Synthesising quantitative evidence in systematic reviews of complex health interventions

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ABSTRACT
Public health and health service interventions are typically complex: they are multifaceted, with impacts at multiple levels and on multiple stakeholders. Systematic reviews evaluating the effects of complex health interventions can be challenging to conduct. This paper is part of a special series of papers considering these challenges particularly in the context of WHO guideline development. We outline established and innovative methods for synthesising quantitative evidence within a systematic review of a complex intervention, including considerations of the complexity of the system into which the intervention is introduced. We describe methods in three broad areas: non-quantitative approaches, including tabulation, narrative and graphical approaches; standard meta-analysis methods, including meta-regression to investigate study-level moderators of effect; and advanced synthesis methods, in which models allow exploration of intervention components, investigation of both moderators and mediators, examination of mechanisms, and exploration of complexities of the system. We offer guidance on the choice of approach that might be taken by people collating evidence in support of guideline development, and emphasise that the appropriate methods will depend on the purpose of the synthesis, the number and similarity of studies included in the review, the level of detail available from the studies, the nature of the results reported in the studies, the expertise of the synthesis team and the resources available.

BACKGROUND
Public health and health service interventions are typically complex. They are usually multifaceted, with impacts at multiple levels and on multiple stakeholders. Also, the systems within which they are implemented may change and adapt to enhance or dampen their impact.3 Quantitative synthesises (‘meta-analyses’) of studies of complex interventions seek to integrate quantitative findings across multiple studies to achieve a coherent message greater than the sum of their parts. Interest is growing on how the standard systematic review and meta-analysis toolkit can be enhanced to address complexity of interventions and their impact.4 A recent report from the Agency for Healthcare Research and Quality and a series of papers in the Journal of Clinical Epidemiology provide useful background on some of the challenges.

This paper is part of a series to explore the implications of complexity for systematic reviews and guideline development, commissioned by WHO.5 Clearly, and as covered by other papers in this series, guideline development encompasses the consideration of many different aspects,6 such as intervention effectiveness, economic considerations, acceptability9 or certainty of evidence,10 and requires the integration of different types of quantitative as well as qualitative evidence.11 12 This paper is specifically concerned with methods available for the synthesis of quantitative results in the context of a systematic review on the effects of a complex intervention. We aim to point those collating evidence in support of guideline development towards methods that are well established and currently available.
of guideline development to methodological approaches that will help them integrate the quantitative evidence they identify. A summary of how these methods link to many of the types of complexity encountered is provided in table 1, based on the examples provided in a table from an earlier paper in the series. An annotated list of the methods we cover is provided in table 2.

We begin by reiterating the importance of starting with meaningful research questions and an awareness of the purpose of the synthesis and any relevant background knowledge. An important issue in systematic reviews of complex interventions is that data available for synthesis are often extremely limited, due to small numbers of relevant studies and limitations in how these studies are conducted and their results are reported. Furthermore, it is uncommon for two studies to evaluate exactly the same intervention, in part because of the interventions’ inherent complexity. Thus, each study may be designed to provide information on a unique context or a novel intervention approach. Outcomes may be measured in different ways and at different time points. We therefore discuss possible approaches when data are highly limited or highly heterogeneous, including the use of graphical approaches to present very basic summary results. We then discuss statistical approaches for combining results and for understanding the implications of various kinds of complexity.

In several places we draw on an example of a review undertaken to inform a recent WHO guideline on protecting, promoting and supporting breastfeeding. The review seeks to determine the effects of interventions to promote breastfeeding delivered in five types of settings (health services, home, community, workplace, policy context or a combination of settings). The included interventions were predominantly multicomponent, and were implemented in complex systems across multiple contexts. The review included 195 studies, including many from low-income and middle-income countries, and concluded that interventions should be delivered in a combination of settings to achieve high breastfeeding rates.

