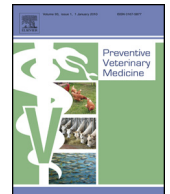




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## The application of knowledge synthesis methods in agri-food public health: Recent advancements, challenges and opportunities



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### ARTICLE INFO

#### Article history:

Received 14 August 2013

Received in revised form

13 November 2013

Accepted 15 November 2013

#### Keywords:

Knowledge synthesis

Systematic reviews

Meta-analysis

Agri-food public health

### ABSTRACT

Knowledge synthesis refers to the integration of findings from individual research studies on a given topic or question into the global knowledge base. The application of knowledge synthesis methods, particularly systematic reviews and meta-analysis, has increased considerably in the agri-food public health sector over the past decade and this trend is expected to continue. The objectives of our review were: (1) to describe the most promising knowledge synthesis methods and their applicability in agri-food public health, and (2) to summarize the recent advancements, challenges, and opportunities in the use of systematic review and meta-analysis methods in this sector. We performed a structured review of knowledge synthesis literature from various disciplines to address the first objective, and used comprehensive insights and experiences in applying these methods in the agri-food public health sector to inform the second objective. We describe five knowledge synthesis methods that can be used to address various agri-food public health questions or topics under different conditions and contexts. Scoping reviews describe the main characteristics and knowledge gaps in a broad research field and can be used to evaluate opportunities for prioritizing focused questions for related systematic reviews. Structured rapid reviews are streamlined systematic reviews conducted within a short timeframe to inform urgent decision-making. Mixed-method and qualitative reviews synthesize diverse sources of contextual knowledge (e.g. socio-cognitive, economic, and feasibility considerations). Systematic reviews are a structured and transparent method used to summarize and synthesize literature on a clearly-defined question, and meta-analysis is the statistical combination of data from multiple individual studies. We briefly describe and discuss key advancements in the use of systematic reviews and meta-analysis, including: risk-of-bias assessments; an overall quality-of-evidence approach; engagement of stakeholders; Bayesian, multivariate, and network meta-analysis; and synthesis of diagnostic test accuracy studies. We also highlight several challenges and opportunities in the conduct of systematic reviews (e.g. inclusion of grey literature, minimizing language bias, and optimizing search strategies) and meta-analysis (e.g. inclusion of observational studies and approaches to address the

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insufficient reporting of data and significant heterogeneity). Many of these developments have yet to be comprehensively applied and evaluated in an agri-food public health context, and more research is needed in this area. There is a need to strengthen knowledge synthesis capacity and infrastructure at the regional, national, and international levels in this sector to ensure that the best available knowledge is used to inform future decision-making about agri-food public health issues.

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## 1. Introduction

Research end-users (e.g. policy-makers, practitioners, and other decision-makers) should be informed with the best available knowledge in order to demonstrate accountable and evidence-informed decision-making for complex issues with important health and socio-economic implications. The process of moving research knowledge into policy and practice and enhancing its utilization among end-users is referred to as knowledge transfer and exchange (Lavis et al., 2003; Mitton et al., 2007; Rajić et al., 2013). Knowledge synthesis is a key foundation of knowledge transfer and exchange because it integrates findings from multiple individual studies and other sources on a given topic or question into the global knowledge base (Grimshaw, 2010; Tricco et al., 2011). Knowledge synthesis provides a more accurate and reliable assessment of the state of knowledge about a topic than individual studies (Lavis et al., 2005), and it follows a more structured and transparent methodology than traditional narrative literature reviews (Sargeant et al., 2006a,b; Waddell et al., 2009).

Two specific knowledge synthesis methods, systematic reviews and meta-analysis, have been widely adopted in multiple sectors over the past several decades in an attempt to improve the general utilization of knowledge among end-users and to inform policy-making with the best available knowledge (Tricco et al., 2011; Rajić et al., 2013). For example, in the agri-food public health sector, meta-analysis was used by an expert panel in 1998–1999 to inform Health Canada's potential approval of recombinant bovine somatotropin (rbST) for use in dairy cattle production (Health Canada, 1998; Dohoo et al., 2003a, 2003b). Based on these findings, the panel concluded that there were several animal health and welfare concerns associated with rbST and this contributed to the subsequent decision not to approve rbST in Canada (Health Canada, 1998; Dohoo et al., 2003a, 2003b). Despite the successful use of meta-analysis to support this policy decision, the formal adoption of knowledge synthesis methods to address agri-food public health issues did not widely occur until the publication of initial systematic review guidelines in this sector in 2005 (Sargeant et al., 2005, 2006a,b).

Since that time, systematic reviews and meta-analysis have been increasingly conducted in this sector to investigate questions about intervention efficacy, risk factors for infection or disease, prevalence and concentration of outcomes, and diagnostic test accuracy in a wide variety of topic areas (Wilkins et al., 2010; Wilhelm et al., 2011a; Bucher et al., 2012a; Snedeker et al., 2012; Tuševljak et al., 2012; Kerr et al., 2013). Additional knowledge synthesis methods, including scoping reviews, structured rapid reviews, and mixed-method reviews, have recently

developed in the health and social science sectors (Arksey and O'Malley, 2005; Mays et al., 2005; Ganann et al., 2010), and these have also begun to be adapted and implemented to address agri-food public health issues (Ilic et al., 2012; Tuševljak et al., 2012; Rajić et al., 2013). Integrated findings based on one or more of these methods can be used to inform policy and programme development, to identify knowledge gaps and prioritize future research, and to inform risk and decision analysis (Fazil et al., 2008; European Food Safety Authority [EFSA], 2010; Rajić et al., 2013).

Many developments in the conduct of knowledge synthesis, particularly systematic reviews and meta-analysis, have been published during the past several years (Sheldon, 2005; Sutton and Higgins, 2008; Higgins and Green, 2011), but these have not been comprehensively described and discussed in previous introductory guides in the agri-food public health context (Sargeant et al., 2005, 2006a,b; EFSA, 2010; Gonzales-Barron and Butler, 2011). In addition, through our conduct of several knowledge synthesis projects over the past decade we have encountered many unique challenges and considerations in the application of these methods to agri-food public health issues. We believe that these experiences and insights would benefit other researchers in this area. The objectives of this review are: (1) to describe and discuss the key knowledge synthesis methods and their contextual applicability to the agri-food public health sector, and (2) to discuss the recent advancements, challenges, and opportunities related to the use of systematic review and meta-analysis methods in this sector. Throughout this review we use the term "agri-food public health" to refer to the cross-cutting and overlapping areas of veterinary public health, food safety, and "One Health" (Sargeant et al., 2006a,b; Rajić et al., 2013). We also refer to "knowledge" as encompassing research as well as other sources of information (e.g. government policies) that could be synthesized and used to inform decision-making.

## 2. Review approach

A structured review was conducted as part of a larger project about knowledge transfer and exchange to identify, classify, and summarize key information about the most promising and recommended knowledge synthesis methods as reported in various sectors (Rajić et al., 2013). Briefly, a comprehensive and pre-tested search was implemented on July 25, 2011, in five online bibliographic databases (Medline, Scopus, Commonwealth Agricultural Bureau [CAB] Direct, Current Contents Connect, and the Cumulative Index to Nursing and Allied Health Literature) to identify reviews, reports, commentaries, case studies, and other comprehensive literature about the subject (Rajić

et al., 2013). We also conducted a Scopus web search, limited to the first 100 hits as sorted by relevance, to identify grey literature, and included two books about the subject (Straus et al., 2009; Bennett and Jessani, 2011). Additional articles about knowledge synthesis methods were identified from the reference lists of relevant articles and procured during article characterization.

Relevance screening of all identified citations was conducted by two independent reviewers using a pre-tested form with two questions (Rajić et al., 2013). Citations were considered relevant if they were published in English, Spanish, or French and if they described one or more knowledge synthesis methods to support or facilitate knowledge transfer and exchange for policy- or decision-making. Two reviewers (I.Y. and A.R.) independently characterized all relevant articles using an iteratively developed form (Rajić et al., 2013). I.Y. extracted key information from the articles about the method descriptions, context of use, advantages and disadvantages, and any noted challenges or opportunities. A narrative synthesis of the extracted information was conducted for each synthesis method (Mays et al., 2005; Rajić et al., 2013). The review was conducted using the online management software DistillerSR (Evidence Partners Incorporated, Ottawa, ON). Additional details about the review methods, including a copy of the specific search algorithm and all forms used, are reported in Rajić et al. (2013).

To obtain more detailed information about specific systematic review and meta-analysis advancements and challenges, four authors (I.Y., L.W., J.S. and A.R.) developed a list of key issues that arose during our collaborative conduct of various knowledge synthesis projects since publication of a previous guide in this sector (Sargeant et al., 2005, 2006a,b). These issues were identified and informed by reviewing published knowledge synthesis articles conducted by the review authors and other key collaborators and through informal and ad hoc group discussions and consultations during this time. The final list of issues included: risk-of-bias assessments; overall quality-of-evidence approaches; summary-of-findings tables; stakeholder engagement; inclusion of grey literature and observational studies; language bias; optimizing search strategies; updating reviews; resource and logistical requirements; Bayesian, multivariate, network, and individual participant data meta-analysis; synthesis of diagnostic test accuracy studies; insufficient data reporting; and meta-analysis of a small number of studies and in the presence of significant heterogeneity. This list is not meant to be exhaustive of all possible advancements and challenges in this area but reflects those considered by the authors to have important implications for knowledge synthesis in agri-food public health. Relevant articles to support these sections of the review were obtained from references previously known to the authors, through searching their reference lists, and via ad hoc literature searches in online bibliographic databases.

