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Estimating true incidence of O157 and non-O157 Shiga toxin-producing *Escherichia coli* illness in Germany based on notification data of Haemolytic Uremic Syndrome

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Running head: Incidence of STEC illness in Germany

Summary

Shiga toxin-producing *Escherichia coli* (STEC) is an important cause of gastroenteritis (GE) and haemolytic uremic syndrome (HUS). Incidence of STEC-illness is largely underestimated in notification data, particularly of serogroups other than O157 ("non-O157"). Using HUS national notification data (2008-2012, excluding 2011), we modelled true annual incidence of STEC-illness in Germany separately for O157 and non-O157 STEC, taking into account the groups' different probabilities of causing bloody diarrhoea and HUS, and the resulting difference in their ascertainment. Uncertainty of input parameters was evaluated by stochastic Monte Carlo simulations. Median annual incidence of STEC-associated HUS and STEC-GE was estimated at 0.11 (95% CrI 0.08-0.20), and 34.6 (95% CrI 12-145) per 100,000 population, respectively. German notification data underestimated STEC-associated HUS and STEC-GE incidences by factors of 1.8 and 32.3, respectively. Non-O157 STEC accounted for 78% of all STEC-GE, 51% of all bloody STEC-GE and 32% of all STEC-associated HUS cases. Non-O157 serogroups dominate incidence of STEC-GE and contribute significantly to STEC-associated HUS in Germany. This might apply to many other countries considering European surveillance data on HUS. Non-O157 STEC should be considered in parallel to STEC O157 when searching aetiology in patients with GE or HUS, and accounted for in modern surveillance systems.

Introduction

Shiga toxin-producing *Escherichia coli* (STEC) is an important cause of gastroenteritis (GE) and life-threatening haemolytic uremic syndrome (HUS) in many countries. STEC has a zoonotic reservoir (mainly ruminants) and is transmitted by inadvertent ingestion of small amounts of faecal matter. The serotype is an indicator of the genomic strain content and incidence of human illness and disease severity varies by serotype [1, 2]. Evidence from observational studies suggest that STEC of serogroup O157 with serotypes H7 or H- (O157 STEC) are, on average, substantially more virulent than other ("non-O157") STEC implicated with human illness [2-4]. O157 STEC is the leading cause of paediatric HUS [5] and the most frequently isolated etiologic agent in STEC outbreaks worldwide [6]. These organisms can be easily identified by culture on selective and differential agar [7], except rarely identified sorbitol-fermenting (sf) clones [8, 9].

Non-O157 STEC represents a genomically heterogeneous group of organisms, comprising STEC with little or no virulence to humans but also, for example, STEC O104:H4 that caused the largest outbreak of HUS thus far [10]. Currently, diagnosis of non-O157 STEC is more complex and requires screening for Shiga toxins or their encoding genes. Culture isolation and subsequent serotyping is often conducted only at public health laboratories. Diagnosis of non-O157 STEC is disproportionately underutilized, even in countries where their diagnosis is recommended. Consequently, surveillance for non-O157 STEC in many countries is less inclusive than for O157 STEC and their contribution to incidence of STEC illness has been insufficiently determined.

Notification data, including statutory, capture only a fraction of illnesses that is occurring in the population. In Germany, median annual incidence (per 100,000 population) of

notifications reports 0.06 cases for STEC-associated HUS (and 1.07 cases for STEC-GE) for 2008-2012 excluding 2011 (https://survstat.rki.de, data version 01/07/2014).

Studies addressing underestimation in notification data and the quantitative relation of non-O157 STEC to O157 STEC are helpful to inform diagnostic and surveillance strategies – as were previous studies for other gastroenteric pathogens [11].

The few available studies suggest a true annual incidence of STEC-associated infections between 47 and 100 per 100000 population for Europe [12] and Northern America [13, 14] and 0.15 STEC-associated HUS [12]. Estimated proportions of non-O157 in STEC-GE were 62% and 64% in Canada [14] and the United States [13] respectively. All available studies extrapolated data from different countries or data on other pathogens than STEC for their estimation models [12-14], thus introducing a further source adding to the inherent uncertainty of stochastic modelling. Furthermore, estimates of overall STEC-GE and the proportion of O157 STEC are based, at best, on STEC-GE surveillance data [13] with all its diagnostic vagaries mentioned afore, or on assumptions [12, 14] but not on HUS statutory surveillance data.

Our objectives were to estimate annual frequency and incidence of STEC-associated HUS and STEC-GE in Germany based on German national notification data for enteropathic HUS – overall and separately for O157 STEC and non-O157 STEC - to inform diagnostic-, and surveillance-strategies.

Methods

Using HUS national notification data as a starting point, we modelled true annual incidence of STEC-illness in Germany separately for O157 and non-O157 STEC, taking into account

group specific underestimation caused by underreporting of notification data and ascertainment, see Figure 1.