THE IMPORTANCE OF THE RESEARCH QUESTION

The starting point in any synthesis of quantitative evidence is a clear purpose. The input of stakeholders is critical to ensure that questions are framed appropriately, addressing issues important to those commissioning, delivering and affected by the intervention. Detailed discussion of the development of research questions is provided in an earlier paper in the series, and a subsequent paper explains the importance of taking context into account. The first of these papers describes two possible perspectives. A complex interventions perspective emphasises the complexities involved in conceptualising, specifying and implementing the intervention per se, including the array of possibly interacting components and the behaviours required to implement it. A complex systems perspective emphasises the complexity of the systems into which the intervention is introduced, including possible interactions between the intervention and the system, interactions between individuals within the system and how the whole system responds to the intervention.

The simplest purpose of a systematic review is to determine whether a particular type of complex intervention (or class of interventions) is effective compared with a ‘usual practice’ alternative. The familiar PICO framework is helpful for framing the review:14 in the PICO framework, a broad research question about effectiveness is uniquely specified by describing the participants (‘P’), including the setting and prevailing conditions) to which the intervention is to be applied; the intervention (‘I’) and comparator (‘C’) of interest, and the outcomes (‘O’), including their time course) that might be impacted by the intervention. In the breastfeeding review, the primary synthesis approach was to combine all available studies, irrespective of setting, and perform separate meta-analyses for different outcomes.15

More useful than a review that asks ‘does a complex intervention work?’ is one that determines the situations in which a complex intervention has a larger or smaller effect. Indeed, research questions targeted by syntheses in the presence of complexity often dissect one or more of the PICO elements to explore how intervention effects vary both within and across studies (ie, treating the PICO elements as ‘moderators’). For instance, analyses may explore variation across participants, settings and prevailing conditions (including context); or across interventions (including different intervention components that may be present or absent in different studies); or across outcomes (including different outcome measures, at different levels of the system and at different time points) on which effects of the intervention occur. In addition, there may be interest in how aspects of the underlying system or the intervention itself mediate the effects, or in the role of intermediate outcomes on the pathway from intervention to impact.16 In the breastfeeding review, interest moved from the overall effects across interventions to investigations of how effects varied by such factors as intervention delivery setting, high-income versus low-income country, and urban versus rural setting.15

The role of logic models to inform a synthesis

An earlier paper describes the benefits of using system-based logic models to characterise a priori theories about how the system operates. These provide a useful starting point for most syntheses since they encourage consideration of all aspects of complexity in relation to the intervention or the system (or both). They can help identify important mediators and moderators, and inform decisions about what aspects of the intervention and system need to be addressed in the synthesis. As an example, a protocol for a review of the health effects of environmental interventions to reduce the consumption
Table 1  Quantitative synthesis possibilities to address aspects of complexity

<table>
<thead>
<tr>
<th>Aspect of complexity of interest</th>
<th>Examples of potential research question(s)</th>
<th>Synthesis possibilities</th>
<th>Further discussion</th>
</tr>
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<tbody>
<tr>
<td>What ‘is’ the system? How can it be described?</td>
<td>What are the main influences on the health problem? How are they created and maintained? How do these influences interconnect?</td>
<td>Map the system, defining pathways and influences. Draw a logic model based on the key aspects for the research question at hand as a basis for thinking about the quantitative synthesis.</td>
<td>See companion paper, and section 2.1.</td>
</tr>
<tr>
<td>Interactions between components of complex interventions</td>
<td>What is the independent and combined effect of the individual components? How do the components work along and in combination to produce effects? (How do they interact to produce outcomes?)</td>
<td>Consider methods such as meta-regression, network meta-analysis and component-based approach that address intervention components, using models that allow investigation of interactions among components.</td>
<td>See sections 5.2 and 6.</td>
</tr>
<tr>
<td>Interactions of interventions with context and adaptation</td>
<td>Do the effects of the intervention appear to be context-dependent? (How) does the system change when the intervention is introduced?</td>
<td>Consider subgroup analysis and meta-regression to examine how features of context impact on effect sizes.</td>
<td>See section 5.2.</td>
</tr>
<tr>
<td>System adaptivity (how does the system change?)</td>
<td>Which aspects of the system are affected? Does this potentiate or dampen its effects?</td>
<td>Identify behaviours or actions that might be affected, and consider these as outcomes in meta-analysis or meta-regression analyses. To account for correlations among them, multivariate methods might be considered.</td>
<td>See section 8.</td>
</tr>
<tr>
<td>Emergent properties</td>
<td>What are the effects (anticipated and unanticipated) which follow from this system change?</td>
<td>Identify other possible effects of the intervention, and consider these as outcomes in meta-analysis or meta-regression analyses. Consider model-driven meta-analysis or mathematical models (including simulation approaches) to investigate these further.</td>
<td>See section 8, box 2 and 3.</td>
</tr>
<tr>
<td>Non-linearity and phase changes</td>
<td>How do effects change over time?</td>
<td>Identify important time points and address these in separate meta-analyses, or using meta-regression analyses. Consider mathematical models to predict how effects might change over time.</td>
<td>See sections 5 and 8, and box 3.</td>
</tr>
<tr>
<td>Positive (reinforcing) and negative (balancing) feedback loops</td>
<td>What explains change in the effectiveness of the intervention over time?</td>
<td>Consider model-driven meta-analysis or mathematical models to investigate these.</td>
<td>See sections 7 and 8, boxes 2 and 3.</td>
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<td>Are the effects of an intervention dampened/ suppressed by other aspects of the system (eg, contextual influences)?</td>
<td>Consider subgroup analysis and meta-regression to examine how features of the system impact on effect sizes.</td>
<td>See section 5.2.</td>
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Table 1  Continued

