Systematic-review and meta-analysis on effect of decontamination interventions on prevalence and concentration of *Campylobacter* spp. during primary processing of broiler chickens

Abstract

Scientific advances in pathogen decontamination offer great potential to reduce *Campylobacter* spp. during primary processing. The aim of this study was to collate data from several studies using systematic review, meta-analysis followed by meta-regression. Random effect meta-analysis revealed heterogenous (τ^2=0.5707, I^2=98%) pooled reduction in prevalence of 0.56 log_{10} CFU/carcass (95% CI: 0.45-0.68, P<0.001) with a 57.02% (95% CI: 43.31-75.06, P< 0.001) decrease in relative risk. The Inside-Outside-Carcass-Wash led to greatest reduction (0.84 log_{10} CFU/carcass) while chilling resulted in least reduction (0.33 log_{10} CFU/carcass). Chemical decontamination (0.51 log_{10} CFU/carcass odds reduction with 30% relative risk reduction) was more effective in concentration reduction but not on prevalence when compared to physical decontamination (0.46 log_{10} CFU/carcass odds with 69% relative risk reduction). Application through immersion (1.01 log_{10} CFU/carcass reduction) was superior on concentration to spraying (0.52 log_{10} CFU/carcass) but was not significant on prevalence. Publication bias and small study effects were high in prevalence trials and low in concentration trials. From the meta-regression, six and eight potential modifier variables for studies on concentration and prevalence respectively were identified as combination of several interventions is common. This meta-analysis provides an overview on the expected magnitude in *Campylobacter* spp. reduction and could form basis of quantitative microbial risk assessment and derivation of intervention measures.

Keywords: Systematic-review, meta-analysis, meta-regression, *Campylobacter* spp., microbial decontamination, slaughter process

1. Introduction

The global chicken meat market has been dynamic, characterized by exponential growth currently hitting 14.86 kg per capita in 2021 (https://data.oecd.org/agroutput/meat-consumption.htm) providing an affordable source of animal proteins with low cholesterol over the past five decades (Windhorst, 2017). With this growth, it's unsurprising that bacterial gastroenteritis is increasingly being associated with the consumption of chicken meat which creates a significant burden to health care systems worldwide (Barrett and Fhogartaigh, 2017; Kim et al., 2019; Sheppard et al., 2009; Skarp et al., 2016; Sukted et al., 2017a). Among the gastroenteritis, campylobacteriosis has been associated with up to 30% of gastroenteritis cases, with poultry being the major reservoir (Kaakoush et al., 2015; Mughini-Gras et al., 2020).

Public health concerns associated with poultry consumption have been on re-contamination with gastrointestinal matter during slaughter, and cross-contamination as broilers from multiple flocks or multiple farms are processed together during bleeding, scalding, defeathering, evisceration, inside-outside washing, and chilling (Dogan et al., 2019; Guerin et al., 2010; Hayama et al., 2011; Nauta et al., 2009; Rothrock et al., 2016; Sasaki et al., 2014). As a result, food safety agencies have been tasked with the development of risk assessment framework and risk assessment model for *Campylobacter* spp. in broiler chickens (FAO/WHO, 2009). For example, in Africa, food safety agencies have adopted the *Campylobacter* spp. criterion for broilers from Codex Alimentarius guidelines (Reich and Klein, 2017). Majority of the interventions have been categorized as “Generally Recognized As Safe” (GRAS) in the regulations with limits set on the maximum usage during processing (Oyarzabal, 2005; Sukted et al., 2017a).

A reduction in concentration and prevalence of *Campylobacter* spp. using existing decontamination interventions can be achieved along the slaughter process using numerous interventions as recently reported (Dogan et al., 2019; Thames and Sukumaran, 2020). None the less, interesting observations have been made on these interventions including mode of application and type of active compound. It is, for example, presumed that immersion is superior to spraying (Okolocha and Ellerbroek, 2005; Sinhamahapatra et al., 2004; Thames and Sukumaran, 2020). On the other hand, chemical antimicrobials are preferred since they possess a residual antimicrobial activity during post-chilling handling (Kim et al., 2017). Use of hot water, additional pre-treatment spray and brushing have supported increased efficacy of chemical decontaminants (Berrang and Bailey, 2009; James et al., 2007). The efficacy of selected chemical antimicrobials increases when applied after the Inside-Outside-Carcass Wash (IOCW) as physical decontamination is more effective prior to IOCW (Loretz et al., 2010). In regards to *Campylobacter* spp., hot water, volume of water, exposure time, agitation and pH influence microbial concentration and prevalence prior to IOCW (Kim et al., 2005; Osiriphun et al., 2012).

Existing literature have emphasized on the effect of individual and combined/hurdle application of decontamination interventions along slaughter operations but accompanying simulation models using data from these interventions have emphasized on specific processing points, that is, at chilling or scalding (Bucher et al., 2015; Guerin et al., 2010; Munther et al., 2015; Osiriphun et al., 2012; Sukted et al., 2017b). Consequently, there still lacks an in-depth understanding of the effect of these interventions across the entire processing chain from scalding to post-chill. In addition, there is a need to understand modifier variables for the efficacy, such as, the mode of application, temperature, time of exposure, type of inoculum, exposed part, part sampled, and the level of initial contamination.

Data on the efficacy is fragmented, from specific points, and from several smaller studies which raises the need to collate these studies into more unified evidence with more statistical power. Systematic review and meta-analysis approach provide a powerful tool in risk assessment model parameterization (Aiassa et al., 2015). Summary effect estimates have been used to shed more information on *Salmonella* spp. decontamination (Bucher et al., 2012), *Campylobacter* spp. decontamination during chilling (Bucher et al., 2015), and *E. coli* and *Enterobacteriaceae* decontamination (Belluco et al., 2016). Systematic review followed by meta-analysis and meta-regression were therefore conducted on concentration and prevalence of *Campylobacter* spp. along the slaughter process to provide more evidence on efficacy of interventions, which has not been performed prevously.

The aim of this study was to collate data from several studies using systematic review followed by meta-analysis and meta-regression to explore potential modifier variables to validate the findings. The findings could form the basis of quantitative evidence-based risk assessment for food safety agencies to derive intervention measures during chicken slaughter with results from this meta-regression addressing the current limitation on practicality on applications of certain interventions in an actual slaughterhouse set-up which is further complicated with differences in legal frameworks, processing environment and acceptability among consumers.