Diagnosis and surveillance of STEC-GE and "enteropathic" HUS in Germany

In Germany, diagnosis of STEC in GE and HUS patients is based on detection of Shiga toxins or their encoding genes in stool enrichment culture or isolates. Subsequent culture isolation and serotyping is recommended but not mandatory and rarely performed in clinical laboratories. In HUS patients, evidence for an STEC infection can also be established by detecting anti-lipopolysacharide IgM antibodies against *E. coli* serogroups in blood by specialised laboratories (which in the study period included only antibodies against the serogroup O157).

According to the German Protection against Infection Act, both laboratory detection of STEC infection in stool and clinically diagnosed "enteropathic" (i.e. GE-associated) HUS are notifiable (see supplementary material for national surveillance case definitions).

Electronic case reports are sent from the local health department via State Health Departments to the federal-level public health institute, the Robert Koch Institute (RKI), where reports are hosted in a national database. In addition, RKI conducts active surveillance for paediatric HUS since 2008 in collaboration with the German Society for Paediatric Nephrology. This surveillance entails monthly inquiries to all paediatric nephrology centres (PNC) in Germany about incident HUS cases in children (<18y) of the past month.

Risk model for STEC illness in Germany

We used German notification data on enteropathic HUS, reported to the RKI for the years 2008-2012 (excl. 2011 because of a large outbreak of STEC O104:H4 [10]) as the basis to estimate the true annual incidence of STEC-GE in Germany.

We computed estimates separately for the groups of STEC O157 and non-O157 STEC, taking into account the groups' different average capability of causing acute bloody diarrhoea [15], and HUS and the resulting difference in underascertainment caused by symptomatic cases not attending health facilities (for differences in clinical severity) or by not being correctly diagnosed as a case (for differences in diagnostics as outlined above). Furthermore, underreporting of cases from health facilities to public health authorities adds to underestimation of STEC-GE incidence.

Our estimations were conducted in the following sequence (see also Figure 1):

a) Adjustment for underreporting of HUS

To estimate the true median annual number of enteropathic HUS, adjustment for underreporting was conducted separately for cases treated in PNCs and non-PNCs. For PNCs, we used a two-source capture-recapture approach (statutorily passive HUS surveillance and active paediatric HUS surveillance) to estimate the magnitude of underreporting of notification data. We assumed underreporting by non-PNCs to be up to ten times more common than in PNCs as HUS cases are infrequently treated in these institutions. Consequently, knowledge of infectious disease notification requirements, otherwise seldom needed in nephrology units, is likely to be less prevalent among medical personnel in non-PNCs.

b) Estimating the proportion of STEC-associated HUS

Evidence of STEC infection cannot be established in every case of "enteropathic" HUS. Using literature (described in detail in the supplementary material) on microbiological evidence of STEC in HUS patients in Germany, we estimated the proportion of enteropathic HUS caused by STEC infection [17]. This proportion was subsequently

multiplied by the estimated number of all HUS cases per year to obtain the number of estimated STEC-associated HUS cases.

c) Estimating the proportion of O157 and non-O157 among STEC-associated HUS

The proportion of O157 among STEC-associated HUS in Germany was derived from literature [17, 18] and combined in a beta distribution as outlined in Table 1. This proportion was multiplied by the annual number of STEC-associated HUS cases to estimate the O157-associated HUS cases (the remaining STEC-HUS cases were thus non-O157 associated). All further calculations were conducted separately for O157 and non-O157 -associated HUS cases.

d) Estimating the number of laboratory confirmed STEC-GE cases per HUS case

Using literature information on the proportion of HUS-cases among laboratory-confirmed STEC-GE cases [19], we multiplied the estimated annual number of STEC-associated HUS cases by the factor for STEC-GE cases per STEC-associated HUS case separately for O157 and non-O157 (beta distribution).

e) Estimating the proportion of bloody diarrhoea among O157 and non O157 STEC-GE cases

In addition, we used literature for estimates on the proportion of bloody diarrhoea among O157 and non-O157 STEC-GE cases [19]. Annual frequencies for STEC-GE with bloody and non-bloody diarrhoea were used to account for underascertainment according to severity in a next step (separately for O157 and non-157).

f) Estimated underascertainment of bloody and non-bloody diarrhoea

Underascertainment was accounted for in a procedure incorporating three steps: Using literature information, we first estimated the proportion of symptomatic patients consulting

154 a physician, thereafter the proportion of patients that provided stool specimens for
155 microbiological testing [20, 21] and finally the proportion of stool samples tested for STEC
156 [22] based on German laboratory recommendations on test strategies for faecal samples
157 [22].

