Community Incidence of Campylobacteriosis and Nontyphoidal Salmonellosis, France, 2008–2013

Dieter C Cauteren, Henriette C de Valk, Cecile C Sommen, Lisa C King, Nathalie Jourdan- da Silva, François-Xavier Weill, Simon C Le Hello, Francis C Mégraud, Veronique C Vaillant, Jean C. C Desenclos

Community incidence of campylobacteriosis and non-typhoidal salmonellosis,

France, 2008-2013

D Van Cauteren [1,§] , H De Valk [1], C Sommen [1], LA King [1], N Jourdan-Da Silva [1], FX Weill [2], S Le Hello [2], F Mégraud [3], V Vaillant [1], JC Desenclos [1]

[1] French institute for public health surveillance, Department of Infectious Diseases, Saint Maurice, France

[2] Institut Pasteur, National reference centre for Salmonella, Unité des Bactéries Pathogènes Entériques, Paris, France

[3] National reference centre for Campylobacter and Helicobacter, University of Bordeaux, France

[§] Corresponding author:

Dieter Van Cauteren

Département des maladies infectieuses, Institut de Veille Sanitaire

12 rue du Val d'Osne

94 415 Saint-Maurice Cedex

France

Phone : 33 (0)1 41 79 67 31

Fax : 33 (0)1 41 79 67 69

d.vancauteren@invs.sante.fr

ABSTRACT

Community incidence estimates are necessary to assess the burden and impact of infections on health and to set priorities for surveillance, research, prevention and control strategies. The current study was performed to estimate the community incidence of campylobacteriosis and non-typhoid salmonellosis in France from the number of laboratory confirmed cases reported to the national reference centre (NRC). The probabilities of a case in the community visiting a doctor, having a stool sample requested, having a positive laboratory test and having the case reported to the NRC were estimated using data of national surveillance systems, national hospitalisation and health insurance databases and specific surveys informing about these parameters. Credible intervals were calculated using Monte Carlo simulation. In addition, we estimated the number of hospitalisations for both infections in France. The annual community incidence rate in France is estimated at 842 cases /100,000 (90%CrI 525 – 1,690) for campylobacteriosis and 307 cases/100,000 (90%CrI 173 – 611) for salmonellosis. The annual number of hospitalisations is estimated at 5,182 for campylobacteriosis and 4,305 for salmonellosis. These results illustrate the importance of community incidence estimates for burden of illness studies as the multiplication factors between cases reported to the NRC and cases in the community were high (115 for campylobacteriosis and 20 for salmonellosis). They are consistent with estimates reported in other countries indicating a high community incidence of campylobacteriosis and salmonellosis in France.

INTRODUCTION

In France, *Campylobacter* and non-typhoidal *Salmonella* (hereafter referred to as *Salmonella*) were estimated to be the two main causes of bacterial foodborne infection and hospitalisation (Vaillant *et al.*, 2004). Surveillance of both infections is based on two national reference centres (NRC) and their laboratory networks (King *et al.*, 2012, Jones *et al.*, 2014). These laboratory based surveillance systems depend on cases seeking medical care, having a stool sample prescribed, submitting a stool sample to the laboratory for microbiological testing, the identification of the pathogen, and the reporting of laboratory confirmed cases or submission of isolates for confirmation to the NRC. Therefore they allow us to monitor trends in incidence, human and microbiological characteristics, but not provide the number of cases that occur in the community, as only a fraction of the cases is reported. The knowledge of this number is important to produce disease burden estimates that are necessary to assess the impact of infections on health and to set priorities for surveillance, research, prevention and control strategies.

Several countries recently estimated community incidence of campylobacteriosis and salmonellosis via a pyramid reconstruction approach in which the different steps that must occur for a symptomatic infection in the community to be reported in a laboratory based surveillance system are estimated (Scallan *et al.*, 2011; Kubota *et al.*, 2011; Thomas *et al.*, 2013; Kirk *et al.*, 2014). Since 2008, several surveys have been carried out in France in the general population, among physicians and laboratories to obtain specific information that was lacking to estimate the proportion of cases (un)recognized at each surveillance step. The current study was performed to estimate the community incidence of campylobacteriosis and salmonellosis from the number of laboratory confirmed cases reported to the NRC in mainland France (overseas French territories not included, hereafter referred to as France). In addition, we estimated the number of hospitalisations for both infections.

