UCL Université catholique de Louvain

Faculté de santé publique (FSP)

Estimation de la vraie incidence de la campylobactériose, listériose, salmonellose et shigellose en Belgique

Mémoire réalisé par
Kim Lothaire

Promotrice
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Niko Speybroeck

Année académique 2017-2018
Master en sciences de la santé publique

Finalité spécialisée

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LE PLAGIAT

Je déclare sur l'honneur que ce mémoire a été décrit de ma plume, sans avoir sollicité d'aide extérieure illicite, qu'il n'est pas la reprise d'un travail présenté dans une autre institution pour évaluation, et qu'il n'a jamais été publié, en tout ou en partie. Toutes les informations (idées, phrases, graphes, cartes, tableaux...) empruntées ou faisant référence à des sources primaires ou secondaires sont référencées adéquatement selon la méthode universitaire en vigueur. Je déclare avoir pris connaissance et adhérer au Code de déontologie pour les étudiants en matière d'emprunts, de citations et d'exploitation de sources diverses et savoir que le plagiat constitue une faute grave sanctionnée par l'Université catholique de Louvain.

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LIST OF ABBREVIATIONS

Camp.: Campylobacter

DM: Decision Maker

FBDs: Foodborne diseases

FERG: Foodborne Disease Burden Epidemiology Reference Group

List.: Listeria

MF: Mulplication Factor

Salm.: Salmonellose

Shig.: Shigellose

SEJ: Structured Expert Judgment

SNL: Sentinel Network of Laboratories

NRC: National Reference Centre

UA: Under-ascertainment

UE: Underestimation

UR: Under-reporting

WHO: World Health Organization

ABSTRACT

Background: Foodborne diseases (FBD's) are known to cause important morbidity and mortality with a significant socio-economic impact worldwide. The incidence of certain diseases causing gastroenteritis disorders such as campylobacteriosis, listeriosis, salmonelosis and shighellosis are underestimated in Belgium. This underestimation (UE) results from under-ascertainment (UA) and under-reporting (UR) of the number of cases. The objectives of this study are: 1) to quantify the UE of campylobacteriosis, listeriosis, salmonellosis and shigellosis reported cases in Belgium through designing of multiplication factors (MFs) and; 2) to estimate the true incidence of these FBDs in Belgium in 2014 by using the previously MFs.

Methods: To quantify UA and UR of the selected FBDs, adapted Delphi and Cooke's methods of expert elicitation were used. Selected Belgian experts firstly answered to 12 calibrations questions, allowing to weight their future answers based on their performance, then experts answered to the target questions, *i.e.* directly linked with the parameters of interest. Finally, they received anonymous answers of the whole panel of experts and had the possibility to adapt their answers. Final probabilities of UA and UE were calculated based on a performance weight (PM) and equal weight (EW) schemes using Excalibur software. True incidence was estimated by multiplying reported incidence in 2014 by the previously calculated MFs.

Results: 10 experts contributed at the whole study. We observed a major difference between the multiplication factors using the EW or PW approach; this has implications for estimating the true incidence for each pathogen. MFs based respectively on the EW and the PW are estimated for the camplylobacteriosis at 50.5 vs 23.9, for the listeriosis at 25.9 vs 8.4, for the salmonellosis at 30.6 vs 22.6 and for the shigellosis at 66.4 vs 53.8. The true incidence (per 100 000 inhabitants) based respectively on the EW and the PW are estimated for the camplylobacteriosis at 3671.12 vs 1735.49, for the listeriosis at 13.97 vs 4.55, for the salmonellosis at 796.55 vs 589.44 and for the shigellosis at 238.08 vs 192.82.

Conclusion: The limited number of experts and a wide variability in their responses result in a high degree of uncertainty of the multipliers. Despite these limitations, the panel of experts, by the method of elicitation, agrees that there is an UE of reported cases of Campylobacter, Listeria, Salmonella and Shigella in Belgium.

Key-words: foodborne pathogen, expert elicitation, true incidence

INTRODUCTION

Foodborne diseases (FBDs), defined as diseases caused by infectious or chemical agents that contaminate water or food, are known to cause important morbidity and mortality with a significant socio-economic impact worldwide [1]. Most of these diseases result in gastroenteritis but the infections can also cause more serious symptoms such as chronic neurological and immunological disorders and even death. Campylobacteriosis, listeriosis, salmonellosis and shigellosis are amongst the pathogens with high public relevance in Belgium [1,2].

Campylobacteriosis is mainly caused in humans by Gram-negative bacilli *Campylobacter jejuni* and *Campylobacter coli* who contaminate undercooked or raw meat, shellfish products and contaminated milk. The main symptoms reported are stomach cramps and diarrhoea but fever and headache can also occur [3-5]. The duration of the illness is about one week [2,4,6].

Listeriosis is caused in humans by the Gram-positive bacillus *Listeria monocytogenes*. High resistance to extreme conditions makes it a pathogen difficult to control [7-9].
For immunocompetent people, *L. monocytogenes* usually only causes gastroenteritis-like symptoms but can lead to serious or life-threatening consequences (septicemia, neuromeningeal infections) for populations at-risk [8-11].

Salmonellosis is caused by a Gram-negative bacillus transmitted by ingestion of contaminated food (eggs, milk, undercooked or raw meat) [2,9,12]. Resistant in dry and wet environments, this bacteria causes mild symptoms in humans such as abdominal pain, fever, diarrhoea or vomiting but can, in case of infection with *Salmonella typhi* or *paratyphi*, cause neurological, digestive and hemorrhagic disorders [2]. The evolution of the illness is often spontaneously resolving with disappearance of fever and diarrhoea in 72 hours [9].