158 The estimated annual number of true STEC-GE cases and STEC-associated HUS cases in
159 Germany, differentiated for O157 and non-O157, were converted to annual cumulative
160 incidence per 100000 population, using the mean population size of Germany 2008-2012,
161 excluding 2011, obtained from Germany's Federal Statistical Office.

162 Evaluation of uncertainty

163 We used Monte Carlo simulation in @RISK version 6.1.1 (Palisade Corporation, Ithaca, NY)
164 with Latin Hypercube sampling and 10000 iterations to evaluate uncertainty in the outputs.
165 All input data was considered to be subject to uncertainty and parameters were therefore
166 described by probability distributions. Generally, proportions were described by beta
167 distributions and the HUS rate was described by a gamma distribution [16]. Pert distributions
168 were used for multiplication factors where sufficient data to inform beta-distributions was
169 unavailable. Distribution parameterization was done as displayed in Table 1. The results are
170 reported as the median and the 95% credible interval.

171 A sensitivity analysis was conducted to evaluate the contribution of the input parameters to
172 the overall uncertainty in outcome estimates to identify which input parameter shows the
173 biggest influence on the output.

174 In addition we examined two scenarios using alternative values of particularly uncertain input
175 parameters to investigate their effect on the outcome estimates (keeping all other variables of
176 the model constant). For details see supplementary material. In a conservative Scenario (1) we

assumed that degree of underreporting of HUS did not differ between PNCs and non-PNCs and that all stool samples submitted for microbiological testing were investigated for STEC regardless of whether blood was visible. In Scenario 2 we re-parameterized the model using input parameters for underascertainment based on findings of a survey in the Federal State of Hesse for in children <16 years of age [21], to account in our estimates for underascertainment for the higher incidence of STEC illness in children.

Literature survey

We searched Medline and SCOPUS literature for information about STEC in Germany published since inception of Medline and SCOPUS bibliographic database to 31/12/2014 with the objective to identify for patients in Germany the proportion of STEC-associated HUS among enteropathic HUS cases (as input parameter for estimation step b), the proportion of O157 STEC among STEC-associated HUS (step c) and the proportion of HUS and bloody diarrhoea among laboratory confirmed STEC-GE separately for O157 and non-O157 serogroups (step d). Our second objective was to identify underascertainment of bloody and non-bloody diarrhoea (step f), including the proportion of physician consultations in cases of bloody and non-bloody diarrhoea and the proportion of physicians taking stool samples in cases of bloody and non-bloody diarrhoea.

We used the search terms (enterohemorrhagic escherichia coli OR stec OR escherichia coli o157 OR e coli o157) AND (Germany) to identify input parameters for step b-e. We used search terms (gastroenteritis OR gastrointestinal illness OR gastrointestinal infections) AND Germany AND (healthcare OR medical care) in titles and abstracts for step f.

We required articles for all steps to provide data in sufficient detail for O157 and non-O157 regarding proportion of HUS and bloody diarrhoea and to refer to data that pertained to

Germany recognizing that serogroup distribution among GE and HUS cases as well as health seeking behaviour may vary between countries. In addition, we required information for steps d-f to be derived from population-based surveys or sentinel surveillance projects to increase accuracy of these estimates. Search results for Medline and Scopus were combined and de-duplicated. Two investigators screened documents independently, in case of discrepancies consensus in discussion was sought. Documents were first screened by reviewing titles and abstracts were available. Identified documents were screened against inclusion and exclusion criteria outlined above. From the identified documents absolute numbers were extracted and used as input variables in the estimation model as outlined in Table 1.

Results

We identified five relevant publications, three for step b to e and two for step f [17-21] that together provided information for all required input parameters, see Figure 2 and supplementary material. These publications, German notification data and German laboratory guidelines formed the backbone of the simulation model and are outlined in Table 1.

We estimated a median annual number of 90 cases of STEC-associated HUS in Germany during the study period, corresponding to an incidence of 0.11 (95% CrI 0.08-0.20) per 100000 population; a median of 60 cases due to STEC O157 (incidence 0.07; 95% CrI 0.05-0.13) and a median of 29 cases due to non-O157 STEC (incidence 0.04; 95% CrI 0.03-0.07), see Table 2. From these, we estimated that a median of 28347 STEC-GE cases occurred per year in the German population, indicating an incidence of 34.6 (95% CrI 12.0-145) per 100000 population; a median of 4969 cases due to O157 STEC (incidence 6.07; 95% CrI 2.2-23.7) and a median of 22019 cases due to non-O157 STEC (incidence 26.9; 95% CrI 8.0-133).

Our estimates correspond to a median annual underestimation of STEC-associated HUS and STEC-GE in the German notification data by a factor of 1.8 (1.3-3.3) and 32.3 (11.2-135) respectively.

Non-O157 STEC accounted for 81% (49%-96%) of all STEC-GE and 51% (16% - 86%) of all bloody STEC-associated diarrhoea.