MATERIAL AND METHODS

The parameters needed to estimate the community incidence were: the proportion of cases consulting a physician; the proportion of cases for whom a stool sample was requested; the proportion of stool samples tested for each pathogen; the diagnostic sensitivity for each pathogen and the completeness of case reporting to the NRC. We made an inventory of data in national surveillance systems, national databases and specific surveys informing about these parameters.

Proportion of cases consulting a physician

Healthcare seeking behaviour for acute gastroenteritis (AG) in France was assessed in a population based survey carried out in 2009-2010 and identified duration of illness as the most important factor associated with consultation (Van Cauteren *et al.*, 2012). Therefore we estimated specific proportions of laboratory confirmed campylobacteriosis or salmonellosis cases who had short (1-2 days), medium (3-5 days) and long (more than 5 days) duration of illness. We used data from a case control study for campylobacteriosis (Gallay *et al.*, 2008) and from outbreak investigations for salmonellosis (unpublished data, InVS). For the outbreak investigation data duration of diarrhoea was used as a proxy for the duration of illness. Consultation rates for short, medium and long duration of illness estimated in the population based survey were then applied to the proportion of reported cases in each category to estimate the proportion of cases of campylobacteriosis and salmonellosis consulting a physician.

Proportion of cases having a stool culture requested

Bloody diarrhoea, a long duration of illness before consultation and occurrence in the summer period were identified as the main factors associated with an increased stool culture request in a survey among general practitioners (GP) in France in 2013-2014 (Van Cauteren *et al.*, 2015). Two different approaches, taking into account seasonality and bloody diarrhoea, were used to estimate the proportion of cases of campylobacteriosis and salmonellosis consulting for their illness that had a stool sample requested. The first approach was based on the proportion of stool samples requested by GP for AG cases consulting in the summer period when incidence of both infections is highest (Van Cauteren *et al.*, 2015). The second approach was based on the proportion of laboratory confirmed campylobacteriosis or salmonellosis cases that had bloody diarrhoea (Gallay *et al.*, 2008; unpublished outbreak investigation data, InVS) and applied stool sample request rates for bloody and non-bloody diarrhoea estimated in the GP survey.

Proportion of stool samples tested

Laboratory practices regarding testing for *Campylobacter* were assessed in a national quality assurance (NQA) survey among the 2,824 registered bacteriology laboratories in France in 2010 (unpublished data, InVS). This survey indicated that 99% of the laboratories used culture as the diagnostic method for *Campylobacter* infection. It also indicated that 47% of the laboratories tested all stool samples submitted for culture for *Campylobacter*, 35% tested depending on different criteria such

as a specific request for testing, the age of the patient or the presence of visible blood or mucus, and 18% of the laboratories did not perform testing for *Campylobacter*. For *Salmonella*, expert consultation estimated that all stool samples submitted for culture are routinely tested in France.

Diagnostic sensitivity

The sensitivity of culture for *Campylobacter* testing was estimated in a study carried out by the NRC in 2009 (Bessède *et al.*, 2011). On 242 stool specimens, 2 culture methods (on selective and non-selective media with filtration) were compared to 2 molecular methods and 3 immunoenzymatic methods. This study estimated the sensitivity of the 2 culture methods at 55% and 65%. For *Salmonella*, expert consultation estimated that the sensitivity of culture was close to 100%.

