to 50 cfu·g^{-1}.

$$Inf \propto C^{\alpha}. \quad [1]$$

We assume that bacterial counts of infected individuals are sampled from the observed distribution of counts (see Fig. 2). Therefore, for a population with a mean transmission rate, β, the *j*th infected individual in the group, with current bacterial count, C_k has an infectiousness βw_j, where w_j is a relative infectiousness given by

$$w_j = \frac{(C_k)^{\alpha}}{\frac{1}{N_c}\sum_{l=1}^{N_c}(C_l)^{\alpha}}. \quad [2]$$

N_c is the total number of counts in the distribution (here N_c = 440) and C_k denotes the *k*th count in the distribution (see Fig. 2).

As bacterial shedding concentrations are known to vary through time within a given host (20, 22), the observed distribution of counts is expected to reflect both within- and between-host variation in natural carriage of the organism. To accommodate this variation in carriage within a host, we allow the bacterial count of an infected host to change during the course of the infection.

Here, we incorporate variation in bacterial carriage and, hence, infectiousness during the course of an infection in a straightforward manner by reselecting the bacterial count of an infected individual from the observed distribution of counts at intervals during the course of the infection. Resampling from this distribution a few times during the course of the infection will tend to produce distributions of counts that are very different from individual to individual. Resampling sufficiently many times, however, will ultimately produce a distribution for each individual that matches the observed distribution of counts.

Thus, resampling a few times during the course of the infection reflects a situation with a high degree of between-host heterogeneity in infection load; increasing the rate of resampling reflects a situation with a greater degree of within-host variability and a lower degree of between-host variability in the pattern of bacterial carriage.

We explore a range of resampling rates, setting *v*, the average number of times the bacterial count is sampled during the course of the infection, equal to 1, 5, 10, and 50. The infection profiles generated by these alternative scenarios each correspond to a different percentage contribution of the between-host variance in counts to the overall variance in bacterial counts. For *v* equal to 1, 5, 10, and 50, the relative contributions of the between-host variance are ≈100%, 20%, 10%, and 2%, respectively.

Within-Farm Transmission Dynamics. Within-farm transmission dynamics are described by a susceptible-infected-susceptible model (2, 29). The typically small cattle group sizes and frequent low prevalences of infection suggest that infection and recovery should be regarded as probabilistic events; we therefore employ a stochastic individual-based model of the transmission dynamics. Infections are assumed to arise in the susceptible population via two possible routes: first, direct transmission from other infected individuals (with transmission rate β), and second, infection (at a rate λ) from some external source. This second route could represent either infection from an environmental reservoir or the movement onto the farm of an already-infected individual (see *Supporting Materials and Methods*, which is published as supporting information on the PNAS web site for a detailed discussion of this parameter broken down into its component parts). Under the latter interpretation, our model provides a simplified representation of animals movements in which a susceptible individual in a group may be replaced by an infected individual from outside the group.

Table 1. Model negative log-likelihood and maximum likelihood parameter estimates for the basic reproduction ratio, R_0, the external infection rate, λ, and the infectiousness parameter, α

Host-to-host contribution to variance in counts, %	Basic reproduction ratio, R_0	Infectiousness parameter, α	External infection rate, λ	Negative log-likelihood
100	1.5 (1.2–2.1)	0.5 (0.4–0.8)	0.009 (0.006–0.011)	531.0
20	1.5 (1.2–1.9)	0.9 (0.8–1.2)	0.01 (0.008–0.011)	531.0
10	1.5 (1.2–1.9)	1.5 (1.0–1.7)	0.01 (0.007–0.011)	531.3
2	1.3 (1.1–1.7)	3.6 (3.2–4.0)	0.009 (0.007–0.012)	532.0

Results are shown for four model scenarios in which host-to-host variability in bacterial carriage contributes 100%, 20%, 10%, or 2% of the observed variance in counts. The 95% confidence limits are indicated in parentheses.

Cattle are not known to acquire permanent immunity to infection. Experimental studies have shown that prior infection does not prevent reinfection with the same strain of *E. coli* O157 (30, 31). Reduced shedding times following reinoculation have been observed in calves (30); however, the observation that the shedding patterns of reinoculated calves are similar to those of adults inoculated once (32) suggests that these changes in shedding patterns in calves are due to changes in bacterial flora with age (30) rather than acquisition of immunity. Serological responses to infection have been detected in some experimentally infected animals but have not been found to have a protective effect on reinoculation (31, 33). We therefore assume that infected individuals recover to the susceptible state.

As the model allows for the possibility that an individual may be moved out of the group during its infectious period, we specify a removal rate σ, which encompasses both the rate of natural recovery of individuals to the susceptible state and the possibility that the infectious duration of an individual within the group is curtailed by its movement out of the group. (See *Supporting Materials and Methods* for a detailed discussion.)