### 3. Overview of knowledge synthesis methods

We identified seven key knowledge synthesis methods from the initial screening of 827 unique abstracts

and characterization of 168 relevant articles during the structured review of the knowledge transfer and exchange literature (Rajić et al., 2013). Systematic reviews and meta-analysis were originally categorized as one comprehensive method due to their complementary nature but are discussed in this review as distinct methods. An overview of five of these knowledge synthesis methods, including their brief description, contextual applicability, and key advantages and disadvantages are shown in Table 1 and discussed below. We primarily focus the discussion on systematic reviews and meta-analysis due to their more extensive development and wider adoption in this sector. Two additional methods, knowledge mapping and synthesis of public policies (Ebener et al., 2006; National Collaborating Centre for Healthy Public Policy, 2010), are not discussed here because they primarily focus on synthesizing sources of knowledge other than research and they were considered beyond the scope of this review.

#### 3.1. Scoping reviews

Scoping reviews are used to map out the distribution and characteristics of a broad knowledge area or issue (Arksey and O'Malley, 2005; Anderson et al., 2008). They can be conducted to summarize the state of knowledge on a particular issue, to identify research gaps, and to prioritize questions for a systematic review (Arksey and O'Malley, 2005; Anderson et al., 2008). In contrast to a systematic review, scoping reviews usually focus on a broader research question that is often policy-driven and they typically do not include a risk-of-bias assessment step (Arksey and O'Malley, 2005; Anderson et al., 2008). They can be conducted in combination with a systematic review to help focus the risk-of-bias assessment, detailed data extraction, and analysis steps to areas where sufficient knowledge is available. For example, the results of a recent scoping review investigating the prevalence of zoonotic bacteria and antimicrobial resistance in farmed and wild aquatic species and seafood were used to prioritize specific areas (i.e. bacteria, aquatic and seafood species, and point in food chain combinations) for targeted systematic review and meta-analysis (Tuševljak et al., 2012).

The initial scoping review framework proposed by Arksey and O'Malley (2005) consists of the following six steps: (1) identify the research question; (2) identify relevant studies (i.e. search strategy); (3) study selection (i.e. relevance screening and extraction of key characteristics from relevant articles); (4) data charting; (5) collating, summarizing, and reporting the results; and (6) an optional stakeholder engagement step. Many of these steps correspond to similar steps in the systematic review process (Fig. 1), with the major differences between these two methods largely related the nature of the review question (broad and policy-driven vs. focused and specific). Based on our experience conducting scoping reviews to address complex etiological questions (e.g. source attribution of infectious diseases), the findings and conclusions can be dependent on the specific variables used to categorize and summarize the published research. For example, in an ongoing review about the role of swine and other animal species in the transmission of emerging viruses to

**Table 1**  
An overview of the key characteristics of five knowledge synthesis methods.

Synthesis method	Brief method description	Agri-food public health example questions	Key advantages	Key disadvantages	Approximate timeline to completion <sup>a</sup>
Structured rapid review	<ul style="list-style-type: none"> <li>Streamlined systematic review conducted within a short timeframe or with limited resources and that feeds directly into decision-making (Ganann et al., 2010)</li> </ul>	What are the public attitudes towards emerging food technologies? (Four-month rapid review conducted for the UK Food Standards Agency) (Lyndhurst, 2009)	<ul style="list-style-type: none"> <li>Less resource-intensive than a full systematic or scoping review</li> <li>Rapid timeframe used to provide urgent advice for policy- and decision-making</li> <li>Some flexibility in the procedures</li> </ul>	<ul style="list-style-type: none"> <li>Lack of standardized and validated procedures</li> <li>Exclusion or modification of some steps can introduce bias</li> </ul>	• ≤3 months
Scoping review	<ul style="list-style-type: none"> <li>Review of a broad research question to map out the key characteristics of a knowledge area and the main sources and types of information available (Arksey and O'Malley, 2005)</li> </ul>	What is the characterization and distribution of published primary research about microbial hazards in leafy green vegetables? (Ilic et al., 2012)	<ul style="list-style-type: none"> <li>Can identify knowledge gaps and inform systematic reviews and decision-making</li> <li>Some flexibility in the procedures</li> <li>Involvement of stakeholders increases relevance of results</li> <li>Broad range of knowledge considered</li> <li>Flexibility in choice of method and procedures</li> <li>Useful to inform policy- and decision-making due to range of contextual knowledge considered</li> </ul>	<ul style="list-style-type: none"> <li>Lack of standardized and validated procedures</li> <li>Usually does not include a risk-of-bias assessment</li> <li>Involvement of stakeholders could introduce bias</li> <li>Difficulties in identifying and evaluating qualitative research</li> <li>Can be subjective and lack transparency</li> <li>Lack of standardized procedures</li> </ul>	• 6–12 months
Mixed-method and qualitative reviews	<ul style="list-style-type: none"> <li>Modified systematic review that includes a diverse range of qualitative and quantitative sources of knowledge (Mays et al., 2005)</li> <li>Many variations exist, including realist review (Pawson et al., 2005), integrative review (Whittemore and Knaf, 2005), and meta-ethnography review (Atkins et al., 2008)</li> </ul>	What are the key principles of knowledge transfer and exchange and their potential applicability to the agri-food public health sector? (Rajić et al., 2013)	<ul style="list-style-type: none"> <li>Is a rigorous, transparent, and reliable method</li> <li>Provides a comprehensive and credible summary of the state of knowledge on a specific topic</li> <li>Framework and procedures are well-defined and established</li> </ul>	<ul style="list-style-type: none"> <li>Is resource- and time-intensive</li> <li>Some study designs typically excluded (e.g. observational)</li> <li>Question might be too narrowly focused for use in policy-making contexts</li> </ul>	• 3–18 months
Systematic review	<ul style="list-style-type: none"> <li>A structured review of a clearly defined question (Sargeant et al., 2006; Higgins and Green, 2011)</li> <li>Uses systematic and explicit procedures to identify, select, critically appraise, extract, and analyze data from primary research (Sargeant et al., 2006; Higgins and Green, 2011)</li> </ul>	<p><i>Intervention:</i> What is the efficacy of chilling interventions to reduce <i>Salmonella</i> contamination of chicken carcasses during processing? (Bucher et al., 2012a)</p> <p><i>Risk factor:</i> What is the role of swine, pork and pork products as a potential source of zoonotic hepatitis E virus in humans? (Wilhelm et al., 2011a)</p> <p><i>Diagnostic test accuracy:</i> What is the diagnostic accuracy of culture and PCR to detect <i>Salmonella</i> in swine? (Wilkins et al., 2010)</p>	<ul style="list-style-type: none"> <li>Is a rigorous, transparent, and reliable method</li> <li>Provides a comprehensive and credible summary of the state of knowledge on a specific topic</li> <li>Framework and procedures are well-defined and established</li> </ul>	<ul style="list-style-type: none"> <li>Is resource- and time-intensive</li> <li>Some study designs typically excluded (e.g. observational)</li> <li>Question might be too narrowly focused for use in policy-making contexts</li> </ul>	• 3–18 months
Meta-analysis	<ul style="list-style-type: none"> <li>The statistical combination of data from multiple individual studies (Borenstein et al., 2009; Gonzales-Barron and Butler, 2011)</li> <li>Refer to Table 2 for an overview of traditional and advanced approaches</li> </ul>	<p><i>Fixed-effect meta-analysis:</i> What is the best estimate of rbST to affect the risk of clinical mastitis in dairy cattle? (Dohoo et al., 2003a)</p> <p><i>Random-effects meta-analysis:</i> What is the average estimate of efficacy of Type III protein vaccines to reduce faecal shedding of <i>E. coli</i> 0157 in cattle faeces? (Snedeker et al., 2012)</p>	<ul style="list-style-type: none"> <li>Can increase precision and power of effect estimates</li> <li>Estimates can be used as credible inputs for risk and decision-analysis models</li> <li>Many procedures exist to pool data and explore heterogeneity under different scenarios</li> </ul>	<ul style="list-style-type: none"> <li>Is only reliable if model assumptions are adhered to, with well-conducted studies, and if data are sufficiently reported and comparable</li> <li>Some advanced methods require specialized expertise and are still under development</li> </ul>	• 1–3 months (in addition to the time required for completion of the systematic review)

<sup>a</sup> Timelines depend on various factors, including available resources and expertise, complexity of the question and topic, and if the review is conducted as part of a larger, experienced team in settings that routinely conduct knowledge synthesis (e.g. designated synthesis units) vs. other contexts (e.g. graduate student research).

