Cost-effectiveness analysis of using probiotics, prebiotics, or synbiotics to control *Campylobacter* in broilers

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ABSTRACT *Campylobacter* is a food safety hazard, which causes a substantial human disease burden. Infected broiler meat is a common source of campylobacteriosis. The use of probiotics, prebiotics, or synbiotics has been associated with controlling *Campylobacter* infections in broilers, although efficacy remains a contentiously debated issue. On-farm use of probiotics, prebiotics, or synbiotics is gaining momentum. Therefore, it is interesting to analyze the economic viability of this potential intervention to reduce *Campylobacter* prevalence in broilers. A normative cost-effectiveness analysis was conducted to estimate the cost-effectiveness ratio of using probiotics, prebiotics, or synbiotics in broiler production in Denmark, the Netherlands, Poland, and Spain. The cost-effectiveness ratio was defined as the estimated costs of probiotics, prebiotics, or synbiotics use divided by the estimated public health benefits expressed in euro (€) per avoided disability-adjusted life year (**DALY**). The model considered differences between the countries in zootechnical and economic farm performance, in import, export, and transit of live broilers, broiler meat and meat products, and in disease burden of *Campylobacter*-related human illness. Simulation results revealed that the costs per avoided DALY were lowest in Poland and Spain (€4,000–€30,000 per avoided DALY) and highest in the Netherlands and Denmark (€70,000–€340,000 per avoided DALY) at an efficacy ranging from 10 to 20%. In Poland and Spain, using probiotics can be classified as a moderately expensive intervention if efficacy is more than 10%, otherwise it is relatively expensive. In the Netherlands and Denmark, using probiotics is a relatively expensive intervention irrespective of efficacy. However, if probiotics, prebiotics, or synbiotics were assumed to enhance broiler performance, it would become a relatively cost-effective intervention for *Campylobacter* even at low efficacy levels of 1 to 10%.

Key words: *campylobacter*, broiler, probiotic, prebiotic, synbiotic, cost-effectiveness, European Union

2020 Poultry Science 99:4077–4084
https://doi.org/10.1016/j.psj.2020.05.003

INTRODUCTION

Campylobacter is one of the leading causes of acute diarrheal disease in humans in the European Union and worldwide (WHO, 2015; Cassini et al., 2019). Broilers are an important reservoir for human *Campylobacter* infections (EFSA Panel on Biological Hazards, 2011). Therefore, it is relevant to control *Campylobacter* on broiler farms. A number of interventions have been proposed to control *Campylobacter* risk factors on broiler farms (Adkin et al., 2006; McDowell et al., 2008; Sommer et al., 2016; Wales et al., 2019). The cost-effectiveness ratio of such interventions has been estimated in a number of studies. Van Wagenberg et al. (2016) analyzed the cost-effectiveness ratio of building an anteroom with hygiene barrier, a maximum downtime of 10 D between flocks, building new farm houses, applying drink nipples without a cup, using designated tools, a ban on partial depopulation, slaughter at 35 D, and fly screens. Elliott et al. (2012) estimated the cost-effectiveness ratio of enhanced biosecurity, slaughter at 35 D, a ban on partial depopulation, applying vaccination, and applying bacteriocins. Gellynck et al. (2008) estimated the cost-effectiveness ratio of applying phage therapy and Mangen et al. (2007) of improving hygiene and applying phage therapy.

Using probiotics, prebiotics, or synbiotics could be an additional intervention to control *Campylobacter* infections in broilers (Gracia et al., 2015; Guyard-Nicodème et al., 2015). In the remainder, we will use probiotics as a short for probiotics, prebiotics, or synbiotics. The use of probiotics aims to create competition between

Received October 8, 2019.
Accepted May 1, 2020.