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<td>Multiple (health and non-health) outcomes</td>
<td>What changes in processes and outcomes follow the introduction of this system change?</td>
<td>Identify behaviours or actions that might be affected, and consider these as outcomes in meta-analysis or meta-regression analyses. To account for correlations among them, multivariate methods might be considered. Consider meta-regression to examine the mediating effects of intermediate outcomes.</td>
<td>See section 8.</td>
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<td>At what levels in the system are they experienced?</td>
<td>Identify units (e.g., individuals or organisations) whose behaviour or actions might be affected, and consider these as outcomes in meta-analysis or meta-regression. Multilevel models might be appropriate to capture the different levels of impact, although may require access to individual participant data.</td>
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<td>Data requirements from each study</td>
<td>Main strengths</td>
<td>Main limitations</td>
</tr>
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<tr>
<td>Forest plot (without overall effect)</td>
<td>Effect size and CI on the same metric</td>
<td>Widely familiar; each study clearly identified</td>
<td>Replication (of similar research questions) across studies is uncommon; effect size data may not be available</td>
</tr>
<tr>
<td>Albatross plot</td>
<td>P value, sample size and direction of effect</td>
<td>Data requirements are basic, so usually met; possibility of making indirect inferences on underlying effect sizes</td>
<td>Does not provide estimate of effect size; studies not clearly identified</td>
</tr>
<tr>
<td>Harvest plot</td>
<td>Conclusion of statistical test for effect; study feature(s) of interest</td>
<td>Data requirements are basic, so usually met; multiple outcomes can easily be displayed</td>
<td>Arbitrary distinction of studies according to statistical test; does not provide estimate of effect size</td>
</tr>
<tr>
<td>Effect direction plot</td>
<td>Conclusion of statistical test for effect; study feature(s) of interest</td>
<td>Data requirements are basic, so usually met; multiple outcomes can easily be displayed</td>
<td>Arbitrary distinction of studies according to statistical test; does not provide estimate of effect size; studies not clearly identified</td>
</tr>
<tr>
<td>Bubble plot</td>
<td>Conclusion of statistical analysis for effect; study feature(s) of interest</td>
<td>Data requirements are basic, so usually met; multiple outcomes can easily be displayed</td>
<td>Arbitrary distinction of studies according to result of statistical analysis; does not provide estimate of effect size; studies not clearly identified</td>
</tr>
<tr>
<td>Binomial test</td>
<td>Direction of effect</td>
<td>Data requirements are basic, so usually met</td>
<td>Does not provide estimate of effect size</td>
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<tr>
<td>Combining p values</td>
<td>P value and direction of effect</td>
<td>Data requirements are basic, so usually met</td>
<td>Does not provide estimate of effect size</td>
</tr>
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<td>Standard meta-analysis (eg, weighted average)</td>
<td>Effect size and CI (or equivalent) on the same metric</td>
<td>Widely familiar; produces effect sizes (important for decision making)</td>
<td>Replication (of similar research questions) across studies is uncommon; effect size data may not be available</td>
</tr>
<tr>
<td>Multiple outcomes meta-analysis (multivariate methods)</td>
<td>Effect size and CI (or equivalent) on the same metric for each outcome; data on correlations between outcomes</td>
<td>Can strengthen analysis of one outcome by ‘borrowing strength’ from other outcomes</td>
<td>Requires reasonably large number of studies for reliable results</td>
</tr>
<tr>
<td>Subgroup analysis</td>
<td>Effect size and CI (or equivalent) on the same metric; study feature(s) of interest</td>
<td>Straightforward and widely familiar; flexible approach appropriate for examining impact of context, settings, participants, intervention characteristics</td>
<td>Addresses one study feature at a time; requires reasonably large number of studies for reliable results; high risk of false-positive conclusions; often has low power to detect true impacts of the features examined</td>
</tr>
<tr>
<td>Meta-regression</td>
<td>Effect size and CI (or equivalent) on the same metric; study feature(s) of interest</td>
<td>Allows multiple study features to be examined together; flexible approach appropriate for examining impact of context, settings, participants, intervention characteristics and for mediating effects of intermediate outcomes</td>
<td>Requires reasonably large number of studies for reliable results; high risk of false-positive conclusions; often has low power to detect true impacts of the features examined</td>
</tr>
<tr>
<td>Multiple interventions meta-analysis (network meta-analysis)</td>
<td>Effect size and CI (or equivalent) on the same metric; category to place each intervention</td>
<td>Facilitates rank ordering of interventions for the outcome</td>
<td>Requires interventions to be grouped into (reasonably homogenous) categories; requires similar target population for all studies; requires all categories of interventions to be ‘connected’ in the network</td>
</tr>
</tbody>
</table>
### Table 2  Continued