Completeness of case reporting

In France, surveillance of both infections is based on voluntary reporting of laboratory confirmed cases by public hospital and private clinical laboratories to the NRC. The number of participating laboratories is about 1,500 for the *Salmonella* network and 350 for the *Campylobacter* network. Both networks allow the monitoring of epidemiological and microbiological characteristics of cases and pathogen (Jones *et al.*, 2014; King *et al.*, 2012). The completeness of case reporting is defined as the match between the number of cases reported to the NRC and the total number of cases that are laboratory confirmed in all bacteriological laboratories in France. The total number of laboratory confirmed cases of salmonellosis (in 2008) and campylobacteriosis (in 2009) were estimated via 2 NQA surveys carried out among all registered bacteriology laboratories in France in 2009 (3,046 laboratories) and 2010 (2,824 laboratories). The completeness of case reporting was estimated at 66% for the *Salmonella* network (Carrillo-Santisteve *et al.*, 2010) and at 21% for the *Campylobacter* network (unpublished data, InVS).

Number of hospitalisations

The national hospital information system (PMSI: Programme de Médicalisation du Système d'Information) was used to estimate the number of cases of campylobacteriosis or salmonellosis hospitalised for their illness. This database records administrative and medical information of all public and private hospitals in France. For each hospitalisation, discharge diagnoses are coded in the database according to the international classification of diseases (ICD-10). Age, gender, length of stay and residential location are also recorded. We selected in the PMSI all records with a discharge date between January 2008 and December 2013 containing codes (principal, related or secondary

diagnoses) for campylobacteriosis (A04.5) or salmonellosis (A02.0 to A02.9). Trends over time, age and gender of the PMSI records were compared to NRC surveillance data in order to assess the validity of the PMSI database to estimate the number of hospitalisations for both pathogens (data not shown). We assumed that all stool samples of cases hospitalised for both pathogens were tested for both pathogens. We applied a diagnostic sensitivity of 55 to 65% for *Campylobacter* and 90% to 100% for *Salmonella* to correct for underdiagnosis.

All data sources were explored and results for each parameter were discussed by a multidisciplinary study committee. For each parameter a minimum and maximum was chosen and a Beta distribution ($\alpha=\beta=2$) was used to incorporate uncertainty and variability. This symmetric unimodal distribution with the mean as the most likely value and a range defined between the minimum, maximum was defined as an appropriate distribution for the different parameters. A number of cases in the community was generated via Monte Carlo simulations (10,000 iterations). Median values are reported and the range between the 5 and 95 percentiles of the output distribution was used to define a 90% credible interval (90%CrI). The software package R was used for simulations.

RESULTS

Proportion of cases consulting a physician

The proportion of laboratory confirmed cases who had short, medium or long duration of illness were estimated at 2%, 27% and 71% for campylobacteriosis and 4%, 47% and 49% for salmonellosis. Consultation rates were estimated in the population based survey (95% confidence Interval) at 10-26% for cases of AG with a short duration of illness, 30–54% for medium and 51–90% for long duration of illness (Table 1).

Proportion of cases having a stool culture requested

The GP survey indicated that in the summer period the proportion of cases of AG having a stool culture requested was 10%. This survey also indicated that a stool sample was requested for 49.2% of the AG cases with and 3.8% of the AG cases without bloody diarrhoea. The proportion of laboratory confirmed salmonellosis or campylobacteriosis cases having bloody diarrhoea was 43% and 47% respectively. Given these data the proportion of cases consulting for their illness that had a stool culture requested was estimated to be between 10 and 25% for *Campylobacter* and between 10 and 23% for *Salmonella*.

Proportion of stool samples tested, diagnostic sensitivity and completeness of case reporting

We assumed that between 25 and 75% of the stool samples were tested in the 35% of the laboratories in the NQA survey that indicated testing for *Campylobacter* depending on different criteria. The total proportion of stool samples tested for *Campylobacter* was therefore estimated to be between 56% and 73%. The sensitivity of culture for *Campylobacter* was estimated to be between 55 and 65%. For *Salmonella* it was assumed that almost all stool samples are routinely tested (90-100%) with a high diagnostic sensitivity (90-100%). The completeness of case reporting was estimated at 21% for the *Campylobacter* network and 66% for the *Salmonella* network.