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species that are naturally present in the intestinal flora of broilers and thus both exclude and suppress colonization of birds with *Campylobacter*. Yet, literature reveals large discrepancies with respect to the effect of probiotics on intestinal *Campylobacter* load and prevalence in broilers (Gracia et al., 2015; Guyard-Nicodème et al., 2015). Studies varied widely in experimental design, so it is difficult to compare results (Guyard-Nicodème et al., 2015). Major variations exist between studies in, for example, the type of probiotic products and dosage used, ultimately, in the duration of *Campylobacter* colonization, and in *Campylobacter* load and prevalence (Meunier et al., 2016). Licensed probiotics have been examined under commercial conditions, yet consistent large-scale results are scarce (Wales et al., 2019). A coherent picture of the efficacy of probiotics to control *Campylobacter* prevalence and load under commercial conditions does not emerge (Meunier et al., 2016). Gracia et al. (2015) indicated that it can be expected that probiotics can be used to control *Campylobacter* infections in broilers, although the efficacy under commercial conditions is yet unclear. In summary, it is likely that *Campylobacter* infections in broilers can be controlled to some extent by administering probiotics, but the efficacy of administering probiotics to broilers to control *Campylobacter* prevalence and load is a contentiously debated issue.

Although probiotics have been around for some decades, the on-farm use of probiotics in broilers is gaining momentum. For example, in a recent Farm Accountancy Data Network survey approximately 40% of Dutch broiler farmers indicated to have used probiotics in one form or the other in 2018 (Bergevoet et al., 2019). These farmers started using probiotics to improve broiler gut health and decrease the risk of broiler illnesses aiming to lower the use of antimicrobials, as required by the Dutch policy to reduce the use of antibiotics in farm animals. Probiotics are easy to administer under commercial conditions. Because of the increasing interest for using probiotics and the association with controlling *Campylobacter* infections in broilers, it is interesting to analyze the cost-effectiveness ratio of this potential intervention to control such *Campylobacter* infections. However, the cost-effectiveness ratio of using probiotics to control *Campylobacter* infections in broilers has not been estimated in literature. Therefore, the objective of this study is to estimate the cost-effectiveness of probiotics use to control *Campylobacter* infections in broilers. Because the efficacy of probiotics on *Campylobacter* prevalence is uncertain, the on-farm relative risk of *Campylobacter* infections in broilers when using probiotics was varied to determine the cost-effectiveness ratio as function of efficacy.

MATERIALS AND METHODS

Cost-Effectiveness Analysis

A deterministic *Campylobacter* control model, hence referred to as CamCon model (Van Wagenberg et al., 2016), was applied to estimate the cost-effectiveness ratio of probiotics on broiler farms. Disability-adjusted life year (**DALY**) was taken as a measure for disease burden, which is a metric that encompasses the number of healthy year of life lost because of premature death and disability. In this study, the cost-effectiveness ratio is expressed in euro (€) per avoided DALY. The lower the estimated cost-effectiveness ratio, the lower the costs for each avoided DALY and the more favorable the intervention.

The cost-effectiveness ratio (**CER_c**) of on-farm probiotics use in a country c was calculated as the estimated annual costs of the use of probiotics (**$Costs_c$**) divided by the estimated annual public health benefits (**PHB_c**), that is, the estimated annual reduction in *Campylobacter*-related disease burden (Equation 1). Annual costs $Costs_c$ were estimated by multiplying the estimated number of typical farms in country c (**F_c**) with estimates of the annual intervention costs in country c (**CF_c**) of using probiotics on a typical farm. The annual intervention costs CF_c were estimated as the difference between annual farm labor income, revenue, minus all costs excluding labor of the farmer and his family, in the situation without and with the use of probiotics following the farm model developed by Van Wagenberg and Van Horne (2016). Effective interventions should reduce the probability of *Campylobacter* colonization of broiler flocks and reduce flock prevalence of *Campylobacter*. If probiotics use to control *Campylobacter* is effectively implemented at broiler farms, the prevalence of contaminated chicken meat decreases, which in turn will decrease the annual human disease burden. Based on risk assessment studies (Rosenquist et al., 2003; Nauta et al., 2009), it was assumed that the *Campylobacter*-related disease burden obtained by the consumption of broiler meat, is proportional to the flock prevalence. Based on Mangen et al. (2007), PHB_c were estimated as the product of the efficacy (**EF_c**) of probiotics use to control the risk of *Campylobacter* infections in broilers, the *Campylobacter*-related disease burden (**DB_c**), the fraction of the *Campylobacter*-related human disease burden which is attributable to consumption of broiler meat contaminated with *Campylobacter* (**AF_c**) (Havelaar et al., 2008, 2012), and the fraction of broiler meat and meat products consumption coming from domestically raised broilers (**$FMDR_c$**). The efficacy of probiotics use in country c is the decrease in relative risk of *Campylobacter* infections in broilers after implementation of probiotics use compared with the situation before implementation. The fraction of broiler meat and meat products consumption in country c coming from domestically raised broilers was estimated based on the export, import, and transit of live broilers, broiler meat, and broiler meat products (Mangen et al., 2007). Meat from imported live broilers and imported broiler meat and meat products that has not been subjected to an intervention on broiler farms will not have a positive impact on the domestic disease burden. On the other hand, measures taken would not only have a positive effect on the health risks of domestic consumers but also on the health of consumers in countries that import live broilers, meat, or meat products from farms subjected to the intervention.