Shigellosis is caused by a Gram-negative bacillus and is transmitted to humans by ingestion of contaminated food or water or by oro-faecally way [13,14]. This bacteria is characterized by the production of a toxin responsible for intense tissue inflammation causing mild to severe diarrhoea symptoms, nausea and vomiting [13,14]. The duration of the illness is between 7 and 10 days but in case of metabolic disorders or sepsis, the duration can last longer [9].

It is noteworthy however that the number of infectious disease known cases is only the tip of iceberg so that their true incidence is underestimated by the reported data [15]. Underestimation is the contribution of under-ascertainment (UA) and under-reporting (UR). UA reflects the symptomatic individuals who are not known by the healthcare system because of lack of medical advice (general practitioner or hospital); reasons for not attending healthcare services are multiple, including poor health literacy, cultural or religion factors, legal, administrative or financial barriers [16]. UR includes cases with medical contact but incorrectly diagnosed, classified or reported to the authorities [17]. UR may arise in cases of inadequate diagnostic tools, in case of lack of knowledge of which tests to perform or which diseases to report and how [16].

In 2007, the World Health Organization (WHO) established a task force, composed of experts, the Foodborne Disease Burden Epidemiology Reference Group (FERG) in order to improve the food safety. Their estimates of the global burden of FBDs were reported in 2015 as a basis for further studies [1]. These estimates were considered in fact as underestimates because of limitations essentially due to uncertainties in the data provided by the different countries [18]. Moreover, the degree of underestimation varies by pathogen and by country due to differences in health care and laboratory techniques [15].

Therefore, facing the lack of reliability of the data due to societal limitations such as sanitation or public health system, WHO organized a structured expert judgment (SEJ) elicitation in order to access judgments from panels of experts about foodborne disease and use their judgments as scientific data [19,20]. In many fields of science, expert elicitation appears as a scientific consensus methodology, allowing to quantify uncertainty of target variables.

Several different elicitation protocols exist. One method is referred to as mathematical aggregation. The most well-known is the classical model, proposed by Cooke [21] and consists to score the expert's performances on the basis of information and calibration (or statistical accuracy) [22]. Another model, the Sheffield method is referred to as behavioral aggregation based on a face to face discussion and interaction between the different experts [23]. The Delphi method combines mathematical and behavioral aggregation; via a facilitator, the experts receive an anonymous feedback from the other group members and have the possibility to adapt their answers [23,24].

The objectives of this study are: 1) to quantify the underestimation of campylobacteriosis, listeriosis, salmonellosis and shigellosis reported cases in Belgium by using expert elicitation and designing of multiplication factors and; 2) to estimate the true incidence of these FBDs in Belgium in 2014 by using the previously calculated multiplication factors.

METHODS

1. *Pathogens*

The pathogens selected for this study were Campylobacter spp., Listeria spp., Salmonella spp. and Shigella spp. because of their public health importance and their reputation to be mainly foodborne.

2. *Public Health surveillance data*

In Belgium, human cases due to foodborne pathogens are reported to the Belgian Scientific Institute (WIV-ISP), newly Sciensano; for Listeria, Salmonella and Shigella, they are notified to the National Reference Centre (NRC) from Belgian laboratories and for Campylobacter they are collected by the Belgian Sentinel Network of Laboratories (SNL) created in 1983 that covers about 60% of Belgian laboratories.

3. *Surveillance pyramid equation*

To estimate the true incidence of disease for the selected pathogens in Belgium and correct the reported number of cases for under-ascertainment and underreporting, we have calculated multiplication factors. This was made by reconstructing the surveillance pyramid as described by Haagsma et al [15] (Figure 1).

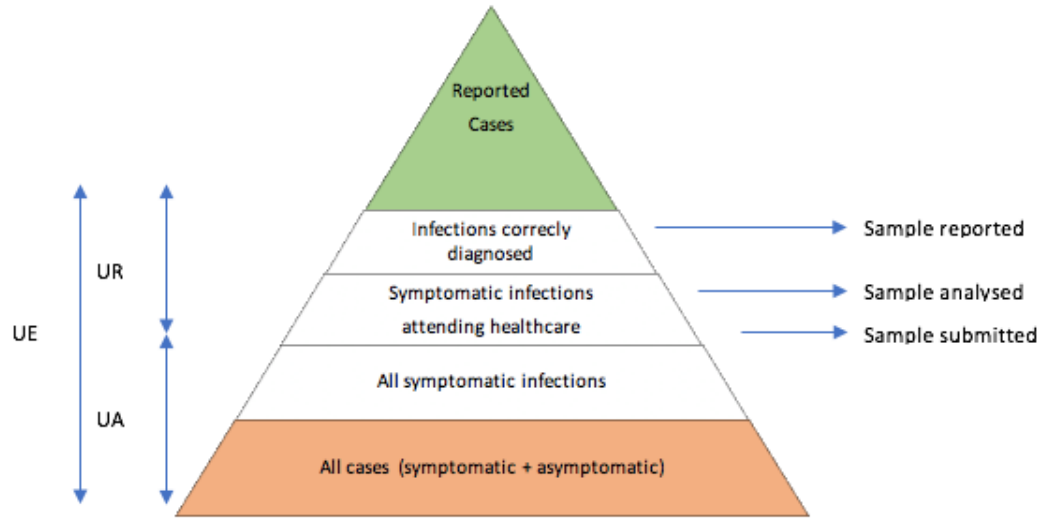

Figure 1. The surveillance disease pyramid.
UE = underestimation ; UR = underreporting ; UA = under-ascertainment

The tip of the pyramid represents the number of reported cases whereas the base represents the total number of symptomatic cases. This model estimates the probability of a case of diarrhoea due to a specific pathogen at different levels of this surveillance pyramid. The model consists of sets of pathogen-specific and general parameters (Table 1).