Community incidence

Between 2008 and 2013, the mean number of cases annually reported by the NRC in France was 4,608 for campylobacteriosis and 9,827 for salmonellosis. Taking into account the parameters described above, the annual number of community cases in France was estimated at 528,780 (90%CrI 329,745 – 1,060,616) for campylobacteriosis and 192,450 (90%CrI 108,445 – 383,362) for salmonellosis (Figure 1). Considering the population of metropolitan France (62,765 million in 2010), the annual community incidence is estimated to be 842 cases/100,000 (90%CrI 525 – 1,690) for campylobacteriosis and 307 cases/100,000 (90%CrI 173 – 611) for salmonellosis.

Hospitalisations

On average, between 2008 and 2013, 3,088 campylobacteriosis and 4,194 salmonellosis associated hospitalisations were annually identified in the PMSI database. After correcting for the diagnostic sensitivity of stool culture the mean annual number of hospitalizations for campylobacteriosis was estimated at 5,182 (min 4,750; max 5,614) and 4,305 (min 4,194; max 4,415) for salmonellosis, resulting in an annual incidence rate of 8.3 hospitalised campylobacteriosis cases/100,000 and 6.9 hospitalised salmonellosis cases/100,000 respectively.

DISCUSSION

We estimated that 528,780 cases (90%CrI 329,745–1,060,616) of campylobacteriosis and 192,450 cases (90%CrI 108,445–383,362) of salmonellosis occur each year in France. The multiplication factors between cases ascertained through surveillance and cases in the community were 115 for campylobacteriosis and 20 for salmonellosis. The lower proportion of stool samples tested, the lower

diagnostic sensitivity, together with a lower completeness of case reporting, explain the higher multiplication factor for campylobacteriosis than for salmonellosis.

Accurately estimating community incidence using a pyramid reconstruction approach is challenging and depends on data sources informing about the different parameters. Duration of illness was derived from laboratory-confirmed cases reported to the NRC and was used in the calculations to estimate the proportion of cases consulting for their illness. Laboratory-confirmed cases may not be representative of all cases of illness and may over-represent those with severe illness (e.g., a long duration of illness) who are more likely to consult and have a stool culture requested. Therefore, we may have overestimated the proportion of cases that consulted, resulting in an underestimate of the true number of community cases. A similar approach has been used in other studies using a pyramid reconstruction model (Scallan et al., 2011; Haagsma et al., 2013; Thomas et al., 2013; Kirk et al., 2014). However, categories (bloody diarrhea and/or duration of illness or duration of diarrhea) and data sources (case–control studies, outbreak investigation, literature) were different between these studies. It is important to notice that these differences may have a major impact on the estimates of the proportion of cases consulting and thus on the final community incidence estimate. In a French case–control study (Gallay et al., 2008), duration of diarrhea of campylobacteriosis cases was shorter than duration of illness. The use of duration of diarrhea rather than illness for campylobacteriosis would have resulted in a higher proportion of cases classified as having a short duration of illness, seeking less medical care. This would have led to a higher estimated incidence (1091 cases versus 842 cases/100,000) and also a much higher degree of uncertainty (90%CrI 535–3303 versus 525–1690 cases/100,000).

The proportion of reported cases with bloody diarrhea in our laboratory-based surveillance systems may be overestimated. Therefore, the proportion of stool samples prescribed for both pathogens using this approach (23% and 25%) was considered a maximum value. Consultations for less severe AG illness, not related to campylobacteriosis or salmonellosis, and for which less laboratory tests are requested, may occur in the summer period. Thus, the proportion estimated among AG cases during the summer period in the GP survey may underestimate the real proportion of stool samples prescribed. The proportion of stool samples prescribed using this approach (10%) was therefore considered as a minimum value.

Culture is currently the main diagnostic method used in France for Campylobacter and is considered to be technically more demanding than for Salmonella. Therefore, many laboratories do not routinely culture for Campylobacter. Recent surveys among clinical laboratories in the United States have shown that, although almost all laboratories routinely included testing for Campylobacter using culture methods, procedures and laboratory practices differ widely, likely resulting in a lower sensitivity compared to a reference laboratory (Hurd et al., 2012; M'ikanatha et al., 2012). We used the sensitivity of Campylobacter culture testing estimated from a study of the NRC on cases in the university hospital where the NRC is located (Bessède et al., 2011). In this study, culture was carried out on fresh stools within 4 h after arriving in the laboratory. Outside the hospital or study setting, transport toward routine diagnostic laboratories and nonoptimal laboratory practices may result in a lower diagnostic sensitivity for Campylobacter in France than the sensitivity estimated in the NRC survey, resulting in an underestimate of the true number of community cases.