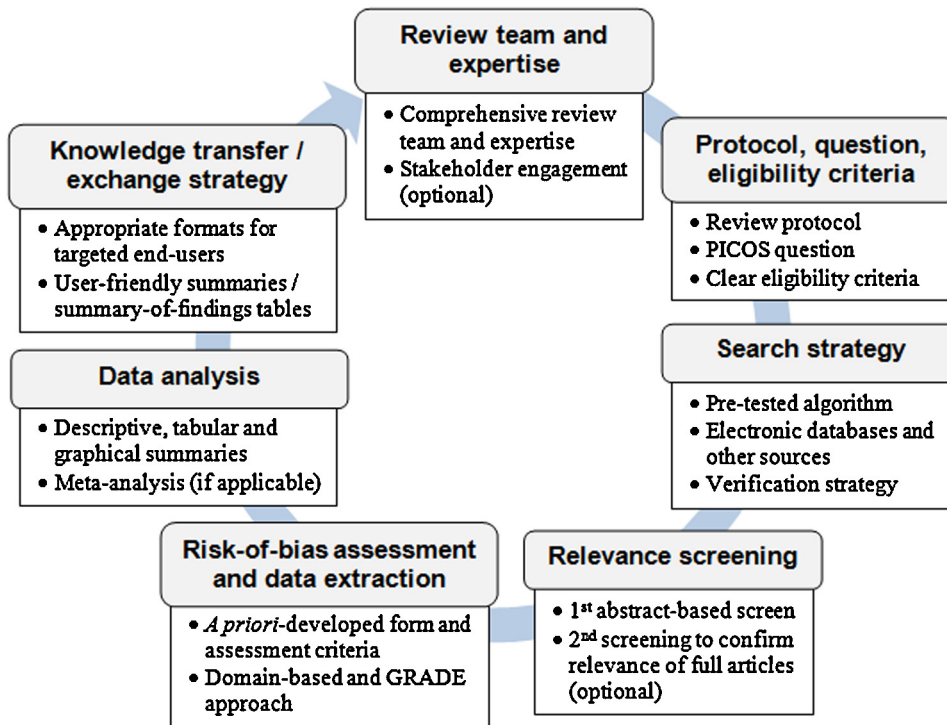


Fig. 1. Overview of the systematic review process and recommended steps.

humans, the most important source of human exposure differed depending on the following variables: animal species most commonly investigated as a potential source, species most commonly confirmed as the exposure source, species with the greatest reported prevalence, and whether articles reported virus detection in the putative exposure source. Therefore, we recommend that sensitivity analysis be conducted in scoping reviews during the categorization and analysis stage to ensure that different possible interpretations are identified and considered.

A comprehensive review was conducted in 2012 to identify and characterize all scoping reviews published from 1999 to 2012 and guidelines for their conduct in all sectors (Pham et al., 2013b). Results indicate that the majority of scoping reviews (>70%) were published in the health sector since 2010 (Pham et al., 2013b). The results of this review will be used to develop a scoping review framework that is specific to the agri-food public health context (Pham et al., 2013b).

### 3.2. Structured rapid reviews

Decision-makers often require knowledge to be presented in a short timeframe, which conflicts with the many months or years it could take to conduct a scoping review followed by one or more focused systematic reviews (Lavis et al., 2005; Ganann et al., 2010). For example, under a research setting, approximately two years were required to complete a large scoping review followed by complementary systematic reviews and meta-analyses evaluating interventions to control *Salmonella* in broiler

chickens at farm and processing (Farrar, 2009). Structured rapid reviews are streamlined and accelerated systematic reviews designed to provide more timely knowledge to inform decision-making for policy and practice (Ganann et al., 2010). They are typically driven by an urgent demand from end-users for information about a topic (Ganann et al., 2010). This could occur in the agri-food public health context, for example, if there is a need to provide knowledge on potential government policy options following a foodborne or zoonotic disease outbreak, if no previously published systematic review exists, and if there is a short window of opportunity to respond with a particular course of action.

There is no consistent and standardized approach to conducting rapid reviews, although various methods have been proposed to shorten the systematic review timeframe, including search strategy limitations (e.g. publication years, language, and number of databases) and use of only one reviewer for relevance screening, risk-of-bias assessment, or data extraction (Ganann et al., 2010; Harker and Kleijnen, 2012). A recent review of rapid reviews published in the area of health technology assessments found a significant positive correlation between the number of recommended systematic review procedures reported and the length of time taken (in months) to complete the review (Harker and Kleijnen, 2012). The use of methodological restrictions in rapid reviews could impact the risk of bias, strength of evidence, and credibility of their findings (Buscemi et al., 2006; Ganann et al., 2010). Therefore, rapid reviews should include detailed descriptions of their modified methods and explicitly highlight their potential limitations.

### 3.3. Mixed-method and qualitative reviews

End-users often must address complex problems that require an analysis of contextual information, such as stakeholder attitudes, values, and opinions and other underlying socio-behavioural mechanisms potentially affecting the success or failure of interventions, and this information is often found only in qualitative research studies (Mays et al., 2005; Dixon-Woods et al., 2006). Mixed-method and qualitative reviews were developed as an extension of systematic reviews to include and synthesize both quantitative and qualitative research studies as well as other sources of knowledge (e.g. review articles, reports, and policy documents) that might contain relevant contextual information about a given topic (Mays et al., 2005; Dixon-Woods et al., 2006). There is no standardized framework for conducting mixed-method or qualitative reviews, although general guidelines are available (Mays et al., 2005; Dixon-Woods et al., 2006). Specific variations of mixed-method and qualitative reviews include realist reviews, which investigate how complex interventions work or why they fail in particular settings (Pawson et al., 2005), and meta-ethnography reviews, which are used to develop higher-order theories about human behaviours and experiences (Atkins et al., 2008). These review methods could have potential applications in the agri-food public health sector given the more frequent use of qualitative research methods to investigate issues such as stakeholder constraints towards food safety policy development and factors related to producers' implementation of good agricultural practices (Sargeant et al., 2007a,b; Young et al., 2011).

### 3.4. Systematic reviews

An overview of the systematic review process is shown in Fig. 1. The process should begin with the establishment of a review team that consists of collaborators with topic, methodological, and information science expertise (Fig. 1). The next and most important step is to formulate a clear and concise review question to address the review objectives (Sargeant et al., 2006a,b). Question development can be facilitated by determining the review question's five PICOS components: Population, Intervention (or Exposure), Comparison, Outcome, and Study design. A protocol, developed at the beginning of the review to guide the process, should include a detailed description of all methods used at each stage of the review, including any eligibility criteria (e.g. study designs, publication types, or languages) (Sargeant et al., 2005, 2006a,b).

A comprehensive search strategy should be developed in consultation with an information specialist or librarian (Fig. 1). It should include searching of multiple bibliographic databases (e.g. PubMed, Scopus, and CAB Direct) supplemented with other sources, such as web searches for grey literature and hand-searching the reference lists of relevant articles (Higgins and Green, 2011; Horsley et al., 2011; Grindlay et al., 2012). Identified citations should be screened for relevance at the abstract level, and relevant articles may undergo a secondary screening (i.e. confirmation of relevance). A risk-of-bias assessment is conducted

concurrently with data extraction to obtain a priori-defined data on the reported study methods, outcomes, and independent and confounding variables of interest. Each step should be conducted by two independent reviewers to minimize errors.

At minimum, all systematic reviews should include a descriptive analysis and narrative summary of the results, data characteristics, and risk of bias for the included studies (Moher et al., 2009). Typically, the generation of pooled or average effect estimates (i.e. meta-analysis) will be one of main goals of a systematic review. Authors will need to determine whether meta-analysis is possible and appropriate given the amount and nature of the data and the objectives of the review. For example, meta-analysis might not be suitable and could be misleading when the included studies have a high risk of bias, when there are serious publication or reporting biases, or when there is significant and unexplained heterogeneity (i.e. the studies are too diverse to be meaningfully combined) (Higgins and Green, 2011). Even when meta-analysis is not possible, authors should consider the possibility of conducting meta-regression to explore reasons for heterogeneity.

Reporting of systematic reviews should follow the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines (Moher et al., 2009), and evidence that these guidelines have been adhered to is now required as part of the submission process for many peer-reviewed journals before consideration for publication. In particular, PRISMA indicates that authors should discuss the implications of their results in the context of other evidence and future research (Moher et al., 2009). One of the common misconceptions with systematic reviews is that they will lead to a definitive truth regarding the research question and any measures of effect, but in many cases the most important implications relate to the careful evaluation and interpretation of major sources of heterogeneity, knowledge gaps, and priorities for future research. Another important guideline indicates that authors should consider the relevance of their findings to various groups of end-users (e.g. researchers, practitioners, producers, and decision-makers). Therefore, authors should have a knowledge transfer and exchange plan to facilitate the uptake and utilization of their results by targeted end-users through multiple audience-specific formats (e.g. journal articles, conference presentations, and user-friendly summaries) (Lavis et al., 2003; Rajić et al., 2013).