Table 1. Parameters used in the disease pyramid reconstruction model

Symbol	Description	Formula
General pathogen parameters		
p	Probability of visiting a GP in case of diarrhoea	Data from expert elicitation
m e	Probability of submitting a stool sample by • a GP • a HP	Data from expert elicitation
f g	Probability of analyzing a specific-pathogen* from a stool sample submitting by • a GP • a HP	Data from expert elicitation
h	Probability of reporting a positive result for a specific-pathogen* for: • a GP or a HP	Data from expert elicitation
Pathogen-specific parameters		
j	Sensitivity of laboratory analysis	Data from Haagsma et al [15], Rundell et al. [25]

GP, General Practitioner ; HP, Hospitalized Practitioner ; * *(Camp., List., Salm., Shig.)*

In our study, these parameters, described as probability distributions, are based either on available data from national surveillance systems or on data collected by the method of expert elicitation (Table 2).

Table 2. Model for reconstructing the surveillance pyramid for a specific-pathogen in 2014

Symbol	Description	Formula
n_R	Number of reported cases per year	Data from Epistat stool BID
n_H	Number of hospitalized cases per year	Data from Epistat stool BID
n_{GP}	Number of cases who are not hospitalized, but visit a GP	$n_R - n_H$
p	Probability of visiting a GP in case of diarrhea	Data from expert elicitation
m	Probability of submitting a stool sample when visiting a GP	Data from expert elicitation
n	Probability of reporting a case for patients visiting a GP	m • f • j • h (cf. Table 1)
o	Probability of reporting a case hospitalized patients	e • g • j • h (cf. Table 1)
N_{GP}	Total number of cases visiting a GP	n_{GP} / n
N_H	Total number of hospitalized cases	n_H / o
N_P	Total cases in the population	$(N_{GP} + N_H)$ / p
M	Multiplier	N_P / n_R

GP, General Practitioner ; HP, Hospitalized Practitioner ; BID : Belgian Infectious Disease

The probabilities of visiting a GP, submitting a stool sample by a GP/HP, analyzing a specific-pathogen from a stool sample submitting by a GP/HP and the probability of reporting a specific-pathogen from SNL/NRC were parameters informed by expert elicitation.

Probability of visiting a GP

This parameter was obtained based on the census of the cases of infectious diarrhoea reported by a GP.

Probability of submitting a stool sample

This parameter was estimated on the basis of expert estimates of the number of cases reported by a GP or by a HP.

Probability of analysing a stool sample

The probability that a laboratory will do a test depends of the specific pathogen.

Probability of reporting a positive laboratory result

The likelihood of reporting a positive result for a specific pathogen was differentiated between sentinel laboratories and national reference centers. Since the census differs between pathogens, we separated pathogens that could be registered by sentinel laboratories and national reference centers. In Belgium, Listeria, Salmonella and Shigella are reported by the National Reference Centers and Campylobacter is referred to by sentinel laboratories. All the cases have been reported whatever the severity of the sickness.

Sensitivity

The sensitivity of a laboratory test varies between laboratory techniques and between pathogens; it's defined as a probability and a pathogen-specific parameter. As laboratory methods do not agree on sensitivities in the literature, we decided to rely on data provided by Haagsma et al [15] ; the sensitivity is 76% for Campylobacter; 88% for Salmonellose and 63% for Shigella. The sensitivity for Listeria (99.9%) was provided by Rundell et al [25].

The annual number of reported cases and hospitalized cases per pathogen for the year 2014 were obtained from the Epistat tool with regards to the Belgian Infectious Disease [26] and Jacquinet et al. (2018) [27]. These are shown in Table 3. The number of hospitalized cases for Listeria was not published for 2014.

Table 3. Average reported and hospitalized cases of specific-pathogen for the year 2014 in Belgium

Pathogen	Total cases	Hospitalized cases
Campylobacter spp.	8098	2921
Listeria spp.	60	NA
Salmonella spp.	2902	1069
Shigella spp.	399	81

NA = Not available

4. Expert elicitation

For parameters without available consistent data and with possible conflicting sources of information, Structured Expert Judgment appears to be an alternative method to fill the knowledge gaps. The study took place from 13 December 2017 to 20 March 2018. In order to take part in the study, 34 selected experts were invited by e-mail on 13 December 2017 to participate in the study and after two weeks, a second e-mail was sent to the non-responding experts. Within this period, 15 experts did not respond and 3 experts refused to participate. A total of 16 experts were included in the study.

The inclusion criteria were: taking part or having published at least one article related to the four pathogens or having scientific knowledge of the four pathogens.

The exclusion criteria were: having used help or consulted literature to answer the calibration questions, having not answered all the calibration questions, having not taken part of the elicitation and the calibration step.

In this study, we chose to use a method of elicitation expert astride between the classical model of Cooke (mathematical aggregation), applied in the international Structured Expert Judgment (SEJ) study to estimate the global burden of foodborne disease [19], and the Delphi method (behavioral aggregation). The advantage of using the Delphi method is to allow participants to discuss their own answers over several rounds while keeping their anonymity. By using this method, experts have the opportunity to share their knowledge and correct likely misunderstandings. The advantage of using Cooke's method allows to obtain more explicit and more objective results but the main reason we integrated this method is that it makes it possible to weight the expert answers.

Our expert's elicitation method was conducted in three steps: 1) Calibration step, 2) Elicitation step and 3) Adjusting step.

The first step, the calibration step, consists in asking the experts to respond instantly, by phone or face-to-face to the first questionnaire. This first questionnaire contained twelve retrospective calibration questions related to the topic of the study (Appendix 1).
They were asked to provide three answers for each question, the best estimate (50^{th} percentile) representing the median and the uncertainty distribution (5th and the 95^{th} percentiles).