Sensitivity analysis indicated that the proportion of HUS cases among laboratory confirmed non-O157 STEC exerted the biggest influence on the outcome of all input parameters, followed by the proportion of stool samples tested for STEC and the completeness of HUS-notifications from non-PNCs, see Figure 3.

In scenario analysis, the median annual incidence of STEC-GE ranged from 17.1 (95%-CI: 7.6-61) per 100000 population in scenario 1 to 72 (95%-CI: 22.3-339) in scenario 2 and of STEC-associated HUS from 0.08 (95%-CI: 0.07-0.09) in scenario 1 to 0.11 (95% CrI 0.08-0.20) in scenario 2 (unchanged to the point estimate).

The proportion of non-O157 STEC among STEC-GE, bloody diarrhoea and STEC-associated HUS did not vary in the different scenarios (see supplementary material for detailed results).

Discussion

We estimated the true frequency and incidence of STEC illness in the German population, separately for O157 and non-O157 STEC, based on statutory notification data on HUS. The study yielded the following main findings: The median annual incidence per 100000 population was estimated at 34.6 (95% CrI 12.00-145.00) for STEC-GE and 0.11 for STEC-associated HUS (95% CrI 0.08-0.20). German notification data underestimated STEC-associated HUS and STEC-GE incidences by factors of 1.8 and 32.3, respectively. Non-O157

STEC accounted for approximately 80% of all STEC-GE, half of all bloody STEC-associated diarrhoea and one-third of all STEC-associated HUS cases, hence contributing to STEC-illness to an even larger extent than previously estimated [13, 14].

Our incidence point estimates for STEC-GE and HUS are slightly lower than those published for Europe (47 and 0.15 respectively) [12], the United States (59 for STEC-GE) [13] and Canada (100 for STEC-GE) [14], but in keeping considering the degree of uncertainty accompanying our estimate. Particularly the incidence for O157-STEC-GE is lower than estimated for other European countries such as the Netherlands [20, 23], Denmark or the United Kingdom [20], and for the United States and Canada [12, 13]. In Germany, neither laboratory-based (passive) surveillance of STEC-GE nor (active) HUS-surveillance ever identified an outbreak with "classical" non-sorbitol fermenting O157-STEC comprising five persons or more, but did so for outbreaks with other serotypes [24, 25]. We are unaware of specific control plans for O157 STEC in animal reservoirs or the food-production chain that would explain this observation. Thus, our estimation of a comparatively low O157-STEC incidence adds additional weight to the view that O157-STEC pose a limited public health problem in Germany.

Of note, according to surveillance data (2008-2012, excl. 2011) reported to the European Centre for Disease Control and Prevention (ECDC) from other countries in the European Union, a slightly higher percentage (40%, 391/659) of all STEC identified in reported HUS patients belonged to non-O157 serogroups (data provided by ECDC extracted from The European Surveillance System - TESSy). This may indicate that non-O157 STEC contribute to STEC-GE incidence in other European countries even more than in Germany (where non-O157 STEC account for 80% of STEC-GE). Yet, only 33% of STEC-GE captured in surveillance systems in Europe were attributed to infection by non-O157 strains during the

study period [26, 27], underscoring the large degree of underascertainment of these STEC strains in GE patients in Europe. In recent years, the proportion of non-O157 STEC increased, likely indicating a more frequent use of serogroup-independent testing in Europe [26, 27]. In Germany, the contribution of the different non-O157 serogroups to STEC-illness remained fairly constant over the last 10 years (except in 2011) according to German surveillance data with serogroups O26, O103 being the most frequently isolated non-O157 STEC in children and O91 in adults [19, 28]. The numerous different non-O157 STEC vary dramatically in their virulence. On average though, they less frequently causes life-threatening HUS (in children) or disease outbreaks, and, importantly, their diagnosis currently is more complex, time-consuming and expensive. Thus, the question about the cost-effectiveness of screening for non-O157 has been raised [29, 30]. Apart from their markedly more frequent occurrence as etiologic agent in human GE than STEC O157 and their substantial contribution to the burden of bloody diarrhoea and HUS, new STEC strains are likely to evolve of which some will cause outbreaks (e.g., STEC O104:H4)[10]. For the latter reason alone we believe that modern STEC diagnosis and consequently surveillance systems should encompass timely detection of non-O157 STEC (including information on the serotype or other epidemiologically meaningful subtyping information), even in countries where STEC O157 appears to dominate.

Validity of risk model

Our “top-down” approach of estimating STEC incidence based on HUS notification data is new and we believe is advantageous for at least two reasons. Firstly, statutory HUS surveillance is more sensitive than STEC-GE surveillance and in conjunction with active paediatric HUS surveillance in Germany allowed for an accurate estimate of its underreporting. Furthermore, STEC aetiology in (paediatric) HUS patients has been

extensively studied in Germany [17, 18]. Taken together, HUS incidence and the individual contribution of O157 and non-O157 STEC could be estimated with little uncertainty.