$$CER_c = \frac{Costs_c}{PHB_c} = \frac{F_c \cdot CF_c}{EF_c \cdot DB_c \cdot AF_c \cdot FMDR_c} \quad (1)$$

where CER_c = cost-effectiveness ratio in country c (€/avoided DALY); $Costs_c$ = annual costs of implementation of probiotics use on all broiler farms in country c (€/year); PHB_c = annual public health benefits due to implementation of probiotics use on all broiler farms in country c (avoided DALY/year); F_c = number of broiler farms in country c; CF_c = costs to implement probiotics use on a broiler farm in country c (€/farm/year). EF_c = efficacy of probiotics use to control the risk of *Campylobacter* infections in broilers compared with the situation without probiotics use in country c. DB_c = *Campylobacter* disease burden in country *c* (DALY/year). AF_c = Fraction of *Campylobacter* disease burden in country c attributable to consumption of broiler meat. $FMDR_c$ = fraction of broiler meat and meat products consumption in country c coming from domestically raised broilers. c = index for countries.

Because the efficacy of probiotics on *Campylobacter* prevalence in practice is uncertain, the efficacy EF_c was varied to determine the cost-effectiveness ratio. Building on the CamCon model, the analysis was focused on 4 European Union countries: Denmark, the Netherlands, Poland, and Spain.

Zootechnical, Economic, and Epidemiological Input Parameters

Zootechnical and economic parameters in the CamCon model were updated to 2017 levels (Table 1). Farm level costs FC_c of probiotics were estimated based on the price of commercially available multispecies synbiotic product available for broilers at the moment of the study. Additional costs of €0.45 per 100 kg compound feed were assumed in the default scenario. This implies an average increase in feed price of approximately 1.5%. Suppliers of commercially available probiotics also indicated that costs at farm level of administering probiotics in drinking water are in a similar range. The number of typical broiler farms F_c and their size were based on broiler farms with more than 10,000 broilers from Eurostat (https://ec.europa.eu/eurostat) for Denmark, Poland, and Spain and from Agrimatie (www.agrimatie.nl) for the Netherlands. These farms produced more than 98% of the total number of broilers raised in Denmark, the Netherlands, and Spain. On these farms, in Poland, about 92% of the total number of broilers was produced, indicating that relatively many broilers were kept on smaller farms compared with the other countries. For zootechnical parameters, we distinguished between farms that practice partial depopulation and farms that do not because zootechnical and economic performance differ between these farming systems, which can have an impact on the farm intervention costs CF_c.

The incurred annual costs $Costs_c$ were linked with the main nonmonetary public health benefits PHB_c from the avoided disease burden in DALY per year. Key model parameter is the current estimated *Campylobacter* disease burden DB_c in each country in DALY per year. The DB_c in each country and 95% confidence interval used in the model (Table 2) were estimated with the Burden of Communicable Diseases in Europe toolkit developed by the European Centre for Disease Prevention and Control (Colzani et al., 2017). As input in this toolkit, we used the country-specific symptomatic *Campylobacter* incident cases per gender and age class (average 2009–2013) and the country-specific multiplication factors from the studies by Cassini et al. (2019) and Cassini et al. (2018). The attributable fraction AF_c of *Campylobacter* disease burden attributed to broiler meat was estimated at 0.38 for Denmark, the

Table 1. Main zootechnical and economic parameters for Denmark, the Netherlands, Poland, and Spain.