#### 3.4.1. Recent advancements in systematic reviews

**3.4.1.1. Risk-of-bias assessment.** An important development in the systematic review process is in risk-of-bias assessment. The term "risk of bias" is preferred over other terms such as "quality assessment" because it avoids the ambiguity of quality of reporting vs. quality of the research. It recognizes that studies of relatively higher quality might still have a high risk of bias and that some quality criteria might not be true indicators of the risk of bias (Higgins and Green, 2011). The Cochrane Collaboration now recommends a domain-based evaluation of the risk of bias of included studies, and specific tools have been developed for reviews of interventions and diagnostic test accuracy (Higgins and Green, 2011; Whiting et al., 2011).

For intervention reviews, the recommended approach is for reviewers to assess and make judgements about the risk of bias (low, high, or unclear) for each outcome across seven domains: sequence generation (i.e. randomization); allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other issues (Higgins and Green, 2011). Reviewers then summarize the overall risk of bias for each outcome in each study (Higgins and Green, 2011). However, recent testing of this tool showed low reviewer agreement, indicating a need for more detailed reviewer guidance (Hartling et al., 2013).

The risk-of-bias tool developed to assess diagnostic test accuracy studies is referred to as QUADAS (Whiting et al., 2003, 2011). Wilkins et al. (2010) adapted QUADAS to the agri-food public health context in a systematic review and meta-analysis of the accuracy of bacterial culture and PCR to detect *Salmonella* spp. in swine. A domain-based risk-of-bias tool has not been formally developed for reviews that include observational studies. However, many other tools and checklists are available to assist reviewers in assessing the risk of bias of these study designs (Sargeant et al., 2005; Sanderson et al., 2007; von Elm et al., 2007; Farrar, 2009).

**3.4.1.2. Overall quality-of-evidence approach and summary-of-findings tables.** The Cochrane Collaboration's risk-of-bias assessment is part of an overall quality-of-evidence approach called Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) (Guyatt et al., 2011). The GRADE approach combines the study-level risk-of-bias assessment with an assessment of the directness of evidence, heterogeneity, precision of results, and risk of publication bias to determine the overall quality of evidence for each outcome at one of four levels: high, moderate, low, or very low (Guyatt et al., 2011; Higgins and Green, 2011). Wilhelm et al. (2011a, 2012) applied a modified GRADE approach to two systematic reviews in the area of agri-food public health: one investigating the potential of swine and pork products to be a source of zoonotic hepatitis E virus infection in humans and the other investigating the efficacy of five on-farm interventions to reduce *Salmonella* shedding and sero-prevalence in swine. In both reviews, overall evidence was classified as either 'very low' or 'low', primarily due to insufficient reporting of key methodological criteria such as justification of sample size and reported use of convenience instead of random or systematic sampling. A sensitivity analysis conducted by Wilhelm et al. (2012) showed that the GRADE rating was increased from 'low' to 'moderate' for all outcomes when only evidence published after release of international reporting guidelines was considered, indicating the potential impact of these guidelines on improving future reporting of primary research in this area.

The quality of evidence from GRADE can be combined with the overall effect estimates (if applicable) and other key results in a systematic review and meta-analysis for presentation in a summary-of-findings table (Guyatt et al., 2011). The purpose of these tables is to enhance the interpretation and uptake of systematic review and meta-analysis findings among end-users by providing a more concise and user-friendly summary format (Guyatt et al.,

2011). However, evidence from the health sector is inconsistent on the utility of these tables to inform various end-users about knowledge synthesis results compared to the full article alone and other user-friendly summary formats (Rosenbaum et al., 2010; Opiyo et al., 2013). Similarly, a 2012 survey of policy-makers and those who support them (e.g. policy analysts and advisors) in the Canadian agri-food public health sector found that summary-of-findings tables were the least preferred format to inform policy-making (13% of respondents) compared to the full journal article (15%), one-page summaries (23%), and three-page summaries (49%) with additional contextual information (e.g. about intervention costs and practicality) (Pham et al., 2013a). Therefore, summary-of-findings tables might be more suitable as a supplementary resource to systematic reviews rather than a stand-alone summary. An example of a summary-of-findings table adapted to the agri-food public health context can be found in Wilhelm et al. (2012). For assistance developing these tables, the Cochrane Collaboration has created a software program called GRADEpro (Brozek et al., 2008).

**3.4.1.3. Stakeholder engagement.** End-users are increasingly being involved in systematic reviews, as well as scoping reviews, as stakeholders or team members to increase the relevance, practicality, and utilization of the results (Lavis et al., 2005; Keown et al., 2008). End-users are engaged through a variety of processes, including: input meetings and consultations (e.g. to provide input on the review topic, scope, search strategy, or results dissemination); interactive steering committees; or as a full team member throughout each step of the review (Keown et al., 2008). An essential first step in these reviews is to clearly identify and engage the most applicable stakeholder groups that might be affected by or have an interest in the issue under investigation and to ensure appropriate representation from these groups. Benefits of stakeholder engagement include a review scope and question formulation that are more relevant to end-users, additional feedback to improve the clarity and applicability of the methods and results, and increased interest in the findings and enhanced appreciation for and knowledge of SRs among end-users (Keown et al., 2008). Potential challenges include the need for additional time and resources, required flexibility in the review framework, and potential for introduction of bias into the process (Keown et al., 2008). The stakeholder engagement process is currently being used in an interactive scoping review on the role of wildlife in the transmission of pathogenic bacteria and antimicrobial resistance in the food chain (Greig et al., 2012). The review incorporates a stakeholder advisory group of 11 industry experts and end-users to obtain feedback and insights on the review question, scope, and knowledge transfer and exchange strategy (Greig et al., 2012).

### 3.4.2. Key systematic review challenges and potential solutions

**3.4.2.1. Grey literature.** Grey literature is defined as literature that is not formally published in sources such as journals and books and that is generally not indexed

in online bibliographic databases (Higgins and Green, 2011). Examples of grey literature include government and industry reports, conference proceedings, and theses and dissertations. A Cochrane review of randomized controlled trials of healthcare interventions found that grey literature trials tended to be smaller and showed a lower overall treatment effect compared to trials in the published literature (Hopewell et al., 2007b). In addition, in a systematic review of the effect of hazard analysis critical control point programmes to reduce microbial contamination of food-animal carcasses at abattoirs, only a limited amount of relevant literature was identified, and three of the largest studies were non-peer-reviewed articles obtained from an Internet search (Wilhelm et al., 2011b). Therefore, exclusion of grey literature could potentially impact systematic review conclusions. However, many grey literature documents are not peer-reviewed, they are difficult and time-consuming to access, and they might not report sufficient information to allow risk-of-bias assessment, data extraction, and meta-analysis (Eysenbach et al., 2001; Hopewell et al., 2007b; Doshi et al., 2012).

Grey literature can be identified through internet searches, but comprehensive searching can be a challenge because search engines such as Google are not designed for complex queries that are used in systematic reviews and there is no indication of what the limits of an Internet search should be (Eysenbach et al., 2001). Some specialized databases can be used to search for grey literature (e.g. a Scopus web search function that conducts filtered searches for science-specific information), and engagement of stakeholders in reviews can also be useful to identify these sources. Given the above considerations, we recommend that authors consider including grey literature when unpublished or proprietary information might be expected based on the nature of the topic (Wilhelm et al., 2011b). In addition, inclusion of grey literature might be necessary when investigating complex and policy-relevant questions that require analysis of contextual information, which might only be found in these sources (Greenhalgh and Peacock, 2005). In both cases, authors should include a careful evaluation and discussion of the risk of bias and potential impacts of these sources on the review findings.

**3.4.2.2. Language bias.** Language bias is a potential concern if non-English studies are excluded from a systematic review. For example, Egger et al. (1997b) found that authors of randomized controlled trials were more likely to publish statistically significant findings in English-compared to German-language journals. However, other authors in the health sector have found that excluding non-English studies might not have any discernible effects on the outcome for some interventions (Jüni et al., 2002; Moher et al., 2003; Pham et al., 2005). The potential impact of language bias is difficult to predict, and the decision to include non-English articles should be made based on the specific question, context, and scope of the review and availability of resources for translation (Jüni et al., 2002; Moher et al., 2003).

In our experience, most systematic reviews in agri-food public health identify a relatively small number of non-English language articles that appear to be relevant based on relevance screening of the abstract (Wilhelm et al.,

2011b; Mederos et al., 2012; Tuševljak et al., 2012). In these situations, exclusion of non-English articles is not likely to have a large impact on the review findings due to the generally small proportion of these studies. However, in other situations, the nature of the review topic and scope can result in a larger proportion of potentially relevant studies being excluded due to language (Wilhelm et al., 2009, 2011a; Ilic et al., 2012). If the authors have a reason to believe that exclusion of non-English articles might impact the conclusions and resources cannot be readily obtained for translation, authors should acknowledge and discuss the potential significance of this bias and attempt to investigate and evaluate the characteristics of articles that are excluded based on their titles and abstracts (e.g. potential under-representation of a geographical area).