2. Materials and Methods

2.1 Protocol and research question

Systematic review was used to collate existing publications on the efficacy of *Campylobacter* spp. decontamination interventions during primary processing. The main question used in this study was: to what extent do existing decontamination interventions reduce the prevalence and concentration of *Campylobacter* spp. in broiler chickens during primary processing? The systematic review process review was conducted according to PRISMA-P protocol (Moher et al., 2015; Shamseer et al., 2015).

2.2 Literature search strategy

A targeted literature search strategy was conducted in October 2018 and updated in December 2020 using three electronic databases: Web of Science, PubMed and African Index Medicus Database. The search was restricted to publications available in English from Jan 1998.

The algorithm used was: ((Campylobacter* AND (((Chicken* OR Poultry*) OR broiler*) OR gallus)) AND (slaughter* OR process*))

To add to the publications' hits on the search engines, web-searching and handsearching was done to identify grey literature not indexed in the main databases as recommended (Paez, 2017). To web-search, Google, Google Scholar, Scopus and CAB Abstracts were used with potential articles identified and assessed using other platforms due to restrictions on articles access subscription. All the citation hits were exported to EndNote-X9 application for deduplication.

2.3 Criteria for relevance and eligibility screening

Two levels of independent screening were conducted. In the first relevance screening, evaluation identified primary research, with results written in English investigating prevalence and/or concentration of *Campylobacter* spp. in broiler chicken during primary processing. At this point, studies on other non-broiler breeds or with intervention implemented before scalding or after chilling were excluded. Studies that investigated the effect of the decontamination on the processing environment were also excluded.

After the relevance screening, full papers were screened based primarily on the study designs. Only articles using randomized control trials, challenge trials, and before-after-trials were eligible for inclusion. Trials that were based on cohort studies, case-control, surveillance reports, modelling and risk analysis were ineligible for inclusion. In addition, articles with insufficient reporting or with inaccessible results were ineligible.

2.4 Assessing risk of bias and data extraction of included studies

Prior to data extraction, a checklist based on GRADE (Grading of Recommendations Assessment, Development, and Evaluation) guidelines was developed to rank the risk of bias in the trials as recommended (Schünemann et al., 2011). The reviewers evaluated within-study risk of bias using the following variable: (i) study design adequacy, (ii) sample size justification, (iii) sampling process, (iv) study set-up, (v) appropriateness of control group, (vi) statistical analysis, (vii) understated results, and (viii) presentation of estimates and variability.

Publication bias was assessed by observing the funnel plots with asymmetry being indicative of bias. Further analysis of bias was done using Egger's regression test and Begg's rank correlation test as recommended (Macaskill et al., 2001; Rothstein et al., 2005). The potential for publication bias due to small study effects was assessed using a Bubble Plot in prevalence trials. Articles with high risk of bias were excluded at this point. Only primary research published in English was eligible for inclusion to eliminate errors that would arise during article translation. Minimal bias would arise for exclusion of non-English primary research with data showing that up-to 93% of published peer-reviewed work on *Campylobacter* spp. decontamination is in English (Adkin et al., 2006).

Data extraction was done using designed Microsoft® Access forms. Metagear (Version 0.4) in R-package was used to extract data from images. Data extraction encompassed developing a database using standardized forms on article description, intervention points, intervention details, sampling points and protocols, isolation and confirmation media, prevalence and counts. The data was later exported to Microsoft® Excel for final cleaning and editing prior to import to R package (version 3.6.0) for analysis using Metafor package (Version 2.0-0) (Version 1.2.1335) (Viechtbauer, 2015).

2.5 Review Management

Screening and data extraction were done by two independent reviewers while a third reviewer verified the completeness of these processes. Disagreements were solved through consensus. The review process was guided by pre-tested checklists with accompanying guidelines.

2.6 Data processing and analysis

Ratio measures were used to present the effect measure as recommended (Higgins et al., 2019). The Odds ratio was used to present the effect on Campylobacter spp. concentration while relative risk was used for prevalence as recommended (Sterne et al., 2005). Heterogeneity that could arise from differences in the experimental designs was investigated using the risk of bias assessment. Statistical heterogeneity was calculated using Cochran's Q test, τ^2, H^2 statistic and the Higgins' and Thompson's I^2 value as recommended (Schwarzer et al., 2015). Trials/studies that were highly heterogenous were dropped at this point. Since between-study variability, measured using I^2, was considerably high within most sub-groups; a weighted-random-effect model was used to estimate the pooled effect. The between-studies variance in concentration effect, τ^2 (tau-squared), was estimated using the "method of moments" (commonly referred to as DerSimonian and Laird) method (DerSimonian and Kacker, 2007). For prevalence effect, τ^2 was estimated using the Restrictive Maximum Likelihood (REML) in a random-effects model (Viechtbauer, 2007). For homogenous data, the 'Mantel-Haenszel' fixed effect model (FE) was used to estimate the pooled effect (Deeks et al., 2008). Funnel plot asymmetry was reviewed to estimate the publication bias within the trials (Lau et al., 2006; Sutton and Higgins, 2008). Unlike for concentration where points in the funnel plot were symmetrical, slight asymmetry was noted for the prevalence trials which called for an in-depth check using forest, radial, and L'Abbe plots. A mixed-effect meta-regression was used to establish potential modifier variables identified *a priori*. These variables were selected based on their relevance and variability within and between studies. The variables could account for heterogeneity either by influencing (i) study characteristics, (ii) variables hypothesized to increase risk of bias, and (iii) study design variables, as recommended (Higgins and Thompson, 2004).

3. Results

3.1 Literature search and trial inclusion

The literature search using the algorithm resulted in 2,057 articles before de-duplication with an additional 12 articles included after hand-searching other databases. Forty-one articles were included in the systematic review from which 228 trials were extracted. (Detailed description of the trials has been provided in the supplementary materials- Section F.) The flow of studies during screening, eligibility and inclusion is summarized in Figure 1.