The second step, *i.e.* the elicitation step, consisted to send by e-mail a second questionnaire containing seven target questions related to probabilities used to build the surveillance pyramid (Appendix 2). They were asked to respond in a period of time of two weeks by giving, as well as for the calibration questions, the best estimate and the uncertainty distributions (5^{th}, 50^{th} and the 95^{th} percentiles).

Once all the answers of the second questionnaire were collected, the third step, an adjusting phase was conducted by sending by e-mail all the responses to the group of experts in a complete anonymity. The experts were invited to eventually change their responses according the answers of the other members of the group (Appendix 3).

This method allowed to quantify the expert score according to two measures: 1) the calibration score or statistical accuracy and, 2) the relative information or informativeness.

The statistical accuracy, scored between 0 and 1, measures the expert's ability of giving the true uncertainty of the variables, representing the statistical likelihood that his uncertainty distributions corresponds to the known values.
The relative information scores, relative to a group of experts evaluating the same variables, measure the expert's ability to give concentrated distributions around the true answers. For both, the statistical accuracy and the relative information, the higher are the final scores, the better it is. The product of the calibration score (statistical accuracy), the relative information and the alpha score (depends on the significance level) provides a "combined score" based on the expert's performance [19].

5. *Statistical analyses*

Data were put in EXCALIBUR software downloadable at http://www.lighttwist.net/wp/excalibur.

The EXCALIBUR allows to combine several distributions, given by the different experts, in a single distribution, representative of the spectrum of their opinions. In order to find a way to combine the distributions given by the different experts into a single distribution, it is necessary to create a pool gathering all the opinions of the experts called the decision maker (DM). This pooling can use equal weights or performance weights. The equal method gathers the answers provided by the experts to each question and calculates an arithmetic mean of the densities of the experts while the performance weights uses the enhancing of the performance of groups of experts by the performance weighting aggregation [22].

RESULTS

1. Expert elicitation

On the 16 experts who accepted by mail to participate in the study, 11 did it effectively from the beginning to the end. One expert was excluded due to lack of answer to one calibration question. Three experts modified their answers by mail at the adjusting step while seven experts did not modify it.

Table 4 shows the different results obtained following the equal or performance weighting on the calibration variables obtained during the first phase of the expert elicitation used in the classical model.

Table 4. Summary of elicitation results showing statistical accuracy (Sa), informativeness (Inf) and normalized weight with DM optimization (Norm. Weig. with DM) based on Equal Weight (EW) and Performance Weight (PM)

Expert's results	**Equal Weight**			**Performance Weight**		
	Significance level: 0			**Significance level:** 0.0002656		
	Sa	**Inf**	**Norm. Weig. with DM**	**Sa**	**Inf**	**Norm. Weig. with DM**
Expert 1	0.0006036	1.418	0.00493	0.0006036	1.418	0.003418
Expert 2	0.0002656	1.755	0.002685	0.0002656	1.755	0.001861
Expert 3	0.009503	1.464	0.08012	0.009503	1.464	0.05554
Expert 4	3.485×10^{-9}	1.672	3.357×10^{-8}	3.485×10^{-9}	1.672	0
Expert 5	7.385×10^{-10}	2.209	9.399×10^{-9}	7.385×10^{-10}	2.209	0
Expert 6	0.0002656	1.66	0.00254	0.0002656	1.66	0.001761
Expert 7	1.026×10^{-8}	2.45	1.448×10^{-7}	1.026×10^{-8}	2.45	0
Expert 8	1.35×10^{-6}	1.621	1.261×10^{-5}	1.35×10^{-6}	1.621	0
Expert 9	1.186×10^{-5}	1.386	9.472×10^{-5}	1.186×10^{-5}	1.386	0
Expert 10	7.385×10^{-10}	1.245	5.296×10^{-9}	7.385×10^{-10}	1.245	0
PM				0.2857	0.8218	0.9374
EW	0.6784	0.2327	0.9096			

The results obtained for the statistical accuracy is 0.6784 for the decision maker (DM) of the equal weighting (EW) and is 0.2857 for the DM of the performance weighting (PM). This means that for the equal weight, experts show distributions closest to the realization values than in the performance weight; the statistical accuracy is thus higher for the equal weight than the performance weight.

The results obtained for the informativeness is 0.2327 for the DM of the equal weighting and 0.8218 for the DM of the performance weighting (PM). This means that the uncertainty distribution is better concentrated around the true answers to the set of the calibration question for the performance weight.

The significance level is a parameter to take into account when we want to highlight the experts having a greater influence on the results of the experts elicitation. For the equal weighting, the level of significance is 0 because the purpose of this test is not to highlight the experts with the most influence but to adjust the weight of the experts to find an answer taking into account the opinion of each expert. On the other hand, using performance weighting, it is possible to highlight the experts having a greater influence in elicitation depending on the degree of significance level which is 0.0002656 in the performance weight. The experts with a statistical accuracy higher than the level of significance level are considered as most relevant in the study. Their opinions have more weights on the final results.

With a statistical accuracy higher than the level of significance, Expert 1 (Sa = 0.0006036), Expert 2 (Sa = 0.0002656), Expert 3 (Sa = 0.009503) and Expert 6 (Sa = 0.0002656) are considered as more relevant because they have a better performance than other experts (experts 4, 5, 7, 8, 9 and 10).

Table 5 presents the results of the calibration questions using equal and performance weighting. The column “Realization” corresponds to the answers of the calibration questions known by the expert.

The “Equal Weight” and “Performance Weight” columns correspond to the weights performed by the Excalibur program on the answers given for each calibration question by each expert.