#### 3.4.3. Optimizing the search strategy

It is critical to the validity of a systematic review to ensure that all relevant and available knowledge is identified. However, given the time and resource requirements involved in comprehensive literature searches, an optimal balance is needed in the selection of search terms and electronic databases (Royle and Waugh, 2003; Lovarini et al., 2006; Waddell et al., 2008). The complexity of a search depends largely on the breadth and scope of the review question. Waddell et al. (2008) evaluated the effectiveness of brief search strategies for three completed systematic reviews in agri-food public health and found that a combination of three broad and subject-specific databases for 2/3 reviews captured >90% of relevant citations, and nearly all relevant citations were identified after a thorough search verification strategy was used. Based on our experiences and previous research (Waddell et al., 2008; Grindlay et al., 2012), we recommend a selection of 3–5 general (e.g. PubMed, Scopus, and Current Contents Connect) and subject-specific (e.g. CAB Direct and Food Science and Technology Abstracts) databases to provide sensitive results without using excessive resources. The database searches should be supplemented with searches for grey literature (where appropriate) and a search verification strategy (Royle and Waugh, 2003; Hopewell et al., 2007a). To develop an appropriate search algorithm, we recommend that reviewers select a range of 20–30 relevant articles, extract key terms from their titles and abstracts, and through a documented trial-and-error process determine the combination of key terms that results in the highest percentage of recovery of these articles in one or more targeted databases. This process should be conducted in consultation with a librarian or information specialist.

#### 3.4.4. Other systematic review challenges

Currently there is no consensus about the best methods to determine when and how to update systematic reviews (Moher et al., 2008; Higgins and Green, 2011; Tsertsvadze et al., 2011). The Cochrane Collaboration's policy is that a systematic review should be updated every two years, but a review of Cochrane review updates from 1998 to 2002 found that only 9% of updated reviews resulted in changes to the conclusions, indicating that the decision to update a review should be based more on priority than on time alone (French et al., 2005). In determining whether



to update a systematic review, authors should consider the potential for new research to be published and the nature of the research question or issue (French et al., 2005; Tsertsvadze et al., 2011). Another challenge in systematic reviews is the potential inclusion of observational studies, which have traditionally been excluded from reviews of healthcare interventions because they are more prone to bias and provide weaker evidence compared to randomized controlled trials (Egger et al., 1998; Higgins and Green, 2011). However, observational studies are often the only feasible design when investigating risk factor questions, and they tend to have larger sample sizes which are more representative of broader populations (Egger et al., 1998; Shrier et al., 2007). Therefore, it may be beneficial to include observational studies in some situations to ensure that all available knowledge is considered for decision-making (Shrier et al., 2007).

Other logistical challenges include securing sufficient resources and establishing a diverse, multidisciplinary team with the necessary expertise to appropriately conduct systematic reviews within reasonable timeframes. In addition, many systematic reviews are conducted under research and academic settings, which limits their potential timeliness and utility to inform policy- and decision-making contexts (Lavis et al., 2005). Planning, investment, and integration of knowledge synthesis methods within regional, national, and international agri-food public health agencies is necessary to support and maintain sufficient capacity and infrastructure in this area.

### 3.5. Meta-analysis

The objective of a traditional meta-analysis is to combine the results of homogenous studies using the effect estimate and uncertainty from each study to produce a weighted mean or overall measure of effect (Borenstein et al., 2009; Higgins and Green, 2011). Meta-analysis should always be preceded by a systematic review, and authors must evaluate their dataset for suitability to conduct a meta-analysis. Meta-analysis should be considered if there are groups of studies that are evaluating the same effect in similar settings and populations. Any potential sources of variation or heterogeneity in the outcome measures should be predicted and defined before conducting meta-analysis to justify the biological basis for combining studies. The reported data and outcomes should then be evaluated to determine the most appropriate measure of effect. For dichotomous outcomes, it is recommended to use relative (e.g. odds ratios or risk ratio) rather than absolute (e.g. risk difference) measures of effect because they are generally more consistent across studies (Deeks, 2002; Borenstein et al., 2009; Higgins and Green, 2011).

Once the desired measure of effect is specified, authors must determine whether to use a fixed- or random-effects meta-analysis model (Table 2). Random-effects models are the preferred option when authors expect that the studies will vary due to reasons other than random error and when they want to estimate an overall measure of effect that can be generalized to a range of populations (Borenstein et al., 2009; Higgins et al., 2009; Higgins and Green, 2011).

When heterogeneity is detected (i.e. the between-study variance,  $\tau^2$ , is  $>0$ ), consideration of the fixed- vs. random-effects model is warranted because the latter model tends to adjust the weight of larger studies down and smaller studies up to give a more balanced summary effect estimate (Borenstein et al., 2009). This is of particular interest when there are extreme outcome measures in small or large studies (Borenstein et al., 2009). Meta-analysis results should be displayed in the form of a forest plot, which are used to visualize variation in the effect estimates across studies and their weighted contribution to the overall estimate (Lewis and Clarke, 2001). An example of a forest plot from a meta-analysis of the effect of competitive exclusion products to reduce colonization of *Salmonella* spp. in broiler chickens on farms is shown in Fig. 2 (Kerr et al., 2013).

Authors should then quantify heterogeneity in the effect estimates (Table 2). A chi-squared statistic (Cochran's  $Q$ ) can be used to test for the presence of heterogeneity, but it has low power, so a liberal  $P$  value of  $\leq 0.10$  is often used to indicate statistical significance (Higgins et al., 2003; Ioannidis, 2008). A more informative approach is to quantify heterogeneity using  $I^2$ , which measures the percentage (0–100%) of total variation across studies that is due to heterogeneity rather than chance (Higgins et al., 2003; Ioannidis, 2008). However, this test also suffers from low power and it is recommended that the  $I^2$  confidence interval also be calculated (Ioannidis, 2008). If heterogeneity is identified and is considered important for exploration (e.g.  $I^2 > 25\%$ ), sub-group analysis or meta-regression should be used (Thompson and Higgins, 2002; Higgins et al., 2003; Higgins and Green, 2011). Meta-regression investigates whether study-level covariates explain any of the heterogeneity in the effect estimates between studies (Thompson and Higgins, 2002). However, to avoid the identification of spurious relationships, these analyses should only be conducted using a limited number of pre-specified variables that are identified when considering the suitability of undertaking a meta-analysis (Thompson and Higgins, 2002; Higgins and Green, 2011).

The next step in meta-analysis is to test for the presence of systematic biases (e.g. publication bias) and to conduct sensitivity analysis (Table 2). Funnel plots can be used to visualize the relationship between the measure of effect for each study compared to its precision (i.e. standard error), and statistical tests (e.g. Egger's regression test) are available to test this relationship. An example is shown in Fig. 3. Asymmetry in the funnel plot may indicate publication bias or other small-study effects such as selective outcome reporting, differences in the risk of bias, or true differences in the intervention effect due to study size (Egger et al., 1997a; Higgins et al., 2009; Sterne et al., 2011). However, these tests are not reliable when there are  $<10$  studies, when there is substantial heterogeneity (e.g.  $I^2 > 50\%$ ), when none of the studies are significant, or when the variance ratio between the smallest and largest study is  $>4$  (Egger et al., 1997a; Ioannidis and Trikalinos, 2007; Sterne et al., 2011). Sensitivity analysis should be conducted to test the robustness of the meta-analysis effect estimates against arbitrary or uncertain decisions (e.g. exclusion of studies based on characteristics such as study type, population, intervention, or outcome).

**Table 2**

An overview of major meta-analysis methods and selected key resources.