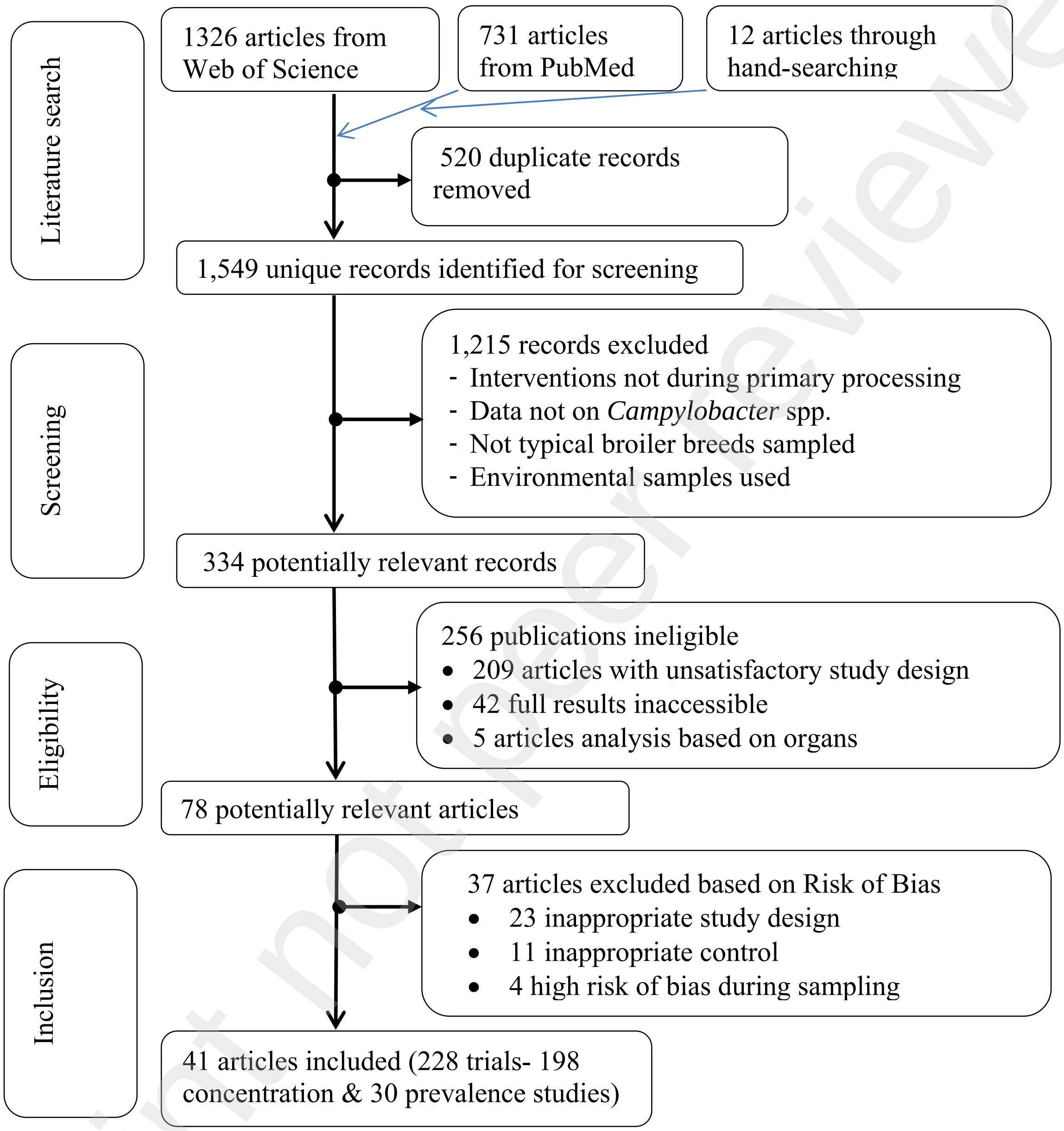

Figure 1: Flow of studies for the systematic-review meta-analysis study for *Campylobacter* spp. in broilers (intervention, concentration & prevalence topics) during primary processing of broiler chicken

3.2 Meta-analysis on studies reporting *Campylobacter* spp. concentration as an outcome

A total of 198 trials were extracted from 37 articles. Figure 3 (funnel plot) visualize the publication bias within the trials. As a result of the high number of trials, the overall forest plot with specific plot at each sub-group are presented in the Supplementary data- Section G, Figure 2 and Figure 3(a-f). The pooled effect was a 0.57 log_{10} CFU/carcass (95% CI: 0.45-0.68, P<0.001) reduction in *Campylobacter* spp. concentration. Between-study heterogeneity was considerably high (τ^2=0.57), which accounted for 98.09% of the total variance. There was minimal publication bias with a considerably symmetrical funnel plot (Figure 2). This was further confirmed by the insignificant Egger's regression test (p = 0.5872) and a low correlation based on the Begg's rank test (p = 0.0002).

Figure 2: Funnel plot representing publications reporting effect of decontamination techniques on *Campylobacter* spp. concentration during broiler chicken primary processing

Sub-group analysis on the sampling point revealed that the Inside-Outside Carcass Wash (IOCW) supported the greatest odds reduction (0.84 log_{10} CFU/carcass) while Chilling resulted in the least odds reduction (0.33 log_{10} CFU/carcass). Except for the IOCW (69%), between-study heterogeneity accounted for over 95% of total variability. Table 1 show the odds of *Campylobacter* spp. reduction on broiler chicken at different points in a slaughterhouse.

Table 1: The odds of a reduction in *Campylobacter* spp. concentration based on sampling point

	n trials (studies)	Pooled effect (log_{10} OR)	95% CI LB; UB	p-value	Heterogeneity (τ^2) & variability (I^2)	Publication bias (p-value)
Overall	198(37)	0.57	0.45; 0.68	<.01	0.57; 98.09%	InT
Scald and Pluck	33(11)	0.64	0.35; 0.93	<.01	0.61; 98.30%	InT
Evisceration	24(9)	0.49	0.06; 0.92	0.04	1.01; 96.25%	InT
IOCW	25(4)	0.84	0.55; 1.12	<.01	0.32; 69.34%	Egger's p=0.46; Begg's p=0.73
Post-IOCW, Pre-Chill	29(7)	0.50	0.28; 0.73	<.01	0.34; 95.19%	InT
Chilling	30(14)	0.33	-0.00; 0.66	0.05	0.70; 97.74%	InT
Post-Chill	57(8)	0.60	0.41; 0.79	<.01	0.50; 96.82%	InT

Heterogeneity high, hence use of Random effect model

CI: confidence interval; LB: lower bound; UB: upper bound

Publication bias tested using Egger's regression asymmetry test and Begg's (continuity corrected) adjusted rank correlation test.