Some differences between the answers using the equal or performance weight compared to the known answers in the “Realization” column can be observed. Question S1 “Infectious diarrhoea incidence in 2016” is the most prominent example. Indeed, with a known answer of the analyst corresponding to 19 988.09 cases, one can see a great disparity in the answers obtained by using the equal or weighted method. The answer obtained by using the equal is 2398 cases [112.40 ; 1.71 x 10^4] compared to 125.6 cases [100.10 ; 6867] with the performance weight. This difference shows an extremely high variability in the answers of the experts.

Table 5. Comparison between expert's results of calibration step using Equal Weight and Performance Weight and the realization

Question number	Heading of calibration question	Equal Weight [95% CI]	Performance Weight [95% CI]	Realization
S1	Infectious diarrhoea incidence in 2016	2398 [112.40 ; 1.71 x 10^4]	125.6 [100.10 ; 6867]	19 988.09
S2	Infectious diarrhoea mortality child < 5 years in 2016	6468 [0.07 ; 82.86]	0.2137 [0.10 ; 31.45]	0.93
S3	Number of CFP in 2011	157.6 [16.88 ; 5.779 x 10^4]	130.8 [72.60 ; 326]	281
S4	Percentage of non-transmitted CFP for analysis in 2014	47.3 [7.44 ; 87.74]	51.01 [19.90 ; 87.23]	38.6
S5	Number of reported cases of campylobacter in 2012	6731 [517.30 ; 1.696 x 10^4]	7948 [3398 ; 8823]	6607
S6	Listeriosis incidence in 2015	1.563 [0.08 ; 112.60]	0.5485 [0.40 ; 7.03]	0.69
S7	Percentage of cases of maternal neonatal listeriosis / total listeriosis 2015	10.02 [0.41 ; 49.55]	5.811 [1.02 ; 30.74]	11.5
S8	Incidence of salmonellosis in West and East Flanders in 2014	70.45 [27.14 ; 1532]	49.41 [30.12 ; 79.97]	64.4
S9	Percentage of cases of salmonellosis child < 5 years in 2014	24.22 [0.20 ; 74.69]	30.16 [1.98 ; 57.61]	35.9
S10	Percentage of foreign shigellosis cases 2014	47.63 [4.23 ; 92.66]	19.87 [1.167 ; 70.69]	7.7
S11	Number of confirmed shigellosis cases October 2014	29.86 [1.39 ; 138.30]	27.38 [1.18 ; 162.80]	37
S12	Number of confirmed cases of campylobacter in 2014	6684 [458.60 ; 2.91 x 10^4]	7848 [3242 ; 8.198 x 10^4]	8098

CFP: Collective food poisoning

The comparison between equal weighting and weighting on target questions is presented in Table 6. The results obtained by using the equal weighting 0.472 [0.001 ; 0.999] and the performance weighting 0.725 [0.144 ; 0.997] for the questions T3.2.4 relative to the probability of analyzing the pathogen Shigella from a stool sample submitting by a HP shows a high divergence.

A medium gap can also be observed for the questions T3.2.1 (EW: 0.552 [0.013 ; 0.999] vs PW: 0.720 [0.129 ; 0.981]) and T3.2.3 (EW: 0.582 [0.013 ; 1.000] vs PW: 0.782 [0.204 ; 0.996]) respectively the probability of analyzing the pathogen campylobacter from a stool sample submitting by a HP and the probability of analyzing the pathogen salmonella from a stool sample submitting by a HP between the equal weighting results and the performance results.

Table 6. Summary of target results using Equal Weight and Performance Weight

Question number	**Heading of target question**	**Equal Weight (EW) [95% CI]**	**Performance Weight (PW) [95% CI]**
T1	Probability of seeking care	0.292 [0.016 ; 0.836]	0.368 [0.030 ; 0.846]
T2.1	Probability of submitting a stool sample by a GP	0.259 [0.001 ; 0.881]	0.295 [0.004 ; 0.842]
T2.2	Probability of submitting a stool sample by a HP	0.673 [0.252 ; 0.991]	0.812 [0.358 ; 0.976]
T3.1.1	Probability of analyzing the pathogen *Camp.* from a stool sample submitting by a GP	0.572 [0.053 ; 0.993]	0.645 [0.183 ; 0.988]
T3.1.2	Probability of analyzing the pathogen *List.* from a stool sample submitting by a GP	0.2742 [0.001 ; 0.976]	0.369 [0.002 ; 0.956]
T3.1.3	Probability of analyzing the pathogen *Salm.* from a stool sample submitting by a GP	0.616 [0.052 ; 0.999]	0.690 [0.201 ; 0.998]
T3.1.4	Probability of analyzing the pathogen *Shig.* from a stool sample submitting by a GP	0.387 [0.001 ; 0.997]	0.450 [0.067 ; 0.995]
T3.2.1	Probability of analyzing the pathogen *Camp.* from a stool sample submitting by a HP	0.552 [0.013 ; 0.999]	0.720 [0.129 ; 0.981]
T3.2.2	Probability of analyzing the pathogen *List.* from a stool sample submitting by a HP	0.300 [0.001 ; 0.998]	0.529 [0.007 ; 0.946]
T3.2.3	Probability of analyzing the pathogen *Salm.* from a stool sample submitting by a HP	0.582 [0.013 ; 1.000]	0.782 [0.204 ; 0.996]
T3.2.4	Probability of analyzing the pathogen *Shig.* from a stool sample submitting by a HP	0.472 [0.001 ; 0.999]	0.725 [0.144 ; 0.997]
T4.1	Probability of reporting a positive result for the pathogen *Camp.* from SL	0.472 [0.013 ; 0.982]	0.596 [0.132 ; 0.900]
T4.2.1	Probability of reporting a positive result for the pathogen *List.* from NRC	0.655 [0.166 ; 0.999]	0.750 [0.270 ; 0.985]
T4.2.2	Probability of reporting a positive result for the pathogen *Salm.* from NRC	0.624 [0.165 ; 0.999]	0.503 [0.209 ; 0.961]
T4.2.3	Probability of reporting a positive result for the pathogen *Shig.* from NRC	0.703 [0.330 ; 0.999]	0.509 [0.301 ; 0.955]

GP, General Practitioner ; HP, Hospitalized Practitioner ; * (Camp., List., Salm., Shig.)