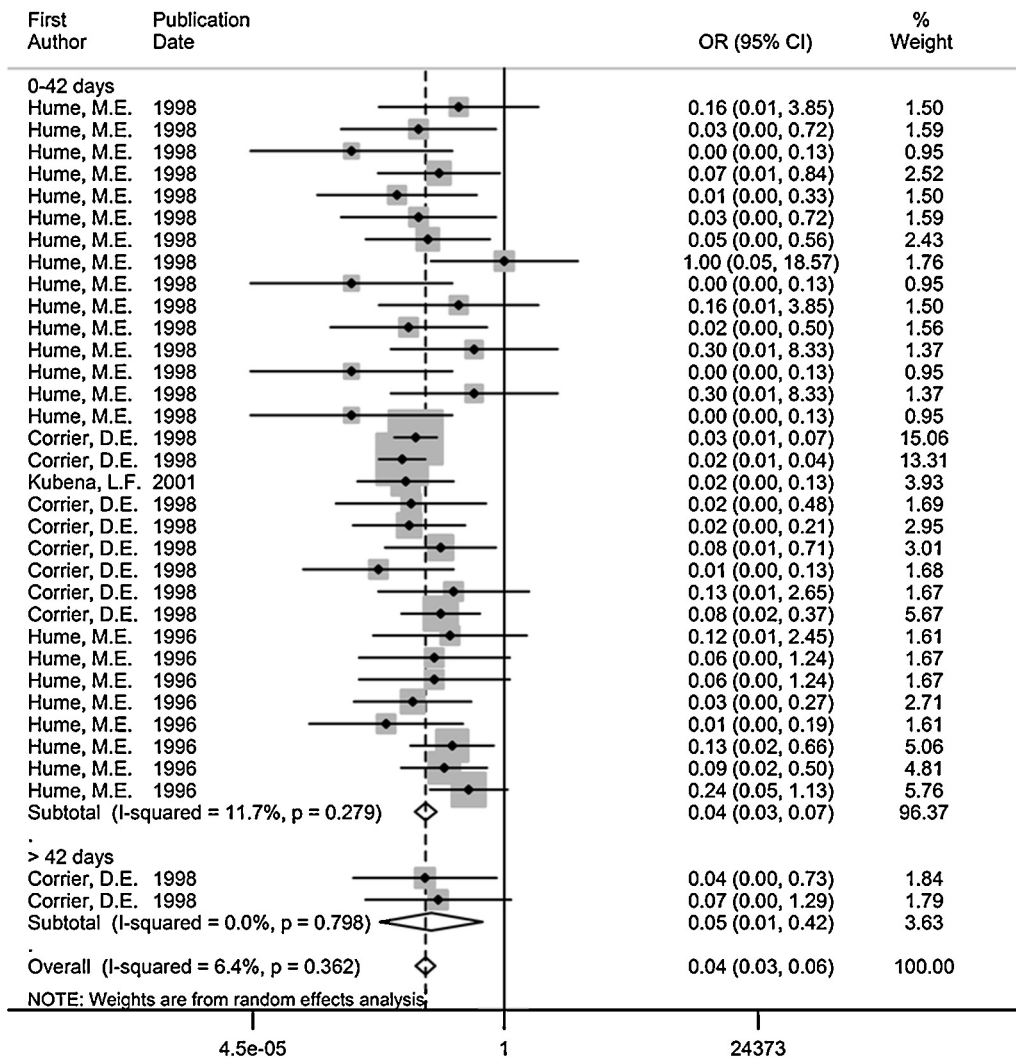
Meta-analysis method <sup>a</sup>	Brief method description	Key resources
<b>Traditional methods</b>		
<i>Fixed-effect model</i>	<ul style="list-style-type: none"> <li>Assumes that each study estimates the same intervention effect</li> <li>Several weighting options are available, including inverse variance (often the default), Mantel-Haenszel (used for 2 × 2 data), and Peto (used for special cases of sparse 2 × 2 data)</li> </ul>	Sutton and Higgins (2008)
<i>Random-effects model (DerSimonian and Laird weighting)</i>	<ul style="list-style-type: none"> <li>Assumes the intervention effects follow a distribution across studies</li> <li>Incorporates the between-study variation using a moment-based estimate and assumes a normal distribution</li> </ul>	DerSimonian and Laird (1986), DerSimonian and Kacker (2007), Higgins et al. (2009), Ioannidis (2008)
<b>Heterogeneity tests</b>		
	<ul style="list-style-type: none"> <li>Forest plots can be used to visually evaluate the consistency of study results, but this method is subjective</li> <li>The Chi-square test (Q statistic) can be used but suffers from low power when there are few studies and when studies have small sample sizes</li> <li><math>I^2</math> can be used to quantify the proportion of total variation between studies that is attributable to heterogeneity</li> </ul>	
<b>Evaluation of sources of heterogeneity</b>		
<i>Sub-group analysis</i>	An evaluation of categorical study-level covariates by conducting separate meta-analyses on each category and testing for homogeneity across categories	Sutton and Higgins (2008), Borenstein et al. (2009)
<i>Meta-regression</i>	<ul style="list-style-type: none"> <li>Conducted to investigate whether study-level covariates explain any of the variation in the intervention effects between studies</li> <li>Should only be conducted using pre-specified covariates and when ≥ 10 studies are available for the model and each additional covariate</li> <li>Is prone to the ecological fallacy</li> </ul>	Thompson and Higgins (2002), Sutton and Higgins (2008)
<b>Systematic bias assessment</b>		
	<ul style="list-style-type: none"> <li>Systematic biases (e.g. publication bias) can be investigated by exploring the presence of asymmetry in funnel plots</li> <li>A variety of statistical tests (e.g. Begg's test and Egger's test) and sensitivity analyses (e.g. the trim and fill method) can also be used</li> <li>These methods should only be used with ≥ 10 studies, when there is little or no heterogeneity, when some studies have statistically significant results, and when there is variation in study size</li> </ul>	Ioannidis and Trikalinos (2007), Higgins and Green (2011), Sterne et al. (2011)
<b>Advanced methods</b>		
<i>Individual participant data meta-analysis</i>	<ul style="list-style-type: none"> <li>Regarded as the “gold standard” approach to meta-analysis</li> <li>Has many advantages, including ability to handle time-to-event data</li> <li>Notable disadvantage is the increased time and costs required to obtain, format, and analyze data and potentially obtain additional ethics approval</li> </ul>	Riley et al. (2010)
<i>Random-effects meta-analysis with complex data</i>	<ul style="list-style-type: none"> <li>Correlation structures can be used for meta-analysis of complex data when dependant, multi-group comparisons are reported and when multiple outcomes or time-points are reported in each study and are measured on the same participants</li> </ul>	Borenstein et al. (2009)
<i>Bayesian meta-analysis</i>	<ul style="list-style-type: none"> <li>Can specify flexible fixed- or random-effects models based on the Bayesian framework</li> <li>Many benefits, including ability to account for full uncertainty in all parameters</li> <li>Requires careful consideration and justification of prior distributions selected and sensitivity analysis to explore their effect on the findings</li> </ul>	Sutton and Abrams (2001), Higgins et al. (2009)
<i>Multivariate and network meta-analysis</i>	<ul style="list-style-type: none"> <li>Developed to make inferences about studies that report multiple correlated outcomes, where each study provides the within-study covariance matrix</li> <li>Some applications include the evaluation of diagnostic test studies (see below), network meta-analysis, and to examine associations in genetic studies</li> <li>Network (or multiple-treatments comparison) meta-analysis is one common application that can be used to extend the simple pairwise comparison of a traditional meta-analysis to include multiple comparisons across a number of intervention groups</li> <li>Within-study correlations are required but are often unknown and there is no consensus about the best approach to address this issue</li> </ul>	Hoaglin et al. (2011), Jackson et al. (2011), Jansen et al. (2011)
<i>Meta-analysis of diagnostic test accuracy</i>	<ul style="list-style-type: none"> <li>A special case of multivariate meta-analysis for diagnostic test accuracy studies</li> <li>Several methods available, including simple pooling of sensitivity and/or specificity without accounting for the correlation between them, summary ROC curves (Littenberg-Moses method), and the bivariate random-effects model and hierarchical summary ROC model</li> </ul>	Harbord et al. (2008), Macaskill et al. (2010)

<sup>a</sup> All meta-analysis methods except advanced Bayesian approaches can be conducted in standard statistical software (e.g. SAS, STATA, and R). The stand-alone software program Comprehensive Meta-Analysis (CMA version 2, <http://www.meta-analysis.com/>) can also conduct each of the traditional methods, but their meta-regression functionality is currently limited to univariate analysis with continuous covariates. Another stand-alone program called Meta-Analysis with Interactive eXplanations (MIX 2.0, an Excel add-in, <http://www.meta-analysis-made-easy.com/>) can support all traditional meta-analysis methods except meta-regression. Bayesian approaches can be conducted using the specialized software WinBUGS and OpenBUGS.

### 3.5.1. Recent advancements in meta-analysis

**3.5.1.1. Bayesian meta-analysis.** Meta-analysis can also be conducted within the Bayesian statistical framework, and although this approach has been long established and

applied in the health and other sectors (Sutton and Abrams, 2001), it has not been widely adopted in systematic reviews of agri-food public health issues. Some advantages of Bayesian meta-analysis include the ability to make direct

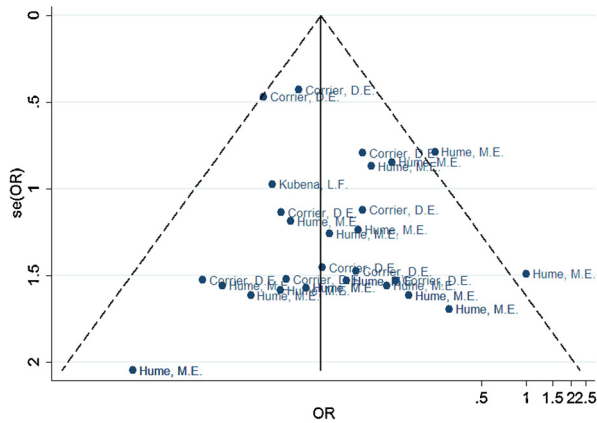


**Fig. 2.** Example of a forest plot from a random-effects meta-analysis of challenge trials reporting the effect of Preempt™ (CF-3) to reduce the odds of *Salmonella* spp. colonization in broiler chickens (reproduced from Kerr et al., 2013). Trials are stratified by age of birds at final sampling. The estimate of intervention efficacy (odds ratio) and 95% confidence interval from each individual trial within each study are represented as unique rows and the size of the box surrounding each estimate represents the relative weight of that trial in producing the average effect estimate. In this case, the average estimate shows a significant beneficial effect (OR = 0.04, 95% CI = 0.03–0.06) and a low amount of heterogeneity ( $I^2 = 6.4\%$ ,  $Q$  test  $P$  value = 0.362).

probability and predictive statements (conditional on the current knowledge) and the ability to incorporate external judgements and additional knowledge (e.g. costs and utility) into prior distributions (Sutton and Abrams, 2001; Higgins et al., 2009; Higgins and Green, 2011). The Bayesian framework can also be used to perform complex analyses such as multivariate and network meta-analysis, hierarchical models, and generalized synthesis models that incorporate multiple study designs (Higgins and Green, 2011; Jansen et al., 2011). However, there are some potential disadvantages of a Bayesian approach: prior beliefs can be subjective (to avoid this, an uninformative prior can be used); there are multiple prior distributions that can lead to different results; there is no direct measure of statistical significance analogous to a  $P$  value, although credibility intervals can be calculated; and they can be

computationally demanding and require specialized statistical expertise (Sutton and Abrams, 2001; Higgins and Green, 2011). Sensitivity analyses should always be conducted in Bayesian meta-analysis due to the subjectivity involved in selecting a prior distribution (Sutton and Abrams, 2001).