Parameter Estimation. Because we are using a nonparametric distribution for the bacterial shedding concentration and corresponding infectiousnesses of infected individuals, model fitting proceeds via direct simulation of the stochastic process (34). In a group of N animals containing S susceptible individuals and I currently infected individuals, the events (see *Supporting Materials and Methods* for a detailed discussion) that may change the current state are as follows: (*i*) an infection, (*ii*) a removal, or (*iii*) a change in infectiousness of one of the infecteds (simulated by resampling its bacterial count from the observed distribution of counts). These events occur with rates R_1, R_2, and R_3, respectively, given by

$$R_1 = S\left(\lambda + \beta\sum_{j=1}^{I} w_j/N\right), \quad [3]$$

$$R_2 = \sigma I, \quad \text{and} \quad [4]$$

$$R_3 = v\sigma I, \quad [5]$$

where, because of the heterogeneity in infectiousness, the standard term βI, has been replaced by $\beta\Sigma_{j=1}^{I} w_j$, the sum over the number of infected individuals weighted by their relative infectiousness.

Event times are sampled from an exponential distribution with parameter equal to $R_1 + R_2 + R_3$ (34). The probability of the next event being an infection, recovery, or change of infectiousness is determined by its relative rate e.g., the probability that the next event is an infection is given by $R_1/(R_1 + R_2 + R_3)$.

For each parameter combination, 100,000 samples from the stochastic process are taken at sufficient time intervals that the samples may be regarded as independent. This process provides the theoretical equilibrium probability distribution for the number of infected individuals in the group. The observed prevalence data, the number of infected pats found in a given group of animals, is assumed to correspond to sampling with replacement from this equilibrium distribution.

This approach enables us to determine the probability of the observation made in each group of animals. The likelihood of the set of observations from all of the sampled groups is then given by the product of these probabilities, allowing us to determine maximum likelihood estimates (35) for the transmission rate, β, the external infection rate, λ, and the infectiousness parameter, α. Because the average relative infectiousness of an individual is, by definition, equal to 1, the average transmission rate is equal to β, and the mean time for which an individual remains infectious within the group is $1/\sigma$. Therefore, the basic reproduction number, R_0, for this system is given by $R_0 = \beta/\sigma$. Note, however, that because we are dealing with cross-sectional data without an explicit timescale, we are free to specify a timescale such that the removal rate, σ, is equal to unity; it is therefore sufficient to estimate β.

Results

Relationship Between Bacterial Count and Infectiousness. Maximum likelihood parameter estimates, obtained by fitting the stochastic susceptible-infected-susceptible model to the distribution of observed prevalences, are shown in Table 1. Estimates are obtained for the within group basic reproduction ratio, R_0, the external infection rate, λ, and the infectiousness parameter, α, which relates bacterial count to infectiousness via Eq. **1**. Results are shown for four different scenarios in which we generate infection profiles for individuals from the observed distribution of counts (see Fig. 2) that correspond to a relative contribution of host-to-host variation to the overall variance in the count data of 100%, 20%, 10%, and 2%.

Estimates for R_0 and the external infection rate, λ, are robust to the choice of scenario, but α increases as the host-to-host variation in bacterial carriage declines. Because increasing this parameter exaggerates the difference in infectiousness associated with different counts, we conclude that, as the host-to-host variation in bacterial carriage declines, the infectiousness parameter, α, increases to maintain host-to-host heterogeneity in infectiousness.

Within- and Between-Host Variability. The very close similarity in the negative log-likelihoods for the four models with different relative contributions from host-to-host variation to the overall variance in the count data indicates that we cannot distinguish

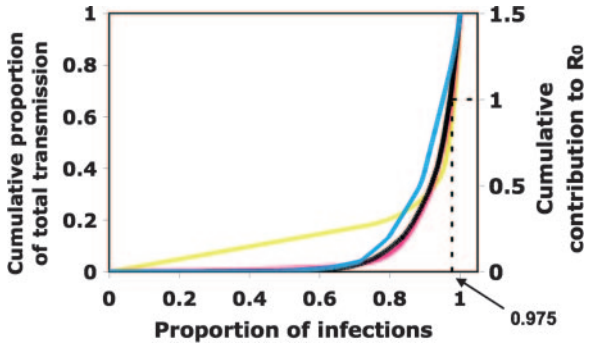

Fig. 3. The cumulative contribution to overall transmission versus proportion of individuals, summed in order of increasing mean infectiousness, for model scenarios with host-to-host variability in bacterial carriage contributing 100% (yellow line), 20% (red line), 10% (black line), or 2% (blue line) of the observed variance in bacterial counts. Also indicated (dotted line) for the scenario with 20% of the observed variance in counts arising from host-to-host variability is the proportion of the infections (the top 2.5%) with the highest mean infectiousness to be prevented to reduce R_0 below 1.

between the scenarios on the basis of goodness of fit to the data. However, available (unpublished) data on experimental infections of calves, monitored daily during the course of the infection, indicates that ≈21% of the variance in the observed counts could be attributed to between-host variability. This observation suggests that the scenario with 20% of the variance in counts attributable to host-to-host variation is most consistent with the available data.