2. Population incidence and multiplication factors

The estimated multipliers that result from the reconstruction of the surveillance pyramid and used to adjust the reported cases in order to determine the true incidence are presented in Table 7. Appendix 4 shows the steps to follow in order to calculate the multiplication factors.

Based on the equal weight, the multiplier was estimated at 50.5 [77 000 570.1 ; 1.8] for Campylobacter, 30.6 [5 276 876.4 ; 1.5] for Salmonella and 66.4 [239 838 283.6 ; 2.1] for Shigella. Based on the performance weight, the multiplier was estimated at 23.9 [292 783.9 ; 2.0] for Campylobacter, 22.6 [143 297.4 ; 1.6] for Salmonella and 53.8 [523 438.7 ; 2.3] for Shigella. The estimated multiplier for Listeria was estimated at 25.9 [1 495 567.1 ; 1.2] using the equal weight and 8.4 [49 313.8 ; 1.3] using the performance weight.
The correction concerning the under-ascertainment and the underreporting based on the equal weight expert elicitation suggests that a total of 408 679 cases of campylobacteriosis, 88 674 cases of salmonellosis and 26 504 cases of shigellosis occurred in the population in Belgium in 2014. Based on the performance weight expert elicitation, the correction of the under-ascertainment and the underreporting suggests that a total of 193 199 cases of campylobacteriosis, 65 618 cases of salmonellosis and 21 466 cases of shigellosis occurred in the population in 2014. Concerning the listeriosis, an estimation of 507 cases using the performance weight and 1555 cases using the equal weight elicitation occurred in the population in 2014.

Table 7. Overview of multiplication factors estimated to correct for underreporting of *Campylobacter spp*., *Listeria spp., Salmonella spp.,* and *Shigella spp.* in 2014 in Belgium

	Multiplication factor	
Pathogen	Based on Equal weight expert elicitation [95% CI]	Based on Performance weight expert elicitation [95% CI]
Campylobacter spp.	50.5 [77 000 570.1 ; 1.8]	23.9 [292 783.9 ; 2.0]
Listeria spp.	25.9 [1 495 567.1 ; 1.2]	8.4 [49 313.8 ; 1.3]
Salmonella spp.	30.6 [5 276 876.4 ; 1.5]	22.6 [143 297.4 ; 1.6]
Shigella spp.	66.4 [23 9838 283.6 ; 2.1]	53.8 [523 438.7 ; 2.3]

Through the calculation of multiplication factors, an estimation of the true incidence of each pathogen for the year 2014 is shown in Table 8. Based on the data published by the federal internal public service, the Belgian population included 11 132 269 people in 2014 [28].

Table 8. Overview of trues incidences, i.e. corrected for underestimation, of *Campylobacter spp*., *Listeria spp., Salmonella spp.,* and *Shigella spp.* in 2014 in Belgium

	True incidence rates (per 100 000 inhabitants)	
Pathogen	Based on Equal weight expert elicitation [95% CI]	Based on Performance weight expert elicitation [95% CI]
Campylobacter spp.	3 671.12 [5 601 289 515.00 ; 127.69]	1735.49 [21 298 122.50 ; 143.96]
Listeria spp.	13.97 [806 071.30 ; 0.65]	4.55 [26 578.84 ; 0.70]
Salmonella spp.	796.55 [137 559 516.60 ; 38.64]	589.44 [3 735 527.32 ; 41.19]
Shigella spp.	238.08 [859 622 374.90 ; 7.58]	192.82 [1 876 095.92 ; 8.17]

Based on the equal weight, the true incidence for Campylobacter was estimated at 3671.12 cases /100 000 [5 601 289 515.00 ; 127.69]; 796.55 cases /100 000 [137 559 516.60 ; 38.64] for Salmonella and 238.08 cases /100 000 [859 622 374.90 ; 7.58] for Shigella. The new incidence for Listeria was estimated at 13.97 cases /100 000 [806 071.30 ; 0.65]. Based on the performance weight, the new incidence for Campylobacter is estimated at 1735.49 cases/100 000 [21 298 122.50 ; 143.96]; 589.44 cases /100 000 [3 735 527.32 ; 41.19] for Salmonella and 192.82 cases /100 000 [1 876 095.92 ; 8.17] for Shigella. The new incidence for Listeria was estimated at 4.55 cases /100 000 [26 578.84 ; 0.70].

DISCUSSION

While maintaining a critical reading of the method, the whole panel of experts, by the method of elicitation, agrees that there is an underestimation of reported cases of Campylobacter, Listeria, Salmonella and Shigella in Belgium in 2014. Our results also highlight the variation of underestimation by pathogen. For campylobacteriosis, salmonellosis and shigellosis, the multipliers are respectively 23.9 [292 783.9 ; 2.0], 22.6 [143 297.4 ; 1.6] and 53.8 [523 438.7 ; 2.3] based on performance weighted expert elicitation. For listeriosis, the multiplier was 8.4 [49 313.8 ; 1.3].

These multipliers estimates vary considerably when we compare countries randomly (for example from 9.3 in Germany to 379.6 in Japan for Campylobacter) but seem to resemble the results of countries around or comparable to Belgium such as the Netherlands or the United Kingdom (Table 9).