Parameters	Denmark	The Netherlands	Poland	Spain
Probiotics price (€ per 100 kg)	0.45	0.45	0.45	0.45
Feed price (€ per 100 kg)[1]	30.75	30.75	31.37	31.45
Number of farms (≥10,000 broilers)[2]	150	530	1,850	2,890
Farm size (number of broilers per farm)[2]	87,933	83,170	39,978	42,394
Farms that practice partial depopulation				
Percentage of farms (%)[3]	24.8	42.2	49.4	49.1
Feed conversion (kg feed/kg final live weight)[1]	1.55	1.58	1.62	1.72
Final live weight 1st delivery (g)[1]	1,790	1,790	2,000	2,200
Final live weight 2nd delivery (g)[1]	2,400	2,600	2,430	2,770
Farms that do not practice partial depopulation				
Feed conversion (kg feed/kg final live weight)[1]	1.62	1.68	1.67	1.79
Final live weight (g)[1]	2,400	2,600	2,430	2,770

[1]Van Horne (2018).
[2]Denmark, Poland, and Spain: Eurostat (https://ec.europa.eu/eurostat); the Netherlands: Agrimatie (www.agrimatie.nl).
[3]Rosenquist et al. (2015).

Table 2. Estimated annual disability-adjusted life year and annual disability-adjusted life year per 100,000 population caused by campylobacteriosis in Denmark, the Netherlands, Poland, and Spain.

	Denmark		The Netherlands		Poland		Spain	
	DALY/year	DALY/100,000 population/year[1]	DALY/year	DALY/100,000 population/year	DALY/year	DALY/100,000 population/year	DALY/year	DALY/100,000 population/year
Average	350	6.03	565	3.27	3,709	9.77	927	1.97
2.5% percentile	305	5.25	498	2.88	2,710	7.14	716	1.53
97.5% percentile	393	6.77	634	3.67	4,720	12.43	1,144	2.44

Abbreviation: DALY, disability-adjusted life year.
[1]Calculated based on the number of inhabitants per 1 January 2019 in Denmark 5,806,081, the Netherlands 17,282,163, Poland 37,972,812, and Spain 46,937,060 (Eurostat).

Netherlands, and Spain and 0.28 for Poland (Hoffmann et al., 2017). The disease burden attributable to broiler meat consumption was estimated without time-discounting, in line with the advice of the World Health Organization (WHO, 2013).

To estimate $FMDR_c$, updated national production and trade statistics of live broilers and chicken meat for 2017 were retrieved from Eurostat for Denmark, Spain, and Poland and from Agrimatie for the Netherlands. In the default situation, we estimated the cost-effectiveness ratio CER_c without accounting for additional human health benefits in other countries because of export.

Sensitivity Analyses

Sensitivity analysis was conducted to determine the range of possible cost-effectiveness ratios CER_c. The CER_c curvature was estimated if also public health benefits in export markets are considered. The size of the public health benefits in other countries were estimated by extrapolating the public health benefits PHB_c in the originating country c (with the use of probiotics) using the fraction of meat and meat products exported from broilers raised in the originating country c in the total production of meat and meat products from broilers raised in the originating country c. In this, we assumed that the public health benefits of a lower *Campylobacter* prevalence on broiler meat in the export market countries are similar to PHB_c in the country of origin c. Furthermore, alternative levels were considered for the farm cost CF_c of probiotic provision (i.e., 50% lower and 50% higher price of probiotics) and disease burden DB_c (i.e., 2.5 and 97.5% percentiles of the DALY per year estimates).