InT = high heterogeneity precluded publication bias testing

The 107 trials extracted from 18 publications on chemical decontamination indicated a pooled reduction in concentration of 0.65 log_{10} CFU/carcass (95% CI: 0.51-0.79, P<0.001). Between-study heterogeneity was considerably high (τ^2= 0.47) accounting for 94.86% of total variability. The funnel plot (Supplementary data- Section G, Figure 4a & 4b) was fairy symmetrical pointing out existence of minimal publication bias among the studies. Table 2 summarizes the odds of *Campylobacter* spp. decontamination using chemical interventions.

Table 2: The effects of specific chemical decontamination techniques on the odds of *Campylobacter* spp. concentration along broiler chicken primary processing

Intervention	*n* trials (studies)	Pooled effect (log_{10} OR)	(95% CI) LB; UB	p-value	Heterogeneity (τ^2); variability (I^2)	Publication bias (p-value)
Overall chemical	107(18)	0.65	0.51; 0.79	<.01	0.47; 94.86%	InT
Acetic acid	1(1)	2.03	1.87; 2.19	<.01	FE	InT
Acidified $NaOCl_3$	8(4)	1.63	0.93; 2.33	< .01	0.92; 97.21%	InT

Cetylpyridinium chloride	1(1)	1.56	-0.27; 3.39	0.10	FE	InT
Chlorine	12(3)	0.83	0.39; 1.27	<.01	0.50; 96.35%	InT
Chlorine dioxide	3(2)	0.06	-0.34; 0.45	0.78	FE	InT
Citric acid	6(1)	0.48	0.17; 0.78	<.01	FE	InT
White vinegar	1(1)	1.70	1.51; 1.89	<.01	FE	InT
Electrolyzed water	9(2)	0.08	-0.05; 0.22	0.23	0.02; 60.24%	InT
Increased pH	2(1)	0.69	0.19; 1.20	0.01	FE	InT
Lactic acid	32(3)	0.43	0.24; 0.61	<.01	0.24; 91.98%	InT
Lysozyme	2(1)	0.13	-0.16; 0.43	0.38	FE	InT
Peracetic acid	5(2)	1.31	1.05; 1.57	<.01	FE	InT
Peroxyacetic acid	4(1)	0.98	0.45; 1.50	<.01	FE	InT
Portable water	8(4)	0.24	-0.01; 0.49	0.06	0.04; 34.65%	InT
Propionic acid	1(1)	1.26	1.37; 1.65	<.01	FE	InT
Sodium hypochlorite	1(1)	1.60	0.81; 2.39	<.01	FE	InT
Trisodium phosphate	11(3)	0.83	0.43; 1.23	<.01	0.36; 80.68%	InT

Heterogeneity high, hence use of Random effect model unless specified FE (Fixed Effect model)
CI: confidence interval; LB: lower bound; UB: upper bound

Publication bias tested using Egger's regression asymmetry test and Begg's (continuity corrected) adjusted rank correlation test.

InT = insufficient number of trials to perform a publication bias test (<10 trials) or high heterogeneity precluded publication bias testing

Further analysis on the chemical decontamination, revealed that carcass immersion (odds 1.01 $\log_{10}$ CFU/carcass reduction) is more effective than spraying/fumigating (odds 0.52 $\log_{10}$ CFU/carcass reduction) in reduction of *Campylobacter* spp. concentration. Table 3 summarizes the effectiveness based on application mode for chemical decontamination.

Table 3: The effects of interventions application mode on the odds of *Campylobacter* spp. concentration along broiler chicken primary processing

Application mode	*n* trials	Pooled effect ($\log_{10}$ OR)	95% CI LB; UB	p-value	Heterogeneity (τ^2) & variability (I^2)	Publication bias (p-value)
Immersion	23	1.01	0.63; 1.39	<.01	0.75; 97.12%	InT
Spray/fumigation	59	0.52	0.35; 0.69	<.01	0.34; 92.56%	InT

Heterogeneity high, hence use of Random effect model
CI: confidence interval; LB: lower bound; UB: upper bound

Publication bias tested using Egger's regression asymmetry test and Begg's (continuity corrected) adjusted rank correlation test.

InT = high heterogeneity precluded publication bias testing

The 91 trials extracted from 20 publications on physical decontamination revealed an odds 0.46 log_{10} CFU/carcass (95% CI: 0.28-0.65, P<0.001) reduction of *Campylobacter* spp. concentration. Between-study heterogeneity was high (τ^2= 0.69) accounting for 98.98% of total variability. The funnel plots were fairly symmetrical pointing out existence of minimal publication bias among the studies. Table 4 summarizes the odds of *Campylobacter* spp. decontamination using physical interventions.

Table 4: The effects of specific physical decontamination techniques on the odds of *Campylobacter* spp. concentration along broiler chicken primary processing

Intervention	*n* trials (studies)	Pooled effect (log OR)	(95% CI) LB; UB	p-value	Heterogeneity, τ^2; variability, I^2	Publication bias (p-value)
Overall physical	91(20)	0.46	0.28; 0.65	<.01	0.69; 98.98%	InT
Additional washers	9 (2)	0.13	-0.19; 0.45	0.39	FE	InT
Increased chill water volume	2(2)	0.27	-0.15; 0.70	0.21	FE	InT
Crust freezing	1(1)	0.43	0.19; 0.67	<.01	FE	InT
Forced air-chill	1(1)	0.44	0.20; 0.68	<.01	FE	InT
Forced fecal expulsion	2(1)	-0.30	-0.50; -0.10	<.01	FE	InT
Hot water	10(3)	0.57	0.20; 0.95	<.01	0.25; 91.59%	InT
Air-chilling	6(4)	-0.58	-1.42; 0.26	0.17	0.96; 95.35%	InT
Vent and cloaca plug	3(2)	1.45	0.19; 2.70	0.02	1.21; 99.37%	InT
Rapid surface cooling	39(1)	0.58	0.39; 0.77	<.01	0.32; 97.24%	InT
Steam-Ultrasound	5(2)	1.25	0.59; 1.91	<.01	0.53; 94.94%	InT
Visible fecal and ingesta	4(3)	-0.39	-1.08; 0.30	0.27	0.47; 96.26%	InT
Process flow realignment	9(2)	0.55	-0.36; 1.45	0.24	1.84; 97.73%	InT

Heterogeneity high, hence use of Random effect unless specified FE (Fixed Effect model)
CI: confidence interval; LB: lower bound; UB: upper bound

Publication bias tested using Egger's regression asymmetry test and Begg's (continuity corrected) adjusted rank correlation test.