The estimated incidence of Salmonella and Campylobacter were within the range of those reported by other countries that used a similar pyramid reconstruction approach (209–450 cases/100,000 for Salmonella and 440–1500 cases/100,000 for Campylobacter) (Kubota et al., 2011; Scallan et al., 2011; Havelaar et al., 2012; Thomas et al., 2013; Kirk et al., 2014). For Campylobacter there was a greater variability in the incidence estimates between countries that may reflect real differences in incidence rather than in methodology used (Vally et al., 2009).

We estimated that around 4300 hospitalizations for salmonellosis and 5200 hospitalizations for campylobacteriosis occur each year in France. These numbers may be underestimated as hospitalizations may have occurred without appropriate diagnostic tests being requested or the ICD-10 coding may have been inaccurate. We corrected for diagnostic sensitivity, but we decided not to assume an additional underdiagnosis multiplier of 2 (CrI1-3), which has been assumed in some studies (Scallan et al., 2011; Kirk et al., 2014). For every case hospitalized, it was estimated that there are 45 salmonellosis cases and 102 campylobacteriosis cases in the community. Despite differences in methodologies, these results are consistent with findings in the United States (Scallan et al., 2011), the Netherlands (Havelaar et al., 2012), and Australia (Kirk et al., 2014), indicating a larger proportion of hospitalization for salmonellosis (factor 19–53) than for campylobacteriosis (factor 56–100).

Our results illustrate that healthcare-seeking behavior, laboratory practices, and reporting of laboratory-confirmed infections are important country-specific and pathogen-specific parameters that need to be taken into account for the estimation of community incidences and the interpretation of the number of reported cases in laboratory-based surveillance systems. Our results indicate a high number of community cases and hospitalizations for both infections in France. The findings suggest a high economic and human cost of these diseases and will help to set priorities for surveillance, prevention, and control strategies.

Acknowledgments

We thank all corresponding laboratories for sending isolates or reporting laboratory confirmed cases to the French NRC.

We thank Javier Nicolau and Laure Fonteneau for their support with data extraction from the national databases.

Disclosure Statement

No competing financial interest exists.

References

Bessède E, Delcamp A, Sifre E, Buissonniere A, Megraud F. New methods for detection of campylobacters in stool samples in comparison to culture. J Clin Microbiol 2011;49:941-944.

Carrillo-Santisteve P, Jourdan-Da Silva N, Weill FX, Le Hello S, Fromage M, de Valk H. Completeness of reporting to the voluntary Salmonella surveillance system in France,2008. European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE), Lisbon, Portugal, 2010

Gallay A, Bousquet V, Siret V, Prouzet-Mauléon V, Valk Hd, Vaillant V, Simon F, Le Strat Y, Mégraud F, Desenclos JC. J Infect Dis. 2008;197:1477-1484.

Haagsma JA, Geenen PL, Ethelberg S, Fetsch A, Hansdotter F, Jansen A, Korsgaard H, O'Brien SJ, Scavia G, Spitznagel H, Stefanoff P, Tam CC, Havelaar AH; Med-Vet-Net Working Group. Community incidence of pathogen-specific gastroenteritis: reconstructing the surveillance pyramid for seven pathogens in seven European Union member states. Epidemiol Infect 2013;141:1625-1639.

Havelaar AH, Haagsma JA, Mangen MJ, Kemmeren JM, Verhoef LP, Vijgen SM, et al. Disease burden of foodborne pathogens in the Netherlands, 2009. Int J Food Microbiol 2012;156:231-238.

Havelaar AH, Ivarsson S, Lofdahl M, Nauta MJ. Estimating the true incidence of campylobacteriosis and salmonellosis in the European Union, 2009. Epidemiol Infect 2013;141:293-302.