<table>
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<th>Data requirements from each study</th>
<th>Main strengths</th>
<th>Main limitations</th>
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<td>Components-based approach to intervention complexity</td>
<td>Effect size and CI (or equivalent) on the same metric; components present in each intervention</td>
<td>Facilitates identification of most important component(s) of complex intervention</td>
<td>Requires reasonably large number of studies for reliable results; Assumptions required about whether components act additively or otherwise</td>
</tr>
<tr>
<td>Qualitative comparative analysis</td>
<td>Effect size estimates and study features of interest</td>
<td>Supports non-linear effects; multiple pathways to effectiveness; operates in ‘small n’ scenarios</td>
<td>Produces explanatory, rather than predictive, findings</td>
</tr>
<tr>
<td>Model-driven meta-analysis</td>
<td>Assumed causal model (logic model); effect size information for each relevant path in the model</td>
<td>Flexible approach to combining evidence; forces thinking about how effects arise</td>
<td>Dependent on appropriate assumptions being made in the causal model and availability of data</td>
</tr>
<tr>
<td>Mathematical models and system science methods</td>
<td>Assumed model; variable data requirements</td>
<td>Flexible approach to combining evidence; can supplement evidence with model-based assumptions when evidence is not available; wider focus beyond the intervention may include contextual information and dynamic interrelationships</td>
<td>Heavily reliant on assumptions going into the model; may require very large data sets</td>
</tr>
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</table>

### PREPARING FOR A QUANTITATIVE SYNTHESIS

Before undertaking a quantitative synthesis of complex interventions, it can be helpful to begin the synthesis non-quantitatively, looking at patterns and characteristics of the data identified. Systematic tabulation of information is recommended, and this might be informed by a prespecified logic model. The Cochrane Consumers and Communication Group succinctly summarise the process as an ‘investigation of the similarities and the differences between the findings of different studies, as well as exploration of patterns in the data’.25 Another useful framework was described by Petticrew and Roberts.26 They identify three stages in the initial narrative synthesis: (1) Organisation of studies into logical categories, the structure of which will depend on the purpose of the synthesis, possibly relating to study design, outcome or intervention types. (2) Within-study analysis, involving the description of patterns and characteristics of the data identified. Systematic tabulation of information is recommended, and this might be informed by a prespecified logic model. The most established framework for non-quantitative synthesis is that proposed by Popay et al.24 The Cochrane Consumers and Communication Group succinctly summarise the process as an investigation of the similarities and the differences between the findings of different studies, as well as exploration of patterns in the data.25