InT = insufficient number of trials to perform a publication bias test (<10 trials) or high heterogeneity precluded publication bias testing

3.3 Meta-analysis on studies reporting *Campylobacter* spp. prevalence as an outcome

The overall reduction in prevalence was a 57.02% (95% CI: 43.31, 75.06, P< 0.001) relative risk reduction after the treatment. The between-study heterogeneity was high (τ^2=0.46) representing 91.51% of the total variance. Publication bias was minimal with a fairy symmetrical funnel plot (Figure 3). This was further confirmed by the insignificant Egger's regression test (p = 0.0955) and considerable correlation based on the Begg's rank test (p = 0.3207). Figure 4 summarizes the effects on interventions on the relative risk, and associated heterogeneity and publication bias within the studies using funnel, radial and L'Abbe plots (Supplementary data, section G, Figure 5a-c).

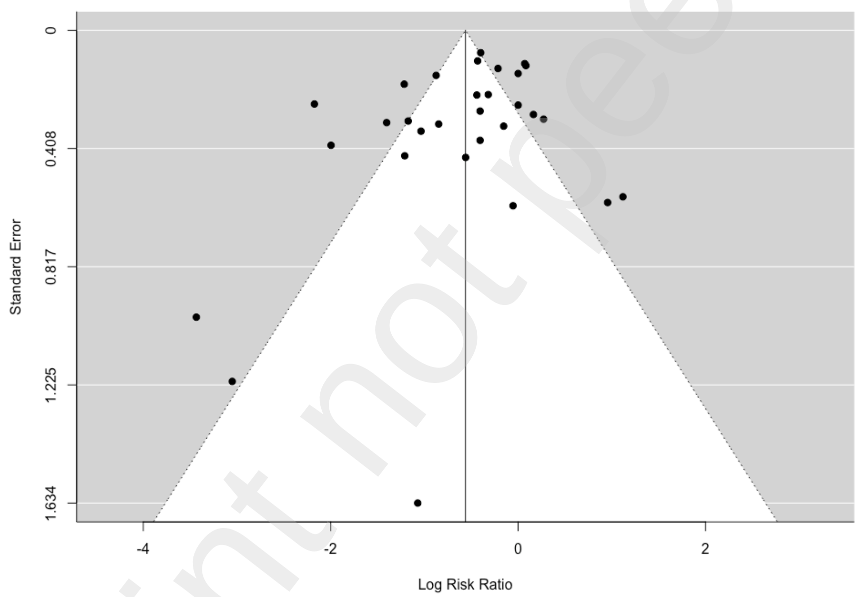

Figure 3: Funnel plot representing publications reporting effect of decontamination techniques on *Campylobacter* spp. prevalence during broiler chicken primary processing

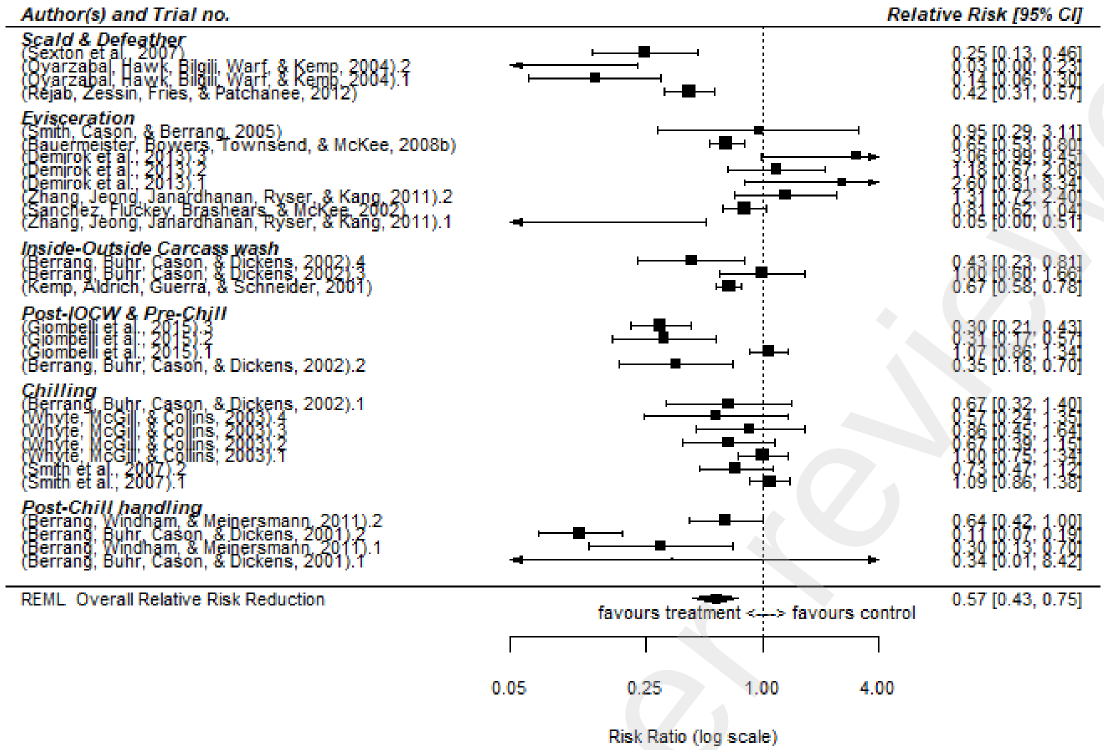

Figure 4: Forest plot to represent the relative risk of *Campylobacter* spp. prevalence reduction during broiler chicken primary processing

This meta-analysis also revealed that physical decontamination techniques are more effective in reducing *Campylobacter* spp. prevalence with relative risk reduction of 68.73% (95 CI: 51.05, 92.52, P<0.05) compared to 30.33% (CI: 16.25, 56.61, P<0.0001) relative risk reduction from application of chemical decontamination. Table 5 presents sub-group analysis on effect of specific interventions in the relative risks of *Campylobacter* spp. prevalence.