Finally, in the sensitivity analysis, we analyzed the effect on the cost-effectiveness ratio CER_c of changed farm costs CF_c when assuming enhanced broiler performance because of the use of probiotics. Several recent reviews analyzed the relationship between providing probiotics to broilers and broiler performance (Alloui et al., 2013; Blajman et al., 2014; Jadhav et al., 2015; Aziz Mousavi et al., 2018). Aziz Mousavi et al. (2018) concluded that some studies show that application of probiotics in feed could lead to increased average daily weight gain and improved feed conversion ratio but also that many studies did not find a significant impact. Blajman et al. (2014) indicated in their meta-analysis comprising almost 50 studies that on average, broilers receiving probiotics had increased BW gain and a reduced feed conversion ratio compared with controls. However, they warn to be cautious with these results because of evidences of publication bias and heterogeneity. Alloui et al. (2013) mention that supplementing prebiotics has shown to improve BW gain in most of the reviewed studies, and feed intake and feed gain ratios generally are decreased but that there still is insufficient evidence regarding the efficacy of probiotics in poultry other than for the competitive exclusion of pathogens. They did not find sufficient studies on the use of synbiotics to draw conclusions but mention that these can apparently be more efficient than separate use. Jadhav et al. (2015) concluded that feeding probiotics to poultry improves feed conversion ratio, feed intake, and BW gain. In summary, literature indicates a potential performance enhancing effect of using probiotics, but it is indecisive on the size of this effect. Based on the quantitative results of Blajman et al. (2014) and the results of a field study in the Netherlands at commercial broiler farms conducted by the Dutch Health Center for Poultry (Biomin & Gezondheidscentrum voor Pluimvee, 2019), we defined a moderate- and high-performance–enhancing effect scenario. In the moderate-performance–enhancing effect scenario, the feed conversion ratio in the Netherlands was assumed to reduce with 0.01 and final live weight in the Netherlands to increase with 35.00 g, simultaneously. In the high-performance–enhancing effect scenario, the feed conversion ratio in the Netherlands was assumed to reduce with 0.02 and final live weight to increase with 70.00 g, simultaneously. The feed conversion ratio and final live weight in the performance-enhancing scenarios in the other 3 countries were estimated using the relative change in feed conversion ratio and final live weight in the performance-enhanced scenarios compared with the default in the Netherlands.

RESULTS

Substantial differences in cost-effectiveness ratio CER_c between countries were estimated (Figure 1). For example, assuming a probiotic efficacy EF_c of 10%, the CER_c ranged from €8,085 per avoided DALY in Poland to €337,330 per avoided DALY in the

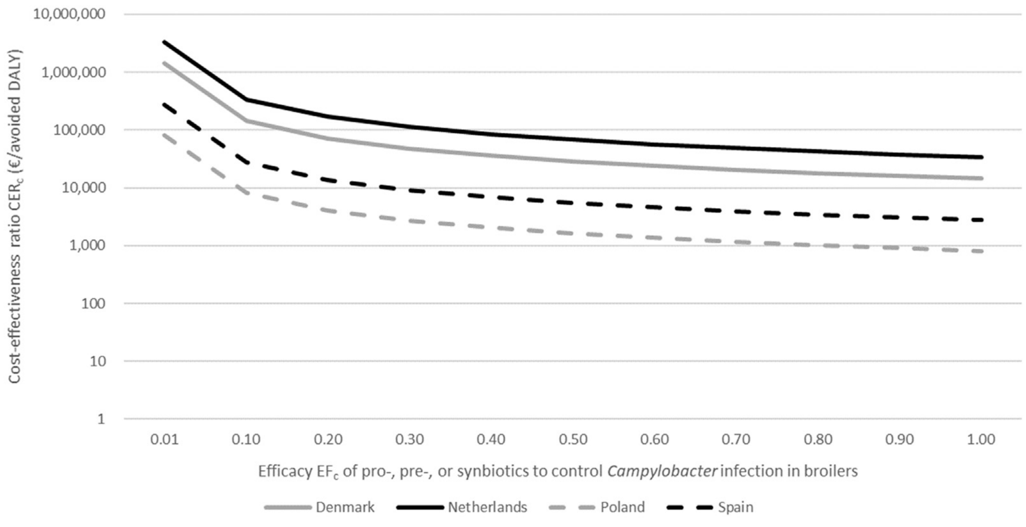

Figure 1. Estimated cost-effectiveness ratio CER_c (€ per avoided DALY) as function of efficacy EF_c of probiotics, prebiotics, or synbiotics to control on-farm *Campylobacter* infections in broilers in Denmark, the Netherlands, Poland, and Spain.