Second, our estimations were purposively based solely on information on STEC in Germany, preventing the need of extrapolating from data gathered in other countries as another source of uncertainty.

By far the greatest source of uncertainty was the proportion of HUS among patients infected by a non-O157 STEC because it was based on small numbers. However, our estimate is in agreement with data from other countries [31]. Likewise, other findings are corroborated by data sources not used in our estimation. For example, the estimated proportion of non-O157 STEC-associated HUS (33%) is consistent with that observed in national HUS notification data during the study period (34%). Furthermore, the proportion of non-O157 serogroups in STEC-GE and STEC-associated bloody diarrhoea in Germany is consistent with both national notification data on STEC-GE and with a nationwide laboratory sentinel conducted at the beginning of the century in Germany [19].

Limitations

As previously published risk models, ours did not account for the effect of age because age-specific data was unavailable for many estimation steps. Yet, the serogroup-specific incidence for STEC-GE and the HUS-incidence vary with age. Most available studies focussed exclusively or primarily on children (who should have the highest true incidence of STEC-GE and HUS in Germany), which is why uncertainty of estimates is likely highest for adults.

In addition, non-O157 STEC consist of different pathogens with a variety of virulence genes and estimates for non-O157 relate to the (fairly stable) distribution of different strains in Germany and can be different in other countries. However, virulence based model input data for different non-O157 strains were not available in sufficient detail.

Furthermore, some input data of our risk model lack an evidence base as no study was available to support our assumptions, such as underreporting from non-PNCs and the adherence to lab guidelines for testing stool samples of gastroenteritis cases. These two parameters were among the top-3 influential parameters in the sensitivity analysis, warranting further data collection to decrease this uncertainty. Furthermore, not all literature sources used for our risk model distinguished between (rare) sf-O157 STEC and ("classic") non-sf O157 STEC. Because sf-O157 STEC infection progresses with a higher probability from diarrhoea to HUS [32], we slightly overestimated STEC-GE incidence of serogroup O157.

Completeness of HUS notification is likely overestimated in this study because concurrently conducted active paediatric surveillance included reminders of notification obligations when continuously monitoring HUS cases ascertained in the active system.

Conclusions

Statutory notification data largely underestimate STEC-GE in Germany, where STEC diagnosis is based on serogroup-independent testing for Shiga toxins or their encoding genes. Contribution of non-O157 serogroups to STEC GE incidence appear to be higher than previously estimated [13, 14], not only including a large number of mild illnesses but also half of all STEC-associated bloody diarrhoea cases. Considering European surveillance data on HUS, this finding is probably true for many other countries in Europe. Surveillance of HUS complements that of STEC-GE, not only by allowing for detecting outbreaks that otherwise go unrecognized [33] and reliably monitoring trends of STEC infection [34], but also by aiding in estimating STEC incidence estimating thereby helping to validate notification data.

Non-O157 STEC should be considered in parallel to STEC O157 when searching aetiology in patients with GE or HUS, and accounted for in modern surveillance systems for STEC illness.

Authors' contributions

DW and AK designed the study and developed the risk model. AK conducted the systematic review of previous evidence and input parameters and provided all figures and tables. MB and AH conducted the mathematical modelling. AK and DW wrote the manuscript. PH and the active HUS surveillance network provided the data for the first step of estimation. KS and AG provided input to the manuscript. All authors reviewed and approved the final manuscript.

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Conflict of Interests

We declare no competing interests.

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Tables

Table 1: Input parameters for the risk model to estimate true incidence of O157 and non-O157 STEC illness in Germany based on notification data of Haemolytic Uremic Syndrome (HUS)