Hurd S, Patrick M, Hatch J, Clogher P, Wymore K, Cronquist AB, Segler S, Robinson T, Hanna S, Smith G, Fitzgerald C. Clinical laboratory practices for the isolation and identification of Campylobacter in Foodborne Diseases Active Surveillance Network (FoodNet) sites: baseline information for understanding changes in surveillance data. Clin Infect Dis 2012;54 Suppl 5:S440-S445.

Jones G, Le HS, Jourdan-da SN, Vaillant V, de VH, Weill F, et al. The French human Salmonella surveillance system: evaluation of timeliness of laboratory reporting and factors associated with delays, 2007 to 2011. Euro Surveill 2014;19(1)

King A, Mégraud F. Surveillance of human campylobacter infections, France, 2003-2010. Bulletin Epidémiologique Hebdomadaire 2012 (Hors-série): 11-13

Kirk M, Ford L, Glass K, Hall G. Foodborne illness, australia, circa 2000 and circa 2010. Emerg Infect Dis 2014;20:1857-1864.

Kubota K, Kasuga F, Iwasaki E, Inagaki S, Sakurai Y, Komatsu M, Toyofuku H, Angulo FJ, Scallan E, Morikawa K. Estimating the burden of acute gastroenteritis and foodborne illness caused by Campylobacter, Salmonella, and Vibrio parahaemolyticus by using population-based telephone survey data, Miyagi Prefecture, Japan, 2005 to 2006. J Food Prot. 2011 Oct;74:1592-1598.

M'ikanatha NM, Dettinger LA, Perry A, Rogers P, Reynolds SM, Nachamkin I. Culturing stool specimens for Campylobacter spp., Pennsylvania, USA. Emerg Infect Dis 2012;18:484-487.

Scallan E, Hoekstra RM, Angulo FJ, Tauxe RV, Widdowson MA, Roy SL, Jones JL, Griffin PM. Foodborne illness acquired in the United States--major pathogens. Emerg Infect Dis 2011;17:7-15.

Thomas MK, Murray R, Flockhart L, Pintar K, Pollari F, Fazil A, Nesbitt A, Marshall B. Estimates of the burden of foodborne illness in Canada for 30 specified pathogens and unspecified agents, circa 2006. Foodborne Pathog Dis 2013;10:639-648.

Vaillant V, de Valk H, Baron E, Ancelle T, Colin P, Delmas MC, Dufour B, Pouillot R, Le Strat Y, Weinbreck P, Jougla E, Desenclos JC. Foodborne infections in France. Foodborne Pathog Dis 2005;2:221-232.

Vally H, Hall G, Scallan E, Kirk MD, Angulo FJ. Higher rate of culture-confirmed Campylobacter infections in Australia than in the USA: is this due to differences in healthcare-seeking behaviour or stool culture frequency? Epidemiol Infect 2009;137:1751-1758.

Van Cauteren D, de Valk H, Vaux S, Le Strat Y, Vaillant V. Burden of acute gastroenteritis and healthcare-seeking behaviour in France: a population-based study. Epidemiol Infect 2012;140:697-705

Van Cauteren D, Turbelin C, Fonteneau L, Hanslik T, de Valk H, Blanchon T. Physician practices in requesting stool samples for patients with acute gastroenteritis, France, August 2013 – July 2014. Epidemiol Infect 2015. doi:10.1017/S0950268814003884

Figure 1. Distribution of the estimates of the annual number of cases of salmonellosis and campylobacteriosis, 10,000 iterations, France, 2008-2013