In comparison with the data from the Netherlands, we observe some similarities with our results. The particularity of comparing our results with those of the Netherlands is that this country also does not cover the entire population in terms of pathogen surveillance [29]. This allows us to get closer to the Belgian situation which covers only 60% of the territory through the sentinel laboratories.

The population of the Netherlands is estimated at 16 865 000 inhabitants in 2014 [30] compared to Belgium, which take a census of 11 132 269 inhabitants in 2014. Belgian Health services reported 8098 cases of Campylobacter in Belgium in 2014 and an average of 6541 cases reported per year of Campylobacter for the Netherlands [15].

The results of the Campylobacter's multiplier show a high similarity compared to the equal weight MF (50.5) and the MF of the Netherlands (49.0). These observations allow us to think that the multiplication factor using the equal weight may be closer to the reality for this pathogen only. On the other hand, with regard to the pathogen Salmonella, the results show more similarity between the MF using the performance weight between Belgium (22.6) and the Netherlands (20.0). These observations can also be observed for the pathogen Shigella with a performance weight MF of 53.8 for Belgium and a MF of 53.0 for the Netherlands. The calculation of the multiplication factor using the performance weight may be closer to the reality for these two pathogens.

All these differences observed between countries can be explained by the differences in surveillance of the different pathogens within each country as well as by the methods used to correct the under-ascertainment and underreporting [29].

The pathogen listeria is a pathogen extremely difficult to estimate due to the lack of data (for example the number of hospitalized cases and test of sensitivity) and the lack of routine research in the stool samples. Because of the oversampling of underestimation, it seems difficult to compare our MF estimates (performance or equal) with the result obtained by Thomas, 2013 with a MF of 1.7 [31].

Table 9. Overview of multiplier factors estimates to correct for underreporting of *Campylobacter spp*., *Listeria spp., Salmonella spp.,* and *Shigella spp.* in different countries worldwide

Country	**Study**	**Multiplication factor**			
		Campylobacter	*Listeria*	*Salmonella*	*Shigella*
Canada	Thomas, 2013	27.2	1.7	12.7	17.5
Denmark	Pires, 2014 - Haagsma, 2012	12.0	NA	7.2	30.0
Germany	Haagsma, 2012	9.3	NA	6.7	11.0
Japan	Pires, 2014	379.6	NA	74.0	NA
Netherlands	Haagsma, 2012	49.0	NA	20.0	53.0
Poland	Haagsma, 2012	72.0	NA	18.0	65.0
Sweden	Haagsma, 2012	17.0	NA	10.0	18.0
United Kingdom	Haagsma, 2012	52.0	NA	40	61.0
Belgium (EW)		**50.5**	**25.9**	**30.6**	**66.4**
Belgium (PW)		**23.9**	**8.4**	**22.6**	**53.8**

NA = Not available, EW: Equal Weight, PW: Performance Weight

It's assumed that the severity of the diarrhoea was not taking into account in the study and we did not distinguish bloody and non-bloody stool sample. As a case of diarrhoea was not clearly defined at the beginning of the study, except that only infectious diarrhoea was taken into consideration, no patient with diarrhoea was excluded. As well, no difference was made between Belgian regions.

Based on their supposed knowledge on the four pathogens and their *curriculum vitae*, we selected a number of 34 experts; only 10 experts were finally included which is probably a limitation of this study even if a minimum of 8 experts are required to perform an expert elicitation [32].

Using Delphi's method can cause some difficulties, due to the lack of relationship between the experts and between the experts and the facilitator [23,33]. To conduct an expert elicitation, the literature incites on the familiarity of the process by the elicitor. In this study, we informed the experts about the purpose of expert elicitation and how they should answer the questions but prior training on expert elicitation should have been presented to each expert [23].

The choice of the aggregation of the expert judgments is still debated. Equal weighting which required no justification for weights is often used in expert elicitations because of its simplicity [34]. This method gathers the answers provided by the experts to each question and calculates an arithmetic mean of the densities of the experts [22]. Some advocate that the performances of experts should be objectively measured with reliable data [20]. One reason for using it is the enhancing of the performance of groups of experts by the performance weighting aggregation [24]. Performance weighting can be obtained in two different ways namely the "global weights" and the "item weights". Item weights allow to adjust the weight for each individual item [35]. The global weight is less accurate than the item weight because of the average of the information score over all variables [19,22].

Item specific performance weights are described to be superior to global weights in 58% of the cases in the updated report of Colson et al [20]. Item weights solutions were then retained for analysis.

In this study, we decided to perform the analysis taking into account an equal and an performance weighting of the experts' answers. However, for the statistical accuracy and the relative information, a difference can be observed between the equal and the performance weights.

Equal weighting of experts show an acceptable level of statistical accuracy at the expense of informativeness. Performance-based weighting seems to increase informativeness comparatively to the equal weighting informativeness; nevertheless, this is obtained at the expense of the statistical accuracy. This confirms the negative correlation between informativeness and statistical accuracy, as already developed by Aspinall et al [19].

In our study, however, the attenuation of this negative correlation, described by Aspinall et al [19] when the statistical accuracy improved, is difficult to confirm. This could be explained by the limitations of our elicitation process. As mentioned above, the absence of prior training for the elicitor and for the experts could be a cause of misunderstanding.

Sharing information seems to improve the performance measures; as this sharing is the result of a simple feedback or the result of a discussion is to be determined but Hanea et all emphasized that the experts who changed their mind did it in the "good" direction [24].
In the Delphi method, several rounds are usually proposed [23] but in our study, for operational reasons, only one round was made. Three of the ten experts change their response after this round; as the "correct" responses are unknown, nothing can be concluded.