Steps in estimation	Parameters	S[#]	Nɸ	Distribution*	Median	95% CrI	Source
1. HUS notifications	Incidence of notified cases	260	327 × 10^{8}‡	Gamma(260, 3×10^{-9})	8×10^{-7}	7×10^{-7} - 9×10^{-7}	German notification data
a. Adjustment for underreporting separately for cases treated in PNCs and non-PNCs	Proportion of HUS-notifications treated by PNCs	153	254	Beta(154, 102)	0.60	0.54 - 0.66	National active and passive surveillance, unpublished
	Completeness of HUS-notification from PNCs	153	183	Beta(154, 31)	0.83	0.78 - 0.88	National active and passive surveillance, unpublished
	Multiplication factor to extrapolate completeness of notification from PNCs to non-PNCs	-	-	Pert(0.1, 0.5, 1)	0.51	0.21 - 0.84	Assumption
b. Proportion of STEC-associated HUS among enteropathic HUS cases	Proportion of STEC-associated-HUS	327	394	Beta(328, 68)	0.83	0.79 - 0.86	Gerber et al. 2002
c. Proportion of O157 and non-O157 among STEC-associated HUS	Proportion of O157 in STEC-associated HUS	138	207	Beta(494, 239)	0.67	0.64 - 0.71	Gerber et al. 2002;
		355	524				Mellmann et al. 2008
d. Number of laboratory confirmed STEC-GE cases per HUS case	Proportion HUS among laboratory-confirmed STEC in O157	3	27	Beta(4, 25)	0.13	0.04 - 0.28	Werber et al. 2007
	Proportion HUS among laboratory-confirmed STEC in non-O157	2	149	Beta(3, 148)	0.02	0.00 - 0.05	Werber et al. 2007
e. Proportion of bloody diarrhoea in O157 and non-O157 among STEC-GE cases	Proportion of cases experiencing bloody diarrhoea in O157	10	27	Beta(11, 18)	0.38	0.22 - 0.56	Werber et al. 2007
	Proportion of cases experiencing bloody diarrhoea in non-O157	16	149	Beta(17, 134)	0.11	0.07 - 0.17	Werber et al. 2007
f. Underascertainment of bloody and non-bloody diarrhoea	Proportion of patients visiting physicians with bloody diarrhoea	21	41	Beta(22,21)	0.51	0.36 - 0.66	Haagsma et al. 2013
	Proportion of patients visiting physicians with non-bloody diarrhoea	458	1342	Beta(555, 1093)	0.34	0.31 - 0.36	Haagsma et al. 2013;
		96	304				Hauri et al. 2011
	Proportion of physicians taking lab samples from patients with bloody diarrhoea	10	20	Beta(11,11)	0.50	0.30 - 0.70	Haagsma et al. 2013
	Proportion of physicians taking lab samples from patients with non-bloody diarrhoea	155	456	Beta(170, 383)	0.31	0.27 - 0.35	Haagsma et al. 2013;
		14	95				Hauri et al. 2011
	Proportion of stool samples tested for STEC from patients with bloody diarrhoea	-	-	None	1.00	1.00 - 1.00	Kist et al. 2013
	Proportion of stool samples tested for STEC from patients with non-bloody diarrhoea	-	-	Pert(0.1, 0.8, 1)	0.74	0.37 - 0.96	Kist et al. 2013, assumption

[#] Nominator ɸ Denominator ‡ The unit of measurement is person-years-at-risk for this parameter

[*] For Gamma(r, λ) r equals s and λ equals $1/N$; For Beta(a, b), a equals Sum(s)+1 and b equals Sum(N)-Sum(s)+1

Table 2: Results of modelling true median annual incidence and cases number of O157 and non-O157 STEC illness in Germany based on notification data of Haemolytic Uremic Syndrome (HUS)

No.			Total	O157 total	O157 bloody GE	O157 non-bloody GE	non-O157 total	non-O157 bloody GE	non-O157 non-bloody GE
	HUS notifications	Median	65 (58 – 74)						
		*Incidence**	*0.08 (0.07 – 0.09)*						
2	Estimated true number of HUS cases	Median	108 (80 – 197)						
		*Incidence**	*0.13 (0.10 – 0.24)*						
3	Estimated true number of STEC-ass. HUS cases	Median	90 (66 – 164)	60 (44 – 110)			29 (21 – 54)		
		*Incidence**	*0.11 (0.08 – 0.20)*	*0.07 (0.05 – 0.13)*			*0.04 (0.03 – 0.07)*		
4	Estimated true number of laboratory confirmed symptomatic STEC cases	Median	2312 (954 – 8864)	486 (199 – 1705)	181 (63 – 678)	299 (116 – 1079)	1706 (577 – 7999)	189 (58 – 908)	1514 (513 – 7096)
		*Incidence**	*2.83 (1.20 – 10.80)*	*0.59 (0.24– 2.08)*	*0.22 (0.08 – 0.83)*	*0.37 (0.14 – 1.32)*	*2.09 (0.70 – 9.80)*	*0.23 (0.07 – 1.11)*	*1.85 (0.60 – 8.7)*
5	Estimated true number of symptomatic STEC cases	Median	28347 (10217 – 119041)	4969 (1835 – 19406)	730 (229 – 3037)	4171 (1449 – 16846)	22019 (6764 – 109046)	769 (211 – 3,925)	21192 (6481 – 105641)
		*Incidence**	*34.63 (12.00 – 145.00)*	*6.07 (2.2 – 23,7)*	*0.89 (0.28 – 3.71)*	*5.10 (1.80 – 20.60)*	*26.90 (8.00 – 133.00)*	*0.94 (0.26 – 4.80)*	*25,89 (8.00 – 129.00)*