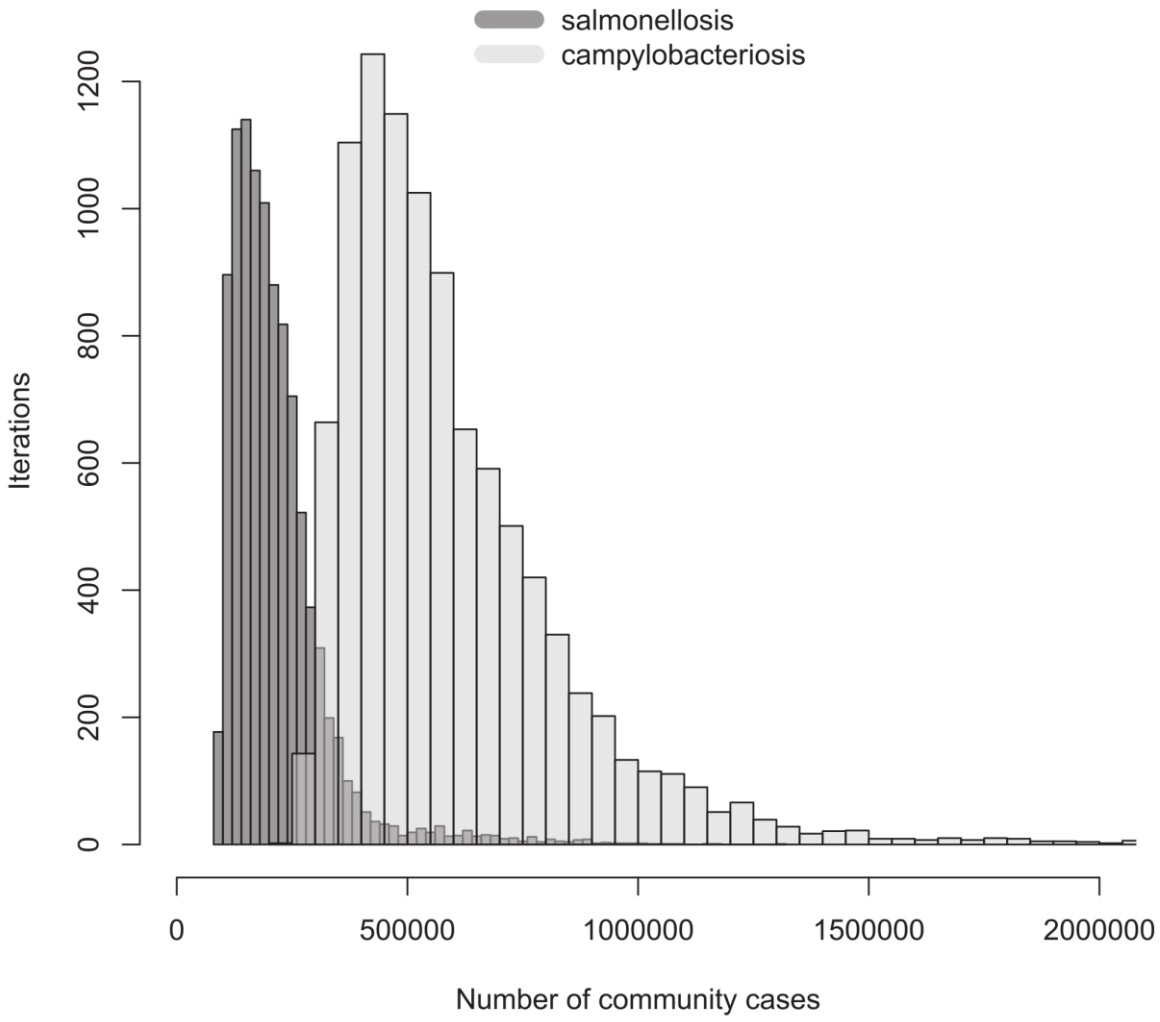

Table 1. Parameters used to estimate the community incidence of *Campylobacter* and *Salmonella*, France, 2008-2013.

Parameters	***Campylobacter***	***Salmonella***
Annual number of cases reported by the NRC	4 608	9 827
Completeness of case reporting to the NRC	21%	66%
Sensitivity of laboratory diagnosis	55 - 65%	90 - 100%
Proportion of stool samples tested	56 - 73%	90 - 100%
Proportion of stool samples requested among consulting cases	10 - 25%	10 - 23%
Proportion of cases consulting a physician:		
duration of illness : 1-2 days	10 - 26 %	
duration of illness : 3-5 days	30 - 54 %	
duration of illness : ≥ 6 days	51 - 90 %	