Table 5: The effects of specific chemical and physical decontamination techniques on the relative risk of *Campylobacter* spp. prevalence along broiler chicken primary processing

Intervention	*n* trials (studies)	Pooled effect (% RR)	95% CI LB; UB %	p-value	Heterogeneity, τ^2; variability, I^2	Publication bias (p-value)
Overall chemical	8(6)	30.33	16.25; 56.61	<.01	0.6064; 93.93%	InT
Acidified sodium chlorite	4(3)	20.88	-7.09; 61.46	<.01	0.9914; 91.37%	InT
Cetylpyridinium chloride	1(1)	4.73	0.44; 51.01	0.01	FE	InT
Chlorine + high pH	2(1)	47.93	23.02; 99.79	0.05	0.1772; 59.84%	InT
Peracetic acid + Hydrogen peroxide	1(1)	64.91	52.79; 79.81	<.01	FE	InT
Overall Physical	22(10)	68.73	51.05; 92.52	0.01	0.39; 88.60%	InT
High pressure spray	3(1)	47.37	20.18; 111.20	0.09	0.52; 93.68%	InT
Hot water	4(1)	85.38	65.43; 111.43	0.24	0.01; 13.19%	InT
Air chilling	5(3)	128.07	82.40; 199.07	0.27	0.13; 59.70%	InT
Plugged cloaca	2(1)	11.67	7.13; 19.10	<.01	FE	InT
Process realignment	4(1)	58.02	35.62; 94.50	0.03	0.14; 57.69%	InT
Modern Vs wet	1(1)	41.69	30.73; 56.56	<.01	FE	InT
Visible fecal/ingesta	3(2)	93.81	67.49; 130.38	0.70	0.03; 37.18%	InT

Heterogeneity high, hence use of random effect unless specified. FE signify use of fixed effect model
CI: confidence interval; LB: lower bound; UB: upper bound

Publication bias tested using Egger's regression asymmetry test and Begg's (continuity corrected) adjusted rank correlation test.

InT = insufficient number of trials to perform a publication bias test (<10 trials) or high heterogeneity precluded publication bias testing

A further test using technique of intervention application revealed that cloaca treatment (P=0.004) and immersion (P=0.055) were important moderator variables while application of interventions as spray did not significant (P=0.32) reduce *Campylobacter* spp. prevalence.

3.4 Meta-regression

A mixed effect meta-regression model was used to run the fifteen modifier variables identified *a priori*. For the studies reporting *Campylobacter* spp. concentration as outcome, six potential modifier variables were found to be significant in the multivariable meta-regression model: intervention type (p=0.08), exposure time (p=0.01), country where study was conducted (p<0.01), inoculum type (p=0.02), type of analyzed sample (0.08), and publication year (p=0.01). For the studies reporting *Campylobacter* spp. prevalence as outcome, eight potential modifier variables were found to be significant in the multivariable meta-regression model: intervention type (p<0.01), study set-up (p=0.05), inoculum type (p<0.01), publication year (p<0.01), microbial confirmation method (p=0.01), Sample size-Treatment group (p<0.01), Sample size- control group (p<0.01) and overall risk of bias (p=0.06). Table 6 gives more insight on the pooled effects and significance of potential modifier variables as revealed by the meta-regression model.

Table 6: Potential effect modifiers and multivariable meta-regression model on *Campylobacter* spp. concentration and prevalence

Potential effect modifiers		Studies with *Campylobacter* spp. concentration as outcome (log Odd's Ratio)				Studies with *Campylobacter* spp. prevalence as outcome (Relative Risk)			
		N	Pooled effect (log_{10} OR)	95% CI Lower; upper	p-value	*n*	Pooled effect (RR)	95% CI Lower; upper	p-value
Intercept			3.99	1.70; 6.28	<.01		0.10	0.00; 8.17	0.22
Sampling point	Scald & pluck	33	0.01	-0.04; 0.06	0.56	4	0.91	0.80; 1.04	0.82
	Evisceration	24				8			
	IOCW	25				3			
	Post IOCW & Pre-Chill	29				4			
	Chilling	30				7			
	Post-chill	57				4			
Intervention type	Physical decontamination	107	-0.01	-0.03; 0.00	0.08	22	1.35	1.16; 1.49	<.01
	Chemical decontamination	91				8			
Exposure Technique	Immersion	23	-0.03	-0.08; 0.03	0.37	12	1.00	0.79; 1.26	0.80
	Spray	59				10			
	Cloaca treatment	34				2			
	Other techniques	82				6			
Exposure time	Less than 1 minute	102	-0.02	-0.04; -0.00	0.01	11	0.95	0.88; 1.04	0.21
	More than 1 min	37				9			
	Not described	58				10			
Study set-up	Laboratory set-up	95	0.14	-0.09; 0.37	0.74	6	0.39	0.13; 1.14	0.05
	Pilot plant	39				3			
	Commercial	64				21			
Country where study conducted	North America	69	-0.26	-0.45; -0.06	<.01	21	1.23	0.93; 1.65	0.81
	Europe	128				4			
	Others	1				5			
Inoculum type	Specific		-0.00	-0.00; 0.00	0.02		1.12	1.04; 1.11	<.01

Exposed part	Whole carcass	145				21			
	Carcass parts	25	-0.06	-0.14; 0.02	0.25	7	1.35	0.90; 2.01	0.75
	Cloaca	28				2			
Type of analysed sample	Whole carcass rinse	50				18			
	Carcass parts swabs	36	-0.03	-0.08; -0.02	0.08	8	0.97	0.85; 1.09	0.46
	Carcass parts rinse	112				4			
Isolation media	Specific		-0.01	-0.17; 0.15	0.62		1.01	0.84; 1.11	0.29
Publication year	1998-2003	15				12			
	2004-2008	20	-0.05	-0.09; -0.01	0.01	7	1.35	1.13; 1.49	<.01
	2009-2013	27				8			
	2014-2018	136				3			
Microbial Confirmation	Morphology only	90				17			
	Morphology & biochemical	86	0.03	-0.05; 0.11	0.33	9	0.73	0.57; 0.93	0.01
	Other	22				4			
Sample size-Treatment group	Less than 10	107				7			
	11 to 30	67	0.01	-0.01; 0.03	0.42	12	0.93	0.90; 0.96	<.01
	31to 100	20				4			
	More than 100	4				7			
Sample size-control group	Less than 10	110				7			
	11 to 30	64	-0.01	-0.-03; 0.01	0.56	13	1.07	1.04; 1.11	<.01
	31 to 100	21				3			
	More than 100	3				7			
Overall RoB		NS	-0.26	-0.61; 0.10	0.47		0.42	0.17; 1.03	0.06

Mixed effects model
CI: confidence interval; LB: lower bound; UB: upper bound

Figure 5 illustrates the univariate relationship between sample size and the log relative risk using a bubble plot. The bubble plot revealed that the log relative risk was higher for publications with less than 30 samples. Sample size effect was not observed for the *Campylobacter* spp. concentration studies. Small study effect was however observed as none of the meta-analysis had non-significant heterogeneity for 10 or more trials. This corroborates the findings from the bubble plot and the meta-regression on the sample sizes.