**3.5.1.2. Multivariate and network meta-analysis.** Multivariate meta-analysis refers to the synthesis of studies that report several interrelated outcome parameters (Jackson et al., 2011). One of the most common applications of multivariate meta-analysis is the synthesis of diagnostic test accuracy studies (described below). Another special application is network meta-analysis, also referred to as mixed- or multiple-treatments meta-analysis (Glenny et al., 2005; Hoaglin et al., 2011; Jansen et al., 2011; Salanti, 2012).



**Fig. 3.** Example of a funnel plot from a random-effects meta-analysis of challenge trials reporting the effect of Preempt™ (CF-3) to reduce the odds of *Salmonella* spp. colonization in broiler chickens (Kerr et al., 2013). The graph plots the estimate of effect (odds ratio) from each trial against its standard error. Smaller studies tend to scatter more widely at the bottom of the plot due to their lower precision and larger studies cluster towards the top. If publication bias were suspected, this could be visualized by a lack of studies in the lower right corner (suggesting that smaller studies showing a non-significant treatment effect are less likely to be published). In this figure, no evidence of publication bias is suggested based on visual examination of the plot symmetry. Begg's rank correlation test ( $P=0.230$ ) and Egger's regression test ( $P=0.742$ ) also did not indicate evidence of asymmetry.

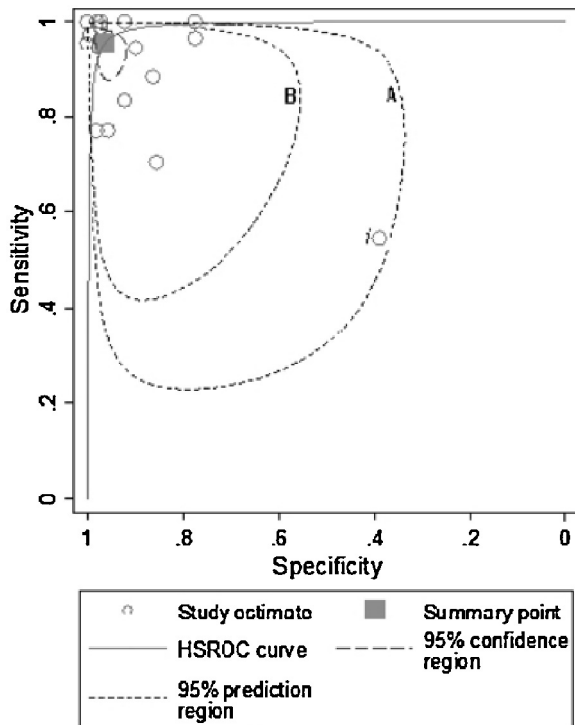
Network meta-analysis can simultaneously evaluate three or more interventions using direct comparisons within a trial and indirect comparisons across trials based on a common control group (Glenny et al., 2005; Hoaglin et al., 2011; Jansen et al., 2011). Results from trials that directly compare the two (or more) interventions can be combined with the indirect results as a weighted average (Hoaglin et al., 2011; Jansen et al., 2011). Benefits of this approach include improved precision in the estimated effect sizes and the ability to compare interventions that have not been directly compared in a given study (Salanti, 2012).

Multivariate and network meta-analysis can be conducted using either a frequentist or Bayesian approach, the latter has the additional benefit of ranking all compared interventions for more intuitive interpretation of the results (Hoaglin et al., 2011; Jansen et al., 2011). O'Connor et al. (2013) recently applied network meta-analysis to investigate the efficacy of various antibiotic treatments for bovine respiratory disease in beef cattle. This type of meta-analysis has increased rapidly in the last few years in the health sector, and a number of methodological issues have been identified (Hoaglin et al., 2011; Jansen et al., 2011; Salanti, 2012). For example, the appropriateness of the network meta-analysis model depends on accurately specifying the direct and indirect relationships between the interventions compared, as well as assumptions that the included studies are clinically and methodologically similar and that indirect evidence is consistent with direct evidence (Hoaglin et al., 2011; Jansen et al., 2011; Salanti, 2012). In response to these concerns, guidelines for the conduct and reporting of network meta-analysis have recently been published (Hoaglin et al., 2011; Jansen et al., 2011). Additional resources about these methodologies are

available from the following Multiple-Treatments Meta-Analysis website: <http://www.mtm.uoi.gr/>.

**3.5.1.3. Meta-analysis of diagnostic test accuracy studies.** Meta-analysis of diagnostic test accuracy studies presents some challenges because multiple outcomes (e.g. sensitivity, specificity, and likelihood ratios) are reported for each study. The first recommended step is to create a summary receiver operating characteristic (ROC) graph of the results of each study (Leeflang et al., 2008; Macaskill et al., 2010). Forest plots can also be produced to show study estimates of sensitivity and specificity, but they do not reflect the correlation and threshold relationships between these two values (Leeflang et al., 2008; Macaskill et al., 2010). These relationships can be incorporated in two specialized models: the hierarchical summary ROC model and the bivariate random-effects model (Harbord et al., 2008; Leeflang et al., 2008; Macaskill et al., 2010). The models have different parameterizations, but they are closely related and estimates from either model can be used to generate a summary ROC curve, summary operating point, and confidence and prediction regions (Harbord et al., 2008; Leeflang et al., 2008; Macaskill et al., 2010). In addition, both models can include one or more covariates to explore heterogeneity (Harbord et al., 2008; Leeflang et al., 2008; Macaskill et al., 2010). Wilkins et al. (2010) used a hierarchical summary ROC model to investigate sources of heterogeneity in the sensitivity of culture and sensitivity and specificity of PCR to detect *Salmonella* spp. in swine, and they found that the former was influenced more by differences in individual test protocols while the latter was influenced more by differences between studies (sample type and sample size). They also found a high risk of bias among included studies, indicating a need for more formal and standardized conduct and reporting of future primary research in this area (Wilkins et al., 2010). An example of a summary ROC curve from Wilkins et al. (2010) is shown in Fig. 4.

**3.5.1.4. Individual participant data meta-analysis.** Analysis of individual participant data is an alternative approach to meta-analysis that is gaining popularity in the health sector (Riley et al., 2010; Higgins and Green, 2011). It requires that the authors obtain the raw data from each study instead of relying on aggregate data obtained from publications and reports. Some important benefits include the ability to analyze data in one step while accounting for clustering by study; to explore both study- and individual-level characteristics; to analyze time-dependant studies; to re-analyze and standardize the method of statistical analysis across studies; to verify data and assumptions; and to potentially include studies that did not provide sufficient or appropriate data in the original publication (Riley et al., 2010). Some notable disadvantages include the considerable increased time and costs required to obtain individual participant data from study authors, format and analyze data, and potentially obtain ethics approval; the potential bias introduced due to missing datasets; and challenges in combining the individual with aggregate data to increase the number of studies included (Riley et al., 2010).



**Fig. 4.** Example of a summary ROC curve from a hierarchical summary ROC meta-analysis of the diagnostic accuracy of PCR compared to culture to detect *Salmonella* spp. in swine (reproduced from Wilkins et al., 2010). The graph illustrates the trade-off between test sensitivity (y axis) and specificity (x axis). The solid square indicates the summary point estimate of sensitivity and specificity, with the 95% confidence region around this estimate shown as a dashed line. The graph also shows the 95% prediction region (dotted line), which indicates the range of values we would expect, with 95% confidence, the true sensitivity and specificity of a future study to lie (Macaskill et al., 2010). In this figure, two prediction regions are shown, one with all 21 test evaluations (A), and another with one influential observation removed (B) (Wilkins et al., 2010).

### 3.5.2. Key meta-analysis challenges and potential solutions

**3.5.2.1. Meta-analysis of observational studies.** If observational studies are included in a meta-analysis, it might be preferable to extract and use adjusted effect estimates rather than raw data due to the risk of confounding bias in these studies (Higgins and Green, 2011). If multiple adjusted estimates are reported for some studies, authors could use the estimates from the final model or from the model that controlled for the most important confounding variables (Higgins and Green, 2011). It is generally recommended that authors do not combine multiple study designs in the same meta-analysis because results from different designs can differ systematically (Borenstein et al., 2009; Higgins and Green, 2011). Instead, the impact of study design on the overall measure of effect should be explored in meta-regression and other advanced models. The Bayesian framework offers a natural extension to account for the variation between study designs (Sutton and Abrams, 2001; Higgins et al., 2009). Evidence from observational studies can be incorporated into prior distributions or can be directly modelled along with other study designs in a generalized synthesis model (Sutton

and Abrams, 2001; Higgins et al., 2009). While the latter approach can assess the influence of observational and other study designs on the meta-analysis effect estimates, it does not explicitly address the potential biases of observational studies (Sutton and Abrams, 2001; Higgins et al., 2009).