*per 100,000

Figures

Figure 1: Modelling true annual incidence of O157 and non-O157 STEC illness in Germany based on notification data of Haemolytic Uremic Syndrome (HUS)

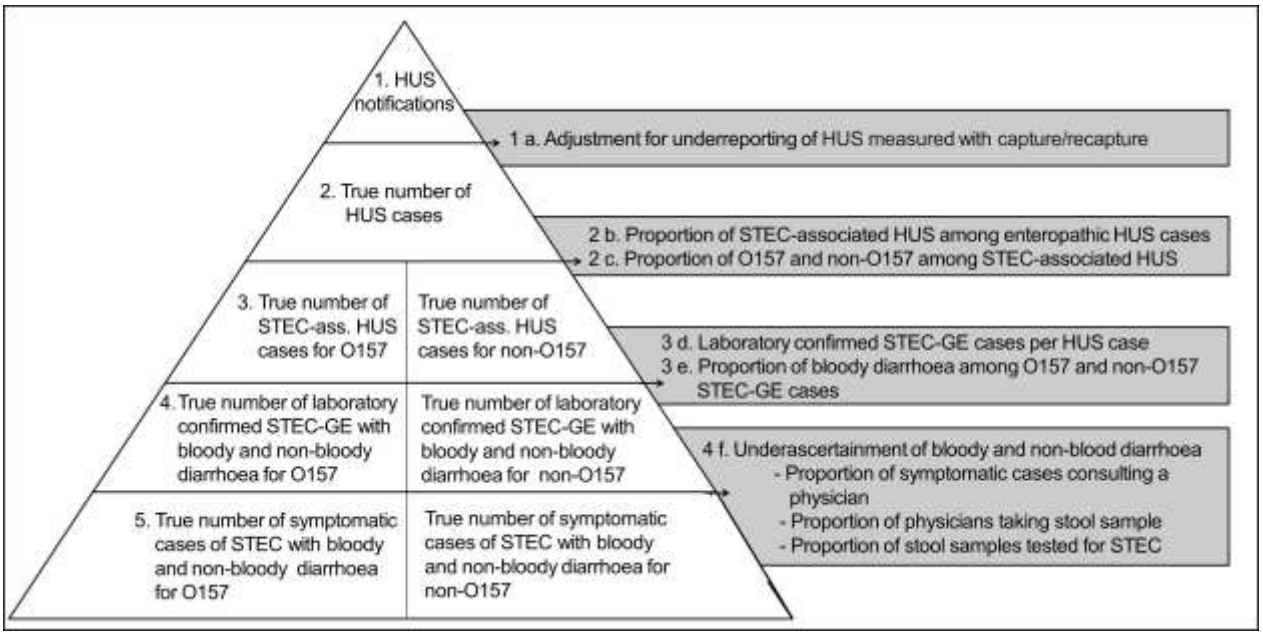


Figure 2: Results of the systematic review to identify input parameters for the estimation of the true incidence of O157 and non-O157 STEC illness in Germany based on notification data of Haemolytic Uremic Syndrome (HUS)