Netherlands. The difference was mainly due to the initial disease burden DB_c in these countries (Table 2). Across countries, Poland and Spain had the highest potential public health benefits PHB_c, whereas Denmark and the Netherlands had the lowest. The CER_c as function of efficacy EF_c of probiotics showed a downward curve. The CER_c reduced to 50, 25, and 12.5% if EF_c was assumed to increase from 10 to 20, 40, and 80%, respectively. This is because the costs per year of using probiotics $Costs_c$ are independent of the efficacy EF_c, whereas PHB_c per year increase with EF_c.

Sensitivity Analysis

The sensitivity analysis of the key underlying assumptions encompasses 4 efficacy levels EF_c to explore the cost-effectiveness ratio CER_c curvature (namely 10, 20, 40, and 80%). Model outcomes with these alternative parameter values were compared with the model default outcomes (Table 3).

If *Campylobacter* interventions are implemented on broiler farms in a country c, live broilers, meat, and meat products of broilers from these farms exported to other countries will also have a lower *Campylobacter* risk, thereby reducing the *Campylobacter*-related human disease burden in these countries. This increases the public health benefits PHB_c for the intervention in country c and decreases the cost-effectiveness ratio CER_c. The estimated reduction in CER_c by including public health benefits of consumers abroad was 11% ((1–€128,404/€143,885)*100%), 76, 9, and 11% for Denmark, the Netherlands, Poland, and Spain, respectively (Table 3). Because a substantial amount of the domestic production in the Netherlands is exported, the corresponding cost-effectiveness ratio improved substantially if benefits for consumers abroad were included.

Higher or lower price levels of administering probiotics per farm, maintaining the same application level in terms of mg per bird per day, resulted through higher of lower farm intervention costs CF_c in a proportional change in cost-effectiveness ratio, as can be directly derived from equation 1. For example, a 50% lower price resulted in 50% lower CER_c.

Taking the 2.5% percentile disease burden estimate DB_c for Denmark, the Netherlands, Poland, and Spain, the CER_c was 15, 13, 37, and 29% higher than in the default, respectively. If the 97.5% percentile DB_c was used, the CER_c was 11, 11, 21, and 19% lower, respectively. Differences between countries stem from substantial differences in the (relative) bandwidth of the 95% confidence intervals. A change in the default DB_c is inversely proportional to the change in CER_c. A 10% lower DB_c in a country resulted in a 11.1% (=1/(1–0.1)) higher CER_c. Similarly (not reported in Table 3), a change in the attributable fraction AF_c of the *Campylobacter* disease burden DB_c to broiler meat consumption is inversely proportional to the change in the CER_c (Van Wagenberg et al., 2016).

In the high-performance–enhancing effect scenario, in all 4 countries the use of probiotics resulted in negative annual $Costs_c$, indicating net economic gains (Table 4). This is because the economic benefits of the enhanced performance exceed the costs of purchase and administering them. In the moderate-performance–enhancing effect scenario, this also holds for Denmark, the Netherlands, and Poland but not for Spain, where the gains of the performance enhancing effects were estimated to be lower than the purchase and administering costs. Net economic gains indicate that using probiotics is always economically viable, even without any control of *Campylobacter* infections. This complicates estimating the cost-effectiveness ratio CER_c. Therefore, Table 4 provides the public health benefits PHB_c for different levels of efficacy EF_c of using probiotics. These PHB_c come on top of the economic gains. Nevertheless, Table 4 can be used to estimate the CER_c. For example, for Spain, in the moderate-performance–enhancing effect scenario, the cost-effectiveness ratio CER_c was substantially lower than in the default for all efficacy levels EF_c (16% of the default CER_c).

Table 3. Sensitivity analysis of the estimated cost-effectiveness ratio CER_c on country level (€ per avoided DALY) as function of efficacy EF_c of probiotics, prebiotics, or synbiotics to control on-farm *Campylobacter* infections in broilers in Denmark, the Netherlands, Poland, and Spain.