Aspects of this process are likely to be implemented in any systematic review, even when a detailed quantitative synthesis is undertaken. In some circumstances, the available data are too diverse, too non-quantitative or too sparse for a quantitative synthesis to be meaningful even if it is possible. The best that can be achieved in many reviews of complex interventions is a non-quantitative synthesis following the guidance given in the above frameworks.
Graphical approaches

Graphical displays can be very valuable to illustrate patterns in results of studies. We illustrate some options in Figure 1. Forest plots are the standard illustration of the results of multiple studies (see Figure 1, panel A), but require a similar effect size estimate from each study. For studies of complex interventions, the diversity of approaches to the intervention, the context, evaluation approaches and reporting differences can lead to considerable variation across studies in what results are available. Some novel graphical approaches have been proposed for such situations. A recent development is the albatross plot, which plots p values against sample sizes, with approximate effect-size contours superimposed (see Figure 1, panel B). The contours are computed from the p values and sample sizes, based on an assumption about the type of analysis that would have given rise to the p values. Although these plots are designed for situations when effect size estimates are not available, the contours can be used to infer approximate effect sizes from studies that are analysed and reported in highly diverse ways. Such an advantage may prove to be a disadvantage, however, if the contours are overinterpreted.

Harvest plots have been proposed by Ogilvie et al as a graphical extension of a vote counting approach to synthesis (see Figure 1, panel C). However, approaches based on vote counting of statistically significant results have been criticised on the basis of their poor statistical properties, and because statistical significance is an outdated and unhelpful notion. The harvest plot is a matrix of small illustrations, with different outcome domains defining rows and different qualitative conclusions (negative effect, no effect, positive effect) defining columns. Each study is represented by a bar that is positioned according to its measured outcome and qualitative conclusion. Bar heights and shadings can depict features of the study, such as objectivity of the outcome measure, suitability of the study design and study quality. A similar idea to the harvest plot is the effect direction plot proposed by Thomson and Thomas.
A device to plot the findings from a large and complex collection of evidence is a bubble plot (see figure 1, panel D). A bubble plot illustrates the direction of each finding (or whether the finding was unclear) on a horizontal scale, using a vertical scale to indicate the volume of evidence, and with bubble sizes to indicate some measure of credibility of each finding. Such an approach can also depict findings of collections of studies rather than individual studies, and was used successfully, for example, to summarise findings from a review of systematic reviews of the effects of acupuncture on various indications for pain.33

**Statistical methods not based on effect size estimates**

We have mentioned that a frequent problem is that standard meta-analysis methods cannot be used because data are not available in a similar format from every study. In general, the core principles of meta-analysis can be applied even in this situation, as is highlighted in the Cochrane Handbook, by addressing the questions: ‘What is the direction of effect?’; ‘What is the size of effect?’; ‘Is the effect consistent across studies?; and ‘What is the strength of evidence for the effect?’34

Alternatives to the estimation of effect sizes could be used more often than they are in practice, allowing some basic statistical inferences despite diversely reported results. The most fundamental analysis is to test the overall null hypothesis of no effect in any of the studies. Such a test can be undertaken using only minimally reported information from each study. At its simplest, a binomial test can be performed using only the direction of effect observed in each study, irrespective of its CI or statistical significance.35 Where exact p values are available as well as the direction of effect, a more powerful test can be performed by combining these using, for example, Fisher’s combination of p values.36 It is important that these p values are computed appropriately, however, accounting for clustering or matching of participants within the studies. Rejecting the null model based on such tests provides no information about the magnitude of the effect, providing information only on whether at least one study shows an effect is present, and if so, its direction.37