Output from a stochastic simulation of this model scenario is shown alongside the observed prevalence distribution in Fig. 1. The model reflects the observed prevalence distribution well, successfully reproducing both the high proportion of zero prevalences (see Fig. 1*a*) and the long tail of the distribution (see Fig. 1*b*) corresponding to the few cattle groups with very high prevalences of infection. Note that all four models shown represent a highly significant improvement in model fit ($P < 0.001$) over a null model that assigns equal infectiousness to all individuals.

Distribution of Mean Infectiousness. We now consider the mean infectiousnesses of an infected individual. In the case that 100% of the variance in bacterial load is attributable to host-to-host variation (i.e., there is no change within the host during the course of the infection), the mean infectiousness equals the initial infectiousness; otherwise, we calculate the mean infectiousness as the bacterial load varies during the course of the infection.

Fig. 3 shows the cumulative contribution to the total transmission for the four different model scenarios, summed in order from individuals with low to high mean infectiousnesses. The curves demonstrate that the infections with a low mean infectiousness, although there are many of them, contribute relatively little to the overall transmission, whereas the relatively few infections with a high mean infectiousness contribute the major part of the transmission. Overall, we can see that typically 20% of the infections are contributing ≈80% of the transmission. This result indicates that as the host-to-host variation in bacterial counts declines, the infectiousness parameter, α, adjusts to maintain a level of between-host variability in mean infectiousness that leads to this robust pattern.

Implementation of Control Measures. ***Targeting the most infectious individuals.*** Our results (see Table 1) provide estimates for R_0 in the region of 1.5. This estimate implies that a reduction in transmission of one-third or greater would be sufficient to bring R_0 below 1. From Fig. 3, we can see that for all four model scenarios, this reduction could be achieved by preventing infection in <5% of the individuals with the highest mean infectiousness. For the model most consistent with the available experimental data (20% of the variance in counts arising from host-to-host variability in bacterial load), this reduction can be achieved by targeting the top 2.5% most infectious individuals (this threshold is indicated by the dotted lines on Fig. 3).

Table 2. Percentage reduction in overall transmission achieved by capping bacterial counts at a threshold level (either 10^5 or 10^4 cfu/g) for four model scenarios in which host-to-host variability in bacterial carriage contributes 100%, 20%, 10%, or 2% of the observed variance in bacterial counts

Host-to-host contribution to variance in counts, %	Transmission remaining when carriage $>10^5$ cfu/g prevented, %	Transmission remaining when carriage $>10^4$ cfu/g prevented, %
100	84	56
20	48	12
10	26	3
2	<1	<0.001

Targeting bacterial carriage at high concentrations. An alternative strategy is to consider the impact of preventing carriage of the organism at high concentrations. Table 2 shows the transmission potential that remains if individuals cannot harbor bacteria at counts above a certain threshold value but instead have their maximal bacterial load capped at that threshold value. We consider thresholds of 10^4 colony-forming unit (cfu)/g and 10^5 cfu/g, which correspond, respectively, to the top 6% and 3% of observed counts. As shown in Table 2, eliminating the highest counts is most effective when a greater level of within-host variability is assumed, because the high counts are more infectious under this scenario.

For an R_0 value of 1.5 (consistent with our estimates above), we can see that eliminating counts above 10^5 cfu/g will reduce $R_0 < 1$ in all cases except when 100% of the variance in counts is due to host-to-host variability, but that eliminating counts $>10^4$ cfu/g will always succeed in reducing $R_0 < 1$. For the model that is most consistent with the available experimental data, capping the bacterial load at 10^4 cfu/g and 10^5 cfu/g produces reductions in transmission of 48% and 12%, respectively, both sufficient to reduce R_0 substantially <1.

Robustness of Results to Sensitivity of Detection of *E. coli* O157. Our results are not qualitatively affected by assuming a limited sensitivity of the immunomagnetic separation test. Simulations were rerun with detection sensitivities of 70% and 50%. Assuming reduced sensitivity increases R_0 estimates (to 2.3 and 3.0 for detection sensitivities of 70% and 50%, respectively), necessitating higher levels of control to achieve a reduction to <1, but the pattern of heterogeneity in between-host infectiousness is preserved.