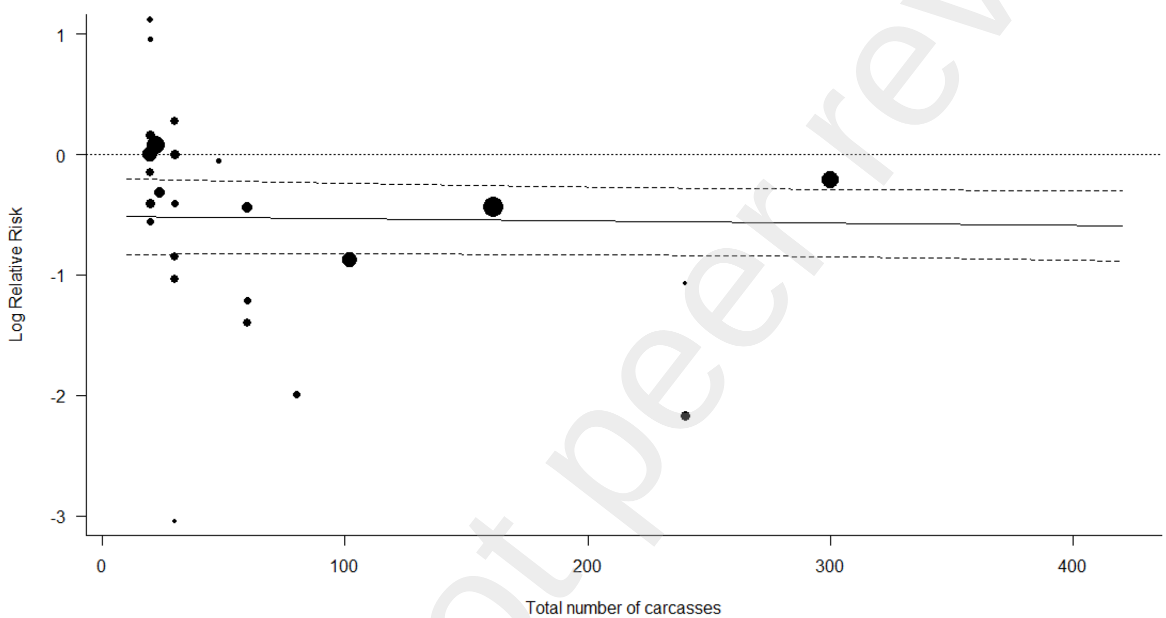

Figure 5: Bubble plot. The size of the bubble is proportional to the weight of studies in the meta-analysis. The dashes represent the upper and lower limits of the mean (continuous line) while the dotted line separated detrimental and beneficial treatments.

4. Discussion

Discussion on the systematic review and publication bias

This systematic review demonstrates that existing microbial decontamination techniques have the potential to reduce *Campylobacter* spp. concentration and prevalence along the slaughter process. The funnel plots revealed publication bias was minimal in concentration studies as compared to prevalence studies. It is worth noting that despite funnels plots being an adequate representation of publication bias, asymmetry within the plots is not solely due to publication bias (Bax et al., 2009; Lau et al., 2006; Sutton and Higgins, 2008). The slight asymmetry in the funnel plots for prevalence studies was further confirmed with the considerable correlation from the Begg's rank test ($p = 0.3207$), and a significant ($p=0.06$) on the meta-regression for overall risk of bias on the meta-data for prevalence studies. Lack of concealment and blinding during sample collection, overreliance on convenient sample sizes, and inadequate generation of allocation sequence may impact on the strength of the meta-analysis findings. Differences in adherence to existing guidelines on study methodology and reporting in food safety have been a major set-back in comparison of different research reports (O'Connor et al., 2010). The meta-regression revealed that the study set-up and overall risk of bias would potentially modify the results for prevalence studies but not for concentration. It is however not possible to differentiate between impact of publication bias and heterogeneity (Higgins and Thompson, 2002). Small study effect was observed as none of the meta-analysis had non-significant heterogeneity for 10 or more trials and this corroborates the findings on the sample sizes as shown by the bubble plots and the meta-regression analysis.

Discussion on meta-analysis

Results from the meta-analysis indicate an overall reduction in the odds concentration of 0.57 $\log_{10}$ CFU/carcass and a 57.02% decrease in the relative risk for *Campylobacter* spp. Sub-group analysis on sampling points revealed that interventions at IOCW resulted in the greatest odds reduction (0.84 $\log_{10}$ CFU/carcass) while chilling led to the least reduction (0.33 $\log_{10}$ CFU/carcass). The findings on the trends in *Campylobacter* spp. concentration and prevalence during primary processing from this systematic review resonate with similar work (Bucher et al., 2015; Guerin et al., 2010).

The meta-analysis indicated that chemical decontamination when compared to physical decontamination is more effective in reducing concentration but less effective on prevalence. The meta-data for specific chemical and physical decontamination interventions revealed similar trends with existing literature (Bucher et al., 2015; Dogan et al., 2019; Loretz et al., 2010). Physical decontamination techniques were more effective prior to IOCW while chemical decontamination techniques were more effective after IOCW. Physical interventions such as crust-freezing, forced air chill, vent/cloaca plug, rapid surface cooling, and steam-ultrasound significantly reduced concentration and prevalence. Despite the effect of hot water during scalding, defeathering and IOCW being within reported range, the meta-analysis revealed that the effect on prevalence was not significant thereby contradicting earlier research as the temperatures used were within normal growth temperature for *Campylobacter* spp. (Loretz et al., 2010; Osiriphun et al., 2012). Increased chill water volume, additional washers, air chilling, and physical removal of visible fecal matter and ingesta did not significantly affect *Campylobacter* spp. concentration and prevalence. Process flow realignment and traditional wet-markets significantly reduced *Campylobacter* spp. prevalence but not concentration. Some physical decontamination techniques prior to evisceration could significantly increase *Campylobacter* spp. concentrations as seen for fecal expulsion but this calls for caution if to be incorporated during processing.