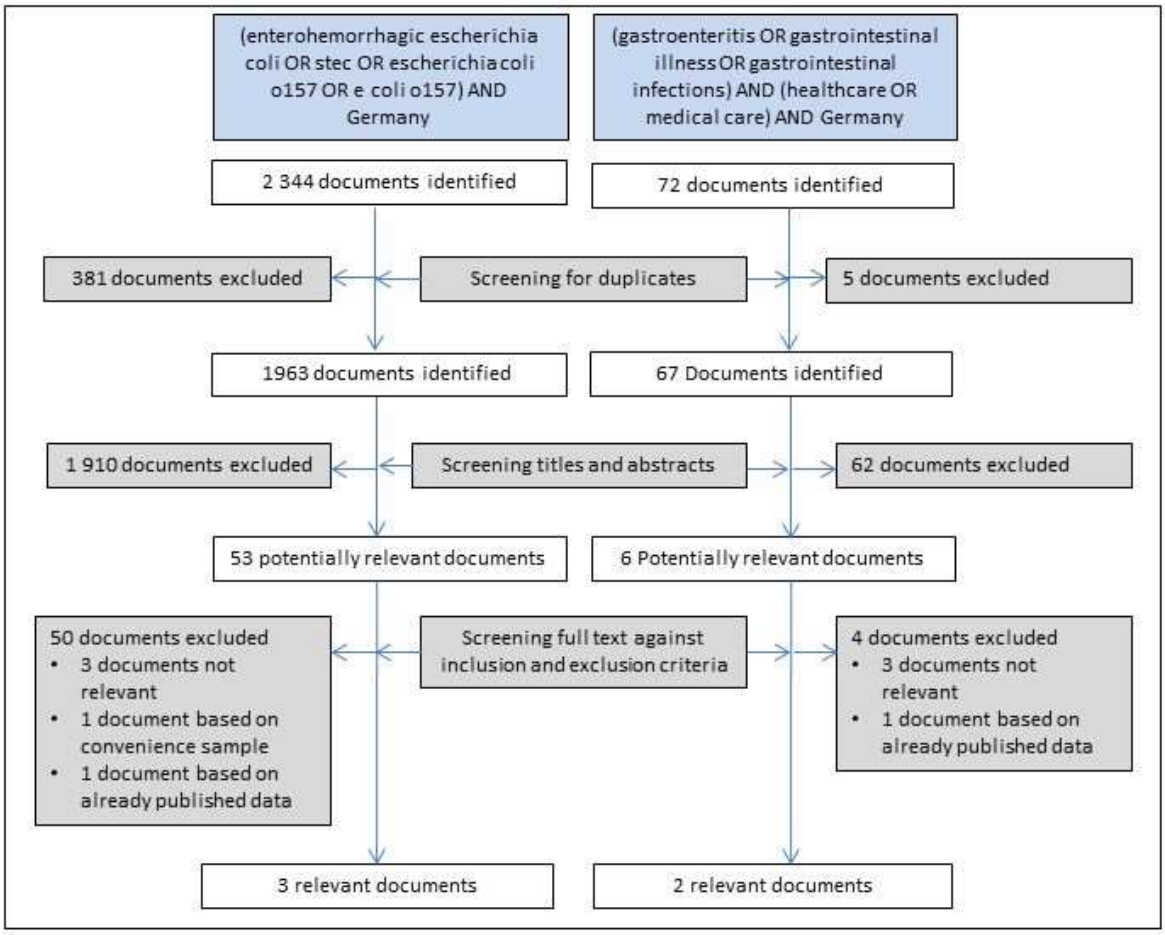
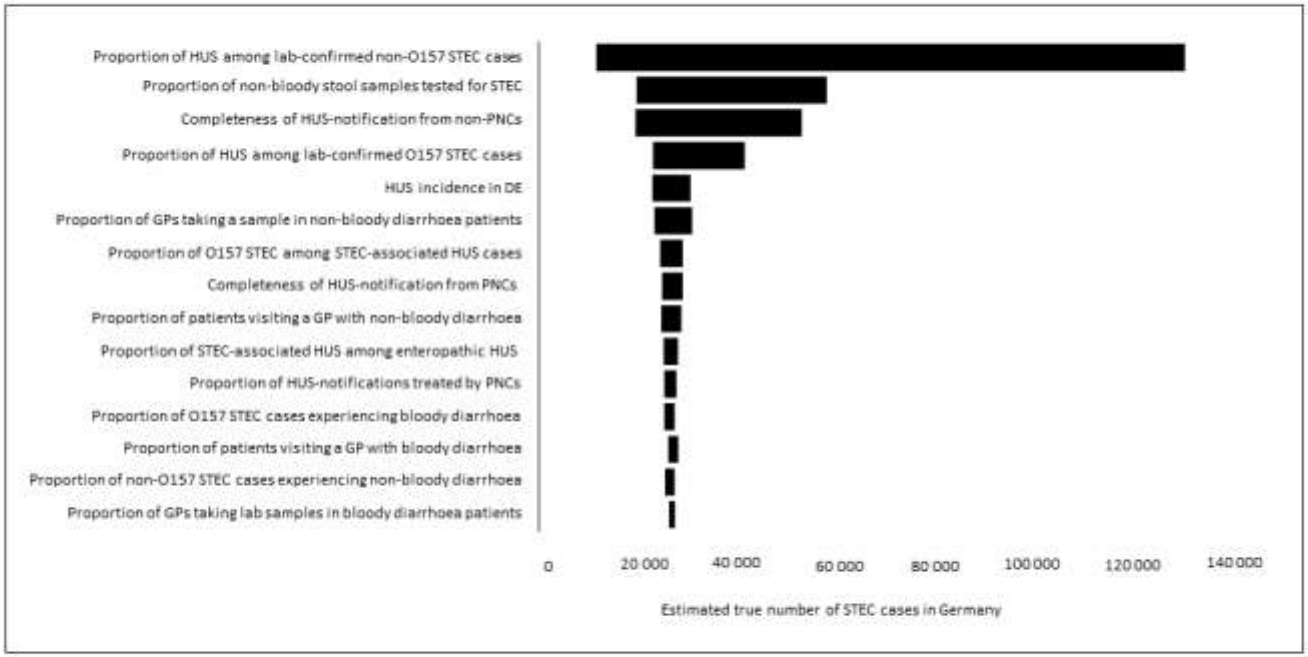


Figure 3: Sensitivity analysis of influence of input parameters on frequency of STEC-GE in Germany based on notification data of Haemolytic Uremic Syndrome (HUS)



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