	Denmark				The Netherlands				Poland				Spain			
Efficacy level	10%	20%	40%	80%	10%	20%	40%	80%	10%	20%	40%	80%	10%	20%	40%	80%
Default	143,885	71,942	35,971	17,986	337,330	168,665	84,333	42,166	8,085	4,042	2,021	1,011	27,379	13,690	6,845	3,422
With export	128,404	64,202	32,101	16,050	81,814	40,907	20,453	10,227	7,392	3,696	1,848	924	24,374	12,187	6,094	3,047
Costs probiotics +50%	215,827	107,914	53,957	26,978	505,995	252,998	126,499	63,249	12,127	6,063	3,032	1,516	41,069	20,534	10,267	5,134
Costs probiotics -50%	71,942	35,971	17,986	8,993	168,665	84,333	42,166	21,083	4,042	2,021	1,011	505	13,690	6,845	3,422	1,711
DALY 2.5% percentile	165,114	82,557	41,278	20,639	382,714	191,357	95,678	47,839	11,065	5,532	2,766	1,383	35,448	17,724	8,862	4,431
DALY 97.5% percentile	128,142	64,071	32,035	16,018	300,618	150,309	75,154	37,577	6,353	3,176	1,588	794	22,186	11,093	5,546	2,773

Abbreviations: DALY, disability-adjusted life year; EF_c, efficacy of probiotics use to control the risk of *Campylobacter* infections in broilers compared with the situation without probiotics use in country c.

DISCUSSION

This study compared the costs of administering probiotics on broiler farms with the potentially avoided human disease burden of campylobacteriosis. The cost-effectiveness ratio estimates from other regular intervention studies provide a benchmark to compare the current outcomes. The estimated cost-effectiveness ratio of relative affordable interventions in Van Wagenberg et al. (2016) was between €10,000 and €20,000 per avoided DALY, depending on the country. Comparing these previous cost-effective ratios directly with the simulation results from the present study reveals that a level of efficacy of using probiotics of 50% or more is required to equal this cost-effectiveness ratio in Denmark and the Netherlands, whereas already at a level of 10% in Poland and Spain. However, the estimated *Campylobacter*-related disease burden in the present study is substantially lower than the estimate used in the study by Van Wagenberg et al. (2016). Van Wagenberg et al. (2016) used estimated *Campylobacter* disease burden of 41,605, 47,308, 2,582, and 476 DALY per year for Poland, Spain, the Netherlands, and Denmark, respectively, compared with 3,709, 927, 565, and 350 in the present study, respectively. For Spain, this is 98% lower; for Poland, 91%; for the Netherlands, 78%; and for Denmark, 26%. This is because of lower multiplication factors to extrapolate reported incidence to total incidence. Moreover, irritable bowel syndrome was not included anymore as a sequela in the most recent version of the Burden of Communicable Diseases in Europe toolkit because of recent insights that the causal relationship between campylobacteriosis and irritable bowel syndrome is not as strong as previously thought. In previous estimates, irritable bowel syndrome contributed substantially to the total disease burden. Because we assumed that the *Campylobacter*-related disease burden obtained by the consumption of broiler meat is proportional to the flock prevalence, a certain reduction in flock prevalence will result in a larger number of avoided DALY at a higher estimated *Campylobacter* disease burden than at a lower estimated *Campylobacter* disease burden. However, the estimated costs will be the same in both situations. Thus, the estimated cost-effectiveness ratio of interventions in the study Van Wagenberg et al. (2016) would increase with the updated disease burden estimates. With the updated disease burden, for Spain, the cost-effectiveness ratios of the interventions are 51 times higher than the cost-effectiveness ratios presented in the study by Van Wagenberg et al. (2016); for Poland, 11.2 times; for the Netherlands, 4.6 times; and for Denmark, 1.4 times. Comparing these updated cost-effectiveness ratio of the interventions in the study by Van Wagenberg et al. (2016) with the cost-effectiveness ratio of using probiotics, we observed the following. For the Netherlands and Denmark, at all efficacy levels, using probiotics is a relatively expensive intervention, together with a ban on partial depopulation, slaughter at 35 D, replacing old houses by new

Table 4. Estimated costs $Costs_c$ of using probiotics, prebiotics or synbiotics in broilers (€/year) and public health benefits PHB_c (€ per avoided DALY) as function of efficacy EF_c of probiotics to control on-farm *Campylobacter* infections in broilers in Denmark, the Netherlands, Poland, and Spain, assuming moderate or high performance enhancing effects of probiotics, prebiotics or synbiotics.