Subgroup analysis on the mode of intervention application confirm that immersion chilling is more effective on *Campylobacter* spp. concentration where chemical decontaminants have been used than spray treatment as previous observed (Bucher et al., 2015, 2012; Gonzalez-Fandos et al., 2020; Loretz et al., 2010; Okolocha and Ellerbroek, 2005; Purnell et al., 2014; Thames and Sukumaran, 2020). The metadata revealed that immersion could result in an almost double reduction in contamination rates. This could be explained by either the fact that immersion interventions resulted in longer exposure time than spray/fumigation or possible residual effect or washing effect as hypothesized in other studies (Bucher et al., 2015; Dogan et al., 2019; Koolman et al., 2014). Possible residual effects of chemical decontaminants from processing water may be present during post-chill handling thereby overstating the treatment effects and this points to variations in minimum residual chemical decontaminants in portable water which is set in legal and industry guidelines and standards (Bucher et al., 2012).

Discussion on the meta-regression

During processing, it is common practice to combine several physical and chemical interventions (Koolman et al., 2014; Loretz et al., 2010). Subgroup analysis on the hurdles revealed massive permutations in this systematic review. Synergistic effects on different interventions in the hurdles could overestimate the findings of this meta-analysis. The meta-regression showed that these permutations did not significantly impact decontamination as hypothesized in a similar systematic review (Higgins and Thompson, 2004). From the meta-regression, six and eight potential modifier variables for studies evaluating effect of an interventions on *Campylobacter* spp. concentration and prevalence respectively were identified.

The meta-regression revealed that the type of intervention used had a significant impact on the effects for both concentration (p=0.08) and prevalence (p<0.01). The type of intervention can be broadly categorized as physical, chemical, and microbial decontamination. Studies on use of microbial interventions failed to meet the inclusion criteria of this systematic review. The inoculum type significantly modified the effect on *Campylobacter* spp. concentration (p=0.02) and prevalence (p<0.01) for the interventions evaluated. This collaborates earlier finding on use of higher-than-normal levels of an organism during artificial inoculation of samples as this have been reported to exaggerate the results (Boysen et al., 2013). The year of publication significantly modified the metadata on the effect on *Campylobacter* spp. concentration (p=0.02) and prevalence (p<0.01) for the interventions evaluated. This could point to advancement in research and regulatory environment as reported for decontamination interventions on *Salmonella spp*. (Kerr et al., 2013; Thomas et al., 2020).

For studies that reported changes in *Campylobacter* spp. concentration as the effect, there was significant difference (p=0.01) for studies where the broiler chicken was exposed to the intervention for less than a minute from those where exposure time exceeded a minute collaborating earlier research (Gonzalez-Fandos et al., 2020). The country (region) where study was conducted significantly (p<0.01) modified the effects on *Campylobacter* spp. concentration for the intervention. Majority of the studies were conducted in either Europe or North America, with one study from Asia meeting the inclusion criteria. Up to 93% of peer-reviewed publications on *Campylobacter* spp. decontamination have been reported to be available in English (Adkin et al., 2006). Differences in regulations on management options for *Campylobacter* spp. during broiler slaughter among food safety authorities across different countries have either a synergistic or inhibitory effect on decontamination studies especially where a study set-up was in an actual factory (Oyarzabal, 2005; Sukted et al., 2017a). The type of analysed samples significantly modified (p=0.08) the effect on *Campylobacter* spp. concentration for the interventions and this collaborates research on variation of decontamination effects on different broiler carcass parts (Purnell et al., 2014; Riedel et al., 2009). Variations in decontamination effects have been reported for different carcass parts of a broiler chicken. For this systematic review, majority of the studies eligible for inclusion had reported the effect using carcass rinse from either a whole carcass or from carcass parts.

For studies that reported changes in *Campylobacter* spp. prevalence as the effect, there was a significant difference on the study set-up (p=0.05). Similar findings have been reported on the odds of *Salmonella* spp. reduction during slaughter (Bucher et al., 2012) and this was attributed to differences in the extent of control of other risk factors during processing. For this study, majority of the studies on prevalence had been conducted in a commercial factory set-up unlike for concentration studies where the majority were in a laboratory set-up. The microbial confirmation method significantly (p=0.01) modified the metadata on prevalence as has been reported (Rossler et al., 2019). Majority of the studies reporting prevalence relied on morphology with limited incorporation of biochemical or other techniques. Small study effect was evident in studies reporting the effect on prevalence with sample size- Treatment group (p<0.01) and sample size- control group (p<0.01) significantly modifying the metadata. This further collaborates with the bubble plot presented for studies on prevalence. The overall risk of bias significantly (p=0.06) modified data on prevalence, and this collaborates the results on publication bias presented using the funnel plots and quantitively analysed using Egger's regression test and Begg's rank correlation test. Small study effect has previously been reported to affect results on *Campylobacter* spp. prevalence (Keithlin et al., 2014).

5. Conclusion

The current study has demonstrated that various interventions result in significant reduction of prevalence and concentration of *Campylobacter* spp. along poultry slaughter process. Based on the meta-analysis, acids such as acetic, citric, peracetic, peroxyacetic, and lactic, acidified sodium chlorite, cetylpyridinium chloride, chlorine, vinegar, sodium hypochlorite and trisodium phosphate result in significant reduction of *Campylobacter* spp. on poultry carcasses during slaughter. Physical techniques such as crust freezing, forced air chill, hot water, vent plug, rapid surface cooling and steam-ultrasound treatment also proved to be effective. Physical decontamination is more effective on prevalence while chemical decontamination is more effective on concentration. Application of decontamination interventions by immersion is more effective than spray-based interventions. For spray-based interventions, modifier variables revealed that pressure exerted by the spray, and exposure time plays a vital role. The meta-regression uncovered existence of other modifier variables to be considered when making recommendations especially in situations where combinations of several interventions are applied during processing. The findings from this research provide an overview of what to expect on use of different interventions in a commercial setting.

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Declaration of Interests

Declarations of interest: none

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