**STANDARD SYNTHESIS METHODS**

**Meta-analysis for overall effect**

Probably the most familiar approach to meta-analysis is that of estimating a single summary effect across similar studies. This simple approach lends itself to the use of forest plots to display the results of individual studies as well as syntheses, as illustrated for the breastfeeding studies in figure 1 (panel A). This analysis addresses the broad question of whether evidence from a collection of studies supports an impact of the complex intervention of interest, and requires that every study makes a comparison of a relevant intervention against a similar alternative. In the context of complex interventions, this is described by Caldwell and Welton as the ‘jumping’ approach,38 and by Guise et al as the ‘holistic’ approach.36 One key limitation of the simple approach is that it requires similar types of data from each study. A second limitation is that the meta-analysis result may have limited relevance when the studies are diverse in their characteristics. Fixed-effect models, for instance, are unlikely to be appropriate for complex interventions because they ignore between-studies variability in underlying effect sizes. Results based on random-effects models will need to be interpreted by acknowledging the spread of effects across studies, for example, using prediction intervals.

A common problem when undertaking a simple meta-analysis is that individual studies may report many effect sizes that are correlated with each other, for example, if multiple outcomes are measured, or the same outcome variable is measured at several time points. Numerous approaches are available for dealing with such multiplicity, including multivariate meta-analysis, multi-level modelling, and strategies for selecting effect sizes.40

A very simple strategy that has been used in systematic reviews of complex interventions is to take the median effect size within each study, and to summarise these using the median of these effect sizes across studies.41

**Exploring heterogeneity**

Diversity in the types of participants (and contexts), interventions and outcomes are key to understanding sources of complexity.9 Many of these important sources of heterogeneity are most usefully examined—to the extent that they can reliably be understood—using standard approaches for understanding variability across studies, such as subgroup analyses and meta-regression.

A simple strategy to explore heterogeneity is to estimate the overall effect separately for different levels of a factor using subgroup analyses (referring to subgrouping studies rather than participants).12 As an example, McFadden et al conducted a systematic review and meta-analysis of 73 studies of support for healthy breastfeeding mothers with healthy term babies.45 They calculated separate average effects for interventions delivered by a health professional, a lay supporter or with mixed support, and found that the effect on cessation of exclusive breast feeding at up to 6 months was greater for lay support compared with professionals or mixed support (p=0.02). Guise et al provide several ways of grouping studies according to their interventions, for example, grouping studies by key components, by function or by theory.16

Meta-regression provides a flexible generalisation to subgroup analyses, whereby study-level covariates are included in a regression model using effect size estimates as the dependent variable.44 45 Both continuous and categorical covariates can be included in such models; with a single categorical covariate, the approach is essentially equivalent to subgroup analyses. Meta-regression with continuous covariates in theory allows the extrapolation of relationships to contexts that were not examined in any of the studies, but this should generally be avoided.
For example, if the effect of an interventional approach appears to increase as the size of the group to which it is applied decreases, this does not mean that it will work even better when applied to a single individual. More generally, the mathematical form of the relationship modelled in a meta-regression requires careful selection. Most often a linear relationship is assumed, but a linear relationship does not permit step changes such as might occur if an interventional approach requires a particular level of some feature of the underlying system before it has an effect.

Several texts provide guidance for using subgroup analysis and meta-regression in a general context and for complex interventions. In principle, many aspects of complexity in interventions can be addressed using these strategies, to create an understanding of the ‘response surface’. However, in practice, the number of studies is often too small for reliable conclusions to be drawn. In general, subgroup analysis and meta-regression are fraught with dangers associated with having few studies, many sources of variation across study features and confounding of these features with each other as well as with other, often unobserved, variables. It is therefore important to prespecify a small number of plausible sources of diversity so as to reduce the danger of reaching spurious conclusions based on study characteristics that correlate with the effects of the interventions but are not the cause of the variation. The ability of statistical analyses to identify true sources of heterogeneity will depend on the number of studies, the sizes of the studies and the true differences between effects in studies with different characteristics.