		Efficacy EF_c of probiotics, prebiotics, or synbiotics use in broilers										
		0.01	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90	1.00
c (Country)	$Costs_c$ (€/year)[1]	Public health benefits PHB_c (avoided DALY/year)										
High-performance enhancing effects												
Denmark	−1,983,545	1	12	24	36	47	59	71	83	95	107	119
The Netherlands	−1,787,914	1	5	10	16	21	26	31	36	42	47	52
Poland	−784,587	9	95	190	285	380	475	570	665	760	855	950
Spain	−586,092	3	31	63	94	125	157	188	220	251	282	314
Moderate-performance–enhancing effects												
Denmark	−864,477	1	12	24	36	47	59	71	83	95	107	119
The Netherlands	−5,566	1	5	10	16	21	26	31	36	42	47	52
Poland	−3,745	9	95	190	285	380	475	570	665	760	855	950
Spain	140,627	3	31	63	94	125	157	188	220	251	282	314

Abbreviations: DALY, disability-adjusted life year; EF_c, efficacy of probiotics use to control the risk of *Campylobacter* infections in broilers compared with the situation without probiotics use in country c; PHB_c,annual public health benefits due to implementation of probiotics use on all broiler farms in country c.

[1]Negative $Costs_c$ indicate net gains, that is that the gains due to the performance enhancing effects exceed the costs of purchase and administering probiotics, prebiotics, or synbiotics.

houses, and applying drink nipples without a cup. For Poland and Spain, if efficacy is less than 10%, then using probiotics can be classified as a relatively expensive intervention. To be classified as an intervention with a relatively intermediate cost-effectiveness ratio (together with applying fly screens), the efficacy of using probiotics should be at least 10%. However, even at high efficacy, using probiotics is more expensive than the cheapest interventions in the study by Van Wagenberg et al. (2016), which were using designated tools and building an anteroom with hygiene barrier in each farm house. The average efficacy of the 8 interventions in the 6 European countries analyzed by Van Wagenberg et al. (2016) was 13%, with a minimum of 0% and maximum of 57%. If the efficacy of using probiotics would be in the same order of magnitude, using probiotics would be a relatively expensive–to–moderately expensive intervention. If using probiotics was assumed to enhance broiler performance, it would be a relatively cost-effective intervention to control *Campylobacter* infections in broilers even at low efficacy levels of 1 to 10%.

This study addressed total costs and benefits at macro level. However, not only the relative risk after the intervention is important but also the costs and benefits that various groups in society are likely to derive or incur. In the default situation, all benefits from the use of probiotics stem from improved public health, yet broiler farmers incur all costs. Without redistribution of the economic consequences of these benefits there are, given the default assumptions, no direct economic incentives for broiler farmers to administer probiotics. For these type of interventions, therefore, a close collaboration of the various agents responsible is vital with cost-sharing arrangements (Van Asseldonk et al., 2017). If in addition, enhanced effects of probiotics on broiler performance are assumed, the need for cost-sharing arrangements may become redundant.

ACKNOWLEDGMENTS

This research was funded through the One Health European Joint Program (EJP) on Monitoring the gut Microbiota and Immune Response to Predict, Prevent, and Control zoonoses in humans and livestock in order to minimize the use of antimicrobials (MoMIR-PPC), which received funding from the European Union's Horizon 2020 research. Additional funding was obtained from the innovation program under grant agreement No 773830, the KB-37 theme "Healthy and safe food system" of Wageningen UR funded by the Dutch Ministry of Agriculture, Nature and Food Quality (grant KB-37-001-007-WEcR), and the agri-food program by the Dutch Ministry of Agriculture, Nature and Food Quality (grant BO-47-002-032-WEcR).

Conflict of Interest Statement: The authors declare no conflict of interest.

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