Discussion

Several recent studies have suggested that some cattle may harbor and shed *E. coli* O157 at much higher concentrations than other individuals (16–22). This paper quantifies the impact of observed heterogeneities in bacterial carriage on the transmission dynamics of the organism and assesses their implications for control.

Fitting dynamic epidemiological models with variable infection loads to the distribution of shedding prevalences has enabled us to relate the distribution of infectiousness to the observed bacterial

count data under a range of assumptions about between- and within-host variability in bacterial carriage. A robust picture emerges in which ≈20% of infections are responsible for 80% of the transmission. The pattern is a common one that we observe in a variety of disease systems (3–5, 36). The consequence of this heterogeneity in infectiousness is that significant reductions in R_0 can be achieved by targeting control measures at a small proportion of the population. Here, over a broad range of assumptions about the relative contribution of between-host variability, we find that preventing infection in 5% of the individuals with highest mean infectiousness would be sufficient to reduce R_0 below 1 and control the spread of infection.

Although our model does not explicitly identify individuals with a predisposition to high levels of carriage, it would accurately reflect a situation in which predisposed individuals are distributed randomly within the cattle population. Although the nature of the predisposition does not alter the impact of control, it does alter the type of intervention that would be effective. Experimental data (37–39) and data from natural infections of calves (22) indicate that high levels of shedding are also associated with colonization and persistence, suggesting that pen-side tests and removal of currently high shedding individuals might be an effective control measure. Additionally, identifying factors such as age, genetics, diet, or other management factors that might predispose an individual to high levels of carriage would create the potential for preemptive control.

A number of interventions have been suggested for the control of *E. coli* O157 that target the ability of the pathogen to colonize and persist in the cattle host (40, 41); these interventions include vaccination (42, 43), the use of probiotics to colonize the gastro-intestinal tract preferentially (44, 45), and application of bacteriophage (46, 47). Our results suggest that such interventions may only need to prevent bacterial carriage at very high levels (10^4 to 10^5 cfu/g) to control the spread of the organism. Conversely, potential measures that eliminate the typically observed low levels of carriage but do not successfully target shedding at high levels are likely to fail.

The within- and between-host variability in infectiousness has been captured here in a simple manner. Experimental infections have shown that the shedding patterns may depend on a number of factors, including dose (48), age (32), time since inoculation (49), prior exposure (30, 31) and host predisposition (unpublished data). Nonetheless, the robustness of our results to different levels of variability between hosts suggests we have identified a general pattern in the distribution of infectiousness.

Factors that influence the prevalence of infection at the farm level could affect our conclusions about the importance of host-to-host variability in infectiousness. However, when one of the most significant of these risk factors, the housing of animals (refs. 15 and 23 and unpublished data), is accounted for in the analysis, we find that the distribution of infectiousness between hosts remains qualitatively unchanged (unpublished data).

Although our conclusions derive from an analysis of prevalence and count data collected from the Scottish cattle population, our results are likely to be relevant to other geographic regions. This conclusion is supported by the observation that studies conducted outside Scotland have identified comparable heterogeneities in bacterial shedding levels (16, 20, 21, 24) and skewed distributions of prevalences (50, 51). However, overall transmission rates may vary by region, climate, season, or management factor, necessitating proportionately higher or lower levels of targeted control accordingly.

In summary, our results show that control policies targeted at individuals with high mean levels of carriage, or interventions aimed at preventing high bacterial loads, could be very effective control strategies for reducing the prevalence of *E. coli* O157. This conclusion highlights the importance of future studies aimed at determining the causes of the high-level shedding of *E. coli* O157.

Materials and Methods

The cross-sectional data comprise pat samples collected from the groups of cattle closest to slaughter (store and finishing beef cattle) on 474 Scottish cattle farms, stratified with respect to region and season at the time of sampling between March 2002 and February 2004. Fecal material from fresh pats was collected and examined for *E. coli* O157 strains by using immunomagnetic separation (52, 53). Of 12,693 samples collected, 512 (4%) were identified as positive for *E. coli* O157. At least one positive sample was found in 18% of the cattle groups sampled (see Fig. 1*a* for the distribution of group prevalences).

Bacterial counts were obtained for the majority of the immunomagnetic separation-positive samples by following the method described in ref. 54. The limit of accurate enumeration for this method is 100 cfu/g (17, 29). Below this threshold, we set all counts to be 50 cfu/g (see Fig. 2), although robustness of our results to alternative assumptions is confirmed. To be conservative about the influence of heterogeneity in observed bacterial counts on the transmission dynamics, an outlying count (of 36,150,000 cfu/g) was excluded from the input to the simulation on the basis that it was unrepresentative of the distribution of counts: This count was 41 times higher than the next highest, whereas typical ratios between a count and the next highest for this data set were between 1 and 2.

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