SYNTHESIS METHODS FOR UNDERSTANDING COMPONENTS OF THE INTERVENTION

When interventions comprise distinct components, it is attractive to separate out the individual effects of these components. Meta-regression can be used for this, using covariates to code the presence of particular features in each intervention implementation. As an example, Blakemore et al analysed 39 intervention comparisons from 33 independent studies aiming to reduce urgent healthcare use in adults with asthma. Effect size estimates were coded according to components used in the interventions, and the authors found that multicomponent interventions including skills training, education and relapse prevention appeared particularly effective. In another example, of interventions to support family caregivers of people with Alzheimer’s disease, the authors used methods for decomposing complex interventions proposed by Czaja et al, and created covariates that reduced the complexity of the interventions to a small number of features about the intensity of the interventions. More sophisticated models for examining components have been described by Welton et al and Madan et al. A component-level approach may be useful when there is a need to disentangle the ‘active ingredients’ of an intervention, for example, when adapting an existing intervention for a new setting. However, component-based approaches require assumptions, such as whether individual components are additive or interact with each other. Furthermore, the effects of components can be difficult to estimate if they are used only in particular contexts or populations, or are strongly correlated with use of other components. An alternative approach is to treat each combination of components as a separate intervention. These separate interventions might then be compared in a single analysis using network meta-analysis. A network meta-analysis combines results from studies comparing two or more of a larger set of interventions, using indirect comparisons via common comparators to rank-order all interventions. As an example, Achana et al examined the effectiveness of safety interventions on the uptake of three poisoning prevention practices in households with children. Each singular combination of intervention components was defined as a separate intervention in the network. Network meta-analysis may also be useful when there is a need to compare multiple interventions to answer an ‘in principle’ question of which intervention is most effective. Consideration of the main goals of the synthesis will help those aiming to prepare guidelines to decide which of these approaches is most appropriate to their needs.

A case study exploring components is provided in Box 1, and an illustration is provided in figure 2. The component-based analysis approach can be likened to...
a factorial trial, in that it attempts to separate out the
effects of individual components of the complex inter-
ventions, and the network meta-analysis approach can
be likened to a multiarm trial approach, where each
complex intervention in the set of studies is a different
arm in the trial. Deciding between the two approaches
can leave the analyst caught between the need to ‘split’
components to reflect complexity (and minimise hetero-
geneity) and ‘lump’ to make an analysis feasible. Both
approaches can be used to examine other features of
interventions, including interventions designed for
delivery at different levels. For example, a review of the
effects of interventions for children exposed to domestic
violence and abuse included studies of interventions
targeted at children alone, parents alone, children and
parents together, and parents and children separately.61
A network meta-analysis approach was taken to the
synthesis, with the people targeted by the intervention
used as a distinguishing feature of the interventions
included in the network.

A common limitation when implementing these quan-
titative methods in the context of complex interventions
is that replication of the same intervention in two or more
studies is rare. Qualitative comparative analysis (QCA)
might overcome this problem, being designed to address
the ‘small N; many variables’ problem. QCA involves:
(1) Identifying theoretically driven thresholds for deter-
mining intervention success or failure. (2) Creating a ‘truth
table’, which takes the form of a matrix, cross-tabulating
all possible combinations of conditions (eg, participant
and intervention characteristics) against each study and its
associated outcomes. (3) Using Boolean algebra to elimi-
nate redundant conditions and to identify configurations
of conditions that are necessary and/or sufficient to trigger
intervention success or failure. QCA can usefully comple-
ment qualitative integration, sometimes in the context of
synthesising diverse types of evidence.

SYNTHESIS METHODS FOR UNDERSTANDING MECHANISMS OF
ACTION
An alternative purpose of a synthesis is to gain insight
into the mechanisms of action behind an intervention, to
inform its generalisability or applicability to a particular
context. Such syntheses of quantitative data may comple-
ment syntheses of qualitative data,11 and the two forms
might be integrated.12 Logic models, or theories of action,
are important to motivate investigations of mechanism.
The synthesis is likely to focus on intermediate outcomes
reflecting intervention processes, and on mediators of
effect (factors that influence how the intervention affects
an outcome measure). Two possibilities for analysis are
to use these intermediate measurements as predictors
of main outcomes using meta-regression methods,63 or
to use multivariate meta-analysis to model the interme-
tiate and main outcomes simultaneously, exploiting
and estimating the correlations between them.64 65 If the
synthesis suggests that hypothesised chains of outcomes
hold, this lends weight to the theoretical model under-
lying the hypothesis.