To introduce the validity of the construction of the pyramid, some points need to be discussed. Regarding the equation to reconstruct the surveillance pyramid, we considered that hospitalized patients had previously been seen by a general practitioner due to a lack of data concerning the probability of being hospitalized. Therefore, the number of patients who went directly to the hospital without first visiting a general practitioner was not taken into account in this study.
The exact sensitivities required to calculate the multiplication factors were relatively difficult to find.

The search for pathogen Listeria in the laboratory is not routinely done in the stool, hence no routine sensitivity is available. We then used the sensitivity of the test using the Polymerase Chain reaction (PCR) method for our calculations. The sensitivity of this test is 99.9% [25].
Moreover, without the number of hospitalized cases for listeria in 2014, we estimated that all the cases discovered by a general practitioner have been hospitalized. We assumed that the disease could have serious consequences for the patient due to a high rate of fatality [7]. Consequently, we assume that an overestimation of the initial underestimation must be taken into account concerning the pathogen Listeria for the year 2014. Indeed, in comparison with the results obtained for the multiplication factor for the listeria (1.7) by Thomas et al (2013) shown in Table 9, the multiplication factors presented for Belgium seem far apart with a multiplication factor corresponding to 8.4 using the performance weight method and 25.9 using the equal weight method [31].

As the purpose of this study is the estimation of the new incidence for the year 2014 based on expert elicitation, we analyzed the equal weights and performance weights results. It was demonstrated that there is some difference between the results obtained by the two types of weight. The multipliers used for the Campylobacter and Shigella show the most importance difference between equal and performance weight results.

For Campylobacter, the difference between the two weights varies from single to double for the multiplication factors based on equal weighting (50.5) and performance weighting (23.9). The difference between the two types of performance for the multiplication factors for Salmonellosis is relatively weak with 30.6 for equal weighting and 22.6 for performance weighting. All these observed differences highlight the importance of the weight.
In relation to the national coverage of sentinel laboratories estimated at only 60% in Belgium, we estimate that a significant proportion of reported cases were not taken into account in the data.

This study attempted to estimate the true incidence of four pathogens in 2014. However, a great uncertainty in the results obtained by the experts suggests that some points could be the subject of more detailed research in the future. Firstly, a better preparation of the experts and the facilitator to the diverse techniques of the expert elicitation would reduce, according to our opinion, the great uncertainty present in this study. Secondly, by increasing the duration of the study, other adjusting steps would allow the experts to discuss their responses and to find better agreements. Finally, to ensure the expertise of each expert, the realization of this study should take into account one pathogen at a time in order to reduce the level of uncertainty of experts who might have less expertise in regard of certain pathogens.

CONCLUSION

For a structure elicitation judgment, the choice of the experts and their elicitation is a difficult and relevant step. For the building of our reconstruction model, some factors were estimated on expert opinion. The limited number of experts and a wide variability in their responses result in a high degree of uncertainty of the multipliers. Despite these limitations of our study, the panel of experts, by the method of elicitation, agrees that there is an underestimation of reported cases of Campylobacter, Listeria, Salmonella and Shigella in Belgium. This should be lead to government efforts in order to improve active prevention in terms of food chain security but also in terms of reporting cases.

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NOM et PRENOM : LOTHAIRE KIM

Titre du mémoire : Estimation de la vraie incidence de la campylobactériose, listériose, salmonellose et shigellose en Belgique

Promoteur et Co promoteur : Charline Maertens de Noordhout et Niko Speybroeck

Background: Foodborne diseases (FBD's) are known to cause important morbidity and mortality with a significant socio-economic impact worldwide. The incidence of certain diseases causing gastroenteritis disorders such as campylobacteriosis, listeriosis, salmonelosis and shighellosis are underestimated in Belgium. This underestimation (UE) results from under-ascertainment (UA) and under-reporting (UR) of the number of cases. The objectives of this study are: 1) to quantify the UE of campylobacteriosis, listeriosis, salmonellosis and shigellosis reported cases in Belgium through designing of multiplication factors (MFs) and; 2) to estimate the true incidence of these FBDs in Belgium in 2014 by using the previously MFs.

Methods: To quantify UA and UR of the selected FBDs, adapted Delphi and Cooke's methods of expert elicitation were used. Selected Belgian experts firstly answered to 12 calibrations questions, allowing to weight their future answers based on their performance, then experts answered to the target questions, *i.e.* directly linked with the parameters of interest. Finally, they received anonymous answers of the whole panel of experts and had the possibility to adapt their answers. Final probabilities of UA and UE were calculated based on a performance weight (PM) and equal weight (EW) schemes using Excalibur software. True incidence was estimated by multiplying reported incidence in 2014 by the previously calculated MFs.

Results: 10 experts contributed at the whole study. We observed a major difference between the multiplication factors using the EW or PW approach; this has implications for estimating the true incidence for each pathogen. MFs based respectively on the EW and the PW are estimated for the camplylobacteriosis at 50.5 vs 23.9, for the listeriosis at 25.9 vs 8.4, for the salmonellosis at 30.6 vs 22.6 and for the shigellosis at 66.4 vs 53.8. The true incidence (per 100 000 inhabitants) based respectively on the EW and the PW are estimated for the camplylobacteriosis at 3671.12 vs 1735.49, for the listeriosis at 13.97 vs 4.55, for the salmonellosis at 796.55 vs 589.44 and for the shigellosis at 238.08 vs 192.82.

Conclusion: The limited number of experts and a wide variability in their responses result in a high degree of uncertainty of the multipliers. Despite these limitations, the panel of experts, by the method of elicitation, agrees that there is an UE of reported cases of Campylobacter, Listeria, Salmonella and Shigella in Belgium.

Key-words: foodborne pathogen, expert elicitation, true incidence