**3.5.2.2. Insufficient data reporting.** It is often difficult to obtain required data to conduct meta-analysis due to poor and inconsistent reporting of primary research studies (Higgins and Green, 2011; Bucher et al., 2012a). For example, in a systematic review and meta-analysis of interventions to reduce *Salmonella* contamination of chicken carcasses at processing, nearly 30% of eligible studies were excluded due to insufficient reporting of data (Bucher et al., 2012a). For most continuous and dichotomous outcomes, formulas are available to convert outcomes and variance parameters when they are not reported in the desired format (e.g. estimating standard deviations from reported P values) (Higgins and Green, 2011; Bucher et al., 2012a; Mederos et al., 2012). If raw data are not reported and conversions cannot be conducted, authors can attempt to contact the study authors to obtain the necessary information (Young and Hopewell, 2009). However, this practice is resource-intensive and authors are often not able or willing to provide the requested data for many reasons, including confidentiality concerns (Sargeant et al., 2007a,b; Riley et al., 2010). Recent reporting guidelines for primary research (e.g. REFLECT for controlled trials conducted in livestock populations and STROBE for observational studies) should help to improve data reporting of future studies in agri-food public health (von Elm et al., 2007; Sargeant et al., 2010).

**3.5.2.3. Small number of studies and significant heterogeneity.** Insufficient reporting and availability of data is often a concern in systematic reviews, but meta-analysis is still technically feasible with as few as two studies (Ioannidis et al., 2008; Borenstein et al., 2009; Valentine et al., 2010). While a meta-analysis of a small number of studies will generate uncertain estimates, it might still be preferable to narrative or semi-quantitative syntheses (e.g. vote counting), which can be less transparent and might misinterpret the results (Ioannidis et al., 2008; Borenstein et al., 2009; Valentine et al., 2010). Significant heterogeneity is another common reason for not conducting meta-analysis, but there is inconsistency in the recommendations for how best to account for this and whether overall measures of effect should be calculated in its presence (Ioannidis et al., 2008). Different methodological approaches to meta-analysis are available depending on the source of heterogeneity identified (e.g. differences in study design, populations, interventions, or outcomes), and their use should be explored by systematic review and meta-analysis authors (Ioannidis et al., 2008). Some of these approaches are highlighted above and in Table 2. Further methodological development and evaluation of these methods is necessary in agri-food public health.

#### 4. Future opportunities for knowledge synthesis methods in agri-food public health

We identified and discussed five key knowledge synthesis methods that can be used in different situations to support evidence-informed decision-making in the agri-food public health sector. Although we refer to each of these approaches as unique methods, many could be considered as modified versions of a systematic review adapted to specific contexts (e.g. scoping reviews for broader, policy-driven questions; rapid reviews for urgent time and resource restrictions; and qualitative and mixed-method reviews when contextual data needs to be considered). Scoping reviews are valuable to researchers as a first step before conducting a systematic review in a specific topic area and they are also useful to governments and funding agencies to determine priority areas for future research. Government agencies in particular could benefit from a wider adoption of structured rapid reviews to enhance the transparency and accountability of evidence-informed decision-making in emergency situations such as during outbreak response. Mixed-method and qualitative reviews will become increasingly relevant as the publication of primary qualitative research grows in this sector. Systematic reviews and meta-analysis are the most widely adopted and applied knowledge synthesis methods in this sector and their utility includes a broad range of situations, from informing end-users about the most efficacious interventions to generating precise and credible inputs to inform risk assessments (Sargeant et al., 2006a,b; EFSA, 2010; Higgins and Green, 2011).

Risk analysis, which consists of the key components of risk assessment, risk management, and risk communication, has a long history of application in the agri-food public health sector to support food safety decision-making (Codex Alimentarius Commission, 1999). There is increasing momentum to formally link the use of knowledge synthesis methods with risk assessments and multi-criteria decision analysis in this sector to enhance the credibility and transparency of the risk analysis process (EFSA, 2010; Bucher et al., 2012b; Wilhelm et al., 2012; Smadi and Sargeant, 2013). For example, systematic reviews and meta-analysis have been conducted and results used as inputs to inform a quantitative exposure assessment of farm and processing interventions to control *Salmonella* in broiler chickens (Bucher et al., 2012b); a quantitative risk assessment of human salmonellosis due to consumption of Canadian broiler chicken meat (Smadi and Sargeant, 2013); and a multi-criteria decision analysis to prioritize selected on-farm interventions to control *Salmonella* in swine (Wilhelm et al., 2012; personal communication, Dr. Sarah Parker). In addition, EFSA has formally adopted systematic reviews and meta-analysis to inform their routine food and feed safety assessments (EFSA, 2010), and the Food and Agriculture Organization of the United Nations has begun to use these methods to support their scientific advice for the Codex Alimentarius Commission. There is a need for other agri-food public health organizations and agencies globally to enhance the integration of knowledge synthesis methods within the risk analysis paradigm to support

more robust and transparent decision-making in this sector.

Many systematic review advancements (e.g. risk-of-bias assessments and GRADE) were developed with the goal of improving the interpretation and utilization of synthesized knowledge among end-users in the healthcare sector (Guyatt et al., 2008; Higgins and Green, 2011). As a result, there are still several unresolved issues with the application of these advancements in the agri-food public health sector, and future research in this area is needed. For example, intervention research in this sector often uses study designs such as before-and-after trials and challenge trials (Sargeant et al., 2006a,b, 2010), and there is no consensus about how these designs should be assessed and rated under the domain-based risk of bias and GRADE frameworks. Stakeholder engagement in knowledge synthesis is another key development that has been shown to increase the relevance and uptake of systematic reviews and meta-analysis findings among end-users (Keown et al., 2008), and the use of this approach should be considered in future knowledge synthesis research of agri-food public health issues. Logistical advancements, such as the use of specialized review software (e.g. DistillerSR or RevMan), should also be considered to facilitate the conduct and management of future knowledge synthesis research. In our experience, these programmes are cost-effective because they decrease time spent on activities such as citation processing and they decrease the likelihood that human error could occur due to the automation of various functions.

Many meta-analysis advancements covered in this review have the potential to improve the overall synthesis of agri-food public health data in complex situations (e.g. when there is a need to compare multiple interventions, outcomes, or study designs), and further research is necessary on their application in this sector. However, the increasing use of these methods can make it difficult to maintain coherence and consistency of knowledge synthesis results and interpretation. In addition, the use of these methods has limited benefit and utility if the analysis is inappropriately conducted, too complex, or not easily understandable among end-users. Thus, we encourage review authors and meta-analysts to carefully consider the objective of their synthesis, known and expected sources of heterogeneity, and the quality of the obtainable data prior to embarking on their analysis.

There is a need to build stronger knowledge synthesis capacity in the agri-food public food sector to support a wider adoption and application of these methods in research and decision-making. For example, specialized knowledge synthesis training programmes, dedicated funding opportunities, and routine synthesis units in different agencies could all contribute to improving the application and uptake of synthesized knowledge. There is also a need for a consolidated infrastructure to support knowledge synthesis research in this sector, similar to the Cochrane Collaboration in healthcare, to improve the standardization of conduct and reporting, to support the exchange of knowledge synthesis resources and expertise, and to maintain a formal repository of systematic reviews, meta-analyses and other synthesis projects. Finally, future

research is necessary to evaluate the effectiveness and utility of different approaches and formats to summarize knowledge synthesis findings for various end-users to improve their uptake in policy and practice decision-making.

## 5. Conclusion

Knowledge synthesis uses robust, systematic, and transparent methods to identify, evaluate, and integrate all available knowledge about a topic. Knowledge synthesis results can be used to identify knowledge strengths, gaps, and opportunities and to inform decision-making for policy and practice. Scoping reviews, structured rapid reviews, mixed-method and qualitative reviews, systematic reviews, and meta-analysis can all be used to synthesize comprehensive knowledge in various situations and contexts. Additional research is needed to evaluate and apply specific advancements and to overcome various challenges related to the application of these methods in the agri-food public health sector. A wider adoption and integration of knowledge synthesis methods in this sector is important to ensure that the best available knowledge is used to support future decision-making.

## Conflict of interest statement

None to declare.

## Acknowledgements

We gratefully acknowledge all of the individuals and groups that have contributed to the development and application of knowledge synthesis methods in the agri-food public health sector. This review was funded by the University of Guelph and Ontario Ministry of Agriculture and Food's Agri-Food and Rural Link "Knowledge Translation and Transfer Funding Program" and the Laboratory for Foodborne Zoonoses, Public Health Agency of Canada.

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