**Appendix B - Methods to Quantify the Acquisition of Rectal Carriage of Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae (ESBL-E) during Hospitalization**

**Pragmatic approach**

Hospital-acquired rectal carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E) was assumed not to be detectable within two days of hospital admission.1 Consequently, ESBL-E rectal carriage that was detected within two days of hospital admission was considered community-acquired. In addition, patients who were discharged within two days of hospital admission were considered not to be at risk for (detectable) hospital-acquired ESBL-E rectal carriage and were excluded from the pragmatic analysis. Admission cultures comprised all cultures taken within two days of hospital admission; discharge cultures were all cultures taken on the day of discharge.

The prevalence of ESBL-E rectal carriage at hospital admission was calculated by dividing the number of ESBL-E positive admission cultures by the number of admission cultures taken. Likewise, the prevalence of ESBL-E rectal carriage at hospital discharge was calculated by dividing the number of ESBL-E positive discharge cultures by the number of discharge cultures taken.

For the SoM study, the software application OpenBUGS2 was used to perform a Bayesian Markov chain Monte Carlo (MCMC) random-effects analysis to estimate the mean prevalence of ESBL-E rectal carriage at hospital admission and at hospital discharge across hospitals, taking into account within-hospital dependency of the data collected in the 14 participating hospitals. For each hospital, the prevalence on admission and at discharge were assumed to be distributed according to a beta-distribution. The beta-distribution is a distribution on (0,1), which has two parameters, *a* and *b*, and has a probability density function $f\left(x\right)=\frac{x^{a-1}(1-x)^{b-1}}{B(a,b)}$ with $B\left(a,b\right)=\frac{Γ(a)Γ(b)}{Γ(a+b)}$. The mean of the beta-distribution is $\frac{a}{a+b}$ and the variance $\frac{ab}{(a+b)^{2}(a+b+1)}$. With the following reparametrisation: $a=ημ$ and $b=η(1-μ)$, the mean equals $μ$ and the variance $\frac{ μ(1-μ)}{1+η}$. A uniform prior on (0,1) was assumed for the mean $μ$ and a uniform prior on (0, *μ(1-μ)*) for the variance given the mean. This is obtained by having as prior density for $η$ the function $\frac{1}{(1+η)^{2}}$. This is beta-prime distribution with parameters (1,1), which is modeled in OpenBUGS as dgpar(0,1,1).2 The observed prevalences at admission and at discharge were modeled as binomial distributions, i.e. *Bin*(*n*,*p*), with *n* the number of cultures taken and *p* the prevalence of ESBL-E rectal carriage that comes from the beta-distribution. The posterior distributions for *μ* are reported in the manuscript as mean prevalence of ESBL-E rectal carriage at hospital admission and at hospital discharge. Leave-one-out sensitivity analyses were conducted to evaluate the robustness of the overall estimates for the SoM study.3 By iteratively removing one hospital at a time and recalculating parameter estimates, the impact of each hospital on the overall estimates was assessed.

The prevalence of hospital-acquired ESBL-E rectal carriage at discharge was estimated by subtracting the prevalence of ESBL-E carriage at hospital admission from the prevalence of ESBL-E carriage at hospital discharge. Dividing the estimated prevalence of hospital-acquired ESBL-E rectal carriage at discharge by the proportion of ESBL-E non-carriers at admission yielded the cumulative incidence of ESBL-E rectal carriage during hospitalization. The acquisition rate of ESBL-E rectal carriage was estimated by multiplying the estimated prevalence of hospital-acquired ESBL-E rectal carriage at discharge by the number of patients cultured at discharge divided by the number of patient days at risk for patients cultured at discharge. The number of patient days at risk was estimated from the length of hospital stay for patients cultured at discharge, taking into account the observed prevalence of ESBL-E rectal carriage at hospital admission and the assumed two-day delay in detectability of hospital-acquired ESBL-E rectal carriage, i.e. the length of hospital stay until two days before culture was multiplied by the proportion of ESBL-E non-carriers at admission.

**Markov chain Monte Carlo model**

A previously developed Markov chain Monte Carlo (MCMC) model was used to quantify the hospital-acquisition of ESBL-E in the R-GNOSIS study.4,5 This model assumes that patients are either colonized with ESBL-E or non-colonized, and distinguishes between patient-dependent acquisition and background acquisition.

The patient-dependent acquisition rate comprises all ESBL-E acquisitions that are dependent on the colonization pressure on the ward6 and includes the transmission of ESBL-E from colonized to non-colonized patients, either directly or indirectly (through the contaminated hands of healthcare workers (HCWs) or the contaminated environment). The background acquisition rate covers all other ESBL-E acquisitions, including acquisition from visitors or HCWs moving between wards, acquisition from the environment when this is independent of the colonization pressure on the ward, and acquisition through the endogenous route. The latter represents the situation where bacteria are already present in the host at undetectable levels and, presumably, reach detectable levels under antibiotic pressure.

The rate of acquisition of ESBL-E is defined by *α*+*β*\**I*/*N*, where *α* is the background acquisition rate, *β* is the patient-dependent acquisition rate, *I* is the number of colonized patients on the ward, *N* is the total number of patients on the ward. The colonization pressure, i.e. the fraction of ESBL-E carriers on the ward, is defined as *I*/*N.*6

A Bayesian framework using a data-augmented MCMC method with Metropolis-Hastings algorithm was used that accounts for false-negative and missing cultures and, therewith, allows estimation of the sensitivity of the method used to detect ESBL-E rectal carriage (*φ*) and the most likely time of ESBL-E acquisition for each patient.

Model parameter estimates were used to obtain estimates for the prevalence of ESBL-E rectal carriage at ward admission and ward discharge, the prevalence of hospital-acquired ESBL-E at discharge, and the cumulative incidence and acquisition rate of ESBL-E rectal carriage during hospitalization. The relative contribution of patient-dependent acquisition to the total ESBL-E acquisition rate was calculated as *β*\*mean prevalence/(*β*\*mean prevalence+*α*). The per-admission reproduction number RA, i.e. the average number of ESBL-E acquisitions caused by one ESBL-E carrier during a single admission, was approximated by multiplying the patient-dependent acquisition rate by the mean length of hospital stay.5,7

The MCMC algorithm was written in C++ and run for 1,000,000 iterations. To account for the burn-in time, the first 200,000 iterations were not used for calculation of parameter estimates.

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