An approach to synthesis closely identified with this
category of interventions is model-driven meta-analysis,
in which different sources of evidence are integrated
within a causal path model akin to a directed acyclic
graph. A model-driven meta-analysis is an explana-
tory analysis.66 It attempts to go further than a stan-
dard meta-analysis or meta-regression to explore how
and why an intervention works, for whom it works, and
which aspects of the intervention (factors) are driving
overall effect. Such syntheses have been described in
frequentist19 67–70  and Bayesian 71 72  frameworks and are
variously known as model-driven meta-analysis, linked
meta-analysis, meta-mediation analysis and meta-analysis
of structural equation models. In their simplest form,
standard meta-analyses estimate a summary correlation
independently for each pair of variables in the model.
The approach is inherently multivariate, requiring the
estimation of multiple correlations (which, if obtained
from a single study, are also not independent). 73–75 Each
study is likely to contribute fragments of the correlation
matrix. A summary correlation matrix, combined either
by fixed-effects or random-effects methods, then serves
as the input for subsequent analysis via a standardised
regression or structural equation model.

**Figure 2** Intervention components in the studies integrated
by Welton et al (a sample of 18 from 56 active treatment
arms). EDU, educational component; BEH, behavioural
component; COG, cognitive component; REL, relaxation
component; SUP, psychosocial support component.
An example is provided in box 2. The model in figure 3 postulates that the effect of ‘Dietary adherence’ on ‘Diabetes complications’ is not direct but is mediated by ‘Metabolic control’.76 The potential for model-driven meta-analysis to incorporate such indirect effects also allows for mediating effects to be explicitly tested and in so doing allows the meta-analyst to identify and explore the mechanisms underpinning a complex intervention.77

SYNTHESIS APPROACHES FOR UNDERSTANDING COMPLEXITIES OF THE SYSTEM

Syntheses may seek to address complexities of the system to understand either the impact of the system on the effects of the intervention or the effects of the intervention on the system. This may start by modelling the salient features of the system’s dynamics, rather than focusing on interventions. Subgroup analysis and meta-regression are useful approaches for investigating the extent to which an intervention’s effects depend on baseline features of the system, including aspects of the context. Sophisticated meta-regression models might investigate multiple baseline features, using similar approaches to the component-based meta-analyses described earlier. Specifically, aspects of context or population characteristics can be regarded as ‘components’ of the system into which the intervention is introduced, and similar statistical modelling strategies used to isolate effects of individual factors, or interactions between them.

When interventions act at multiple levels, it may be important to understand the effects at these different levels. Outcomes may be measured at different levels (eg, at patient, clinician and clinical practice levels) and analysed separately. Qualitative research plays a particularly important role in identifying the outcomes that should be assessed through quantitative synthesis.12 Care is needed to ensure that the unit of analysis issues are addressed. For example, if clinics are the unit of randomisation, then outcomes measured at the clinic level can be analysed using standard methods, whereas outcomes measured at the level of the patient within the clinic would need to account for clustering. In fact, multiple dependencies may arise in such data, when patients receive care in small groups. Detailed investigations of effect at different levels, including interactions between the levels, would lend themselves to multilevel (hierarchical) models for synthesis. Unfortunately, individual participant data at all levels of the hierarchy are needed for such analyses.

Model-based approaches also offer possibilities for addressing complex systems; these include economic models, mathematical models and systems science methods generally.78–80 Broadly speaking, these provide mathematical representations of logic models, and analyses may involve incorporation of empirical data (eg, from systematic reviews), computer simulation, direct computation or a mixture of these. Multiparameter evidence synthesis methods might be used.81 82 Approaches include models to represent systems (eg, systems dynamics models) and approaches that simulate individuals within the system (eg, agent-based models).79 Models can be particularly useful when empirical evidence does not address all important considerations, such as ‘real-world’ contexts, long-term effects, non-linear effects and complexities such as feedback loops and threshold effects. An example of a model-based approach to synthesis is provided in box 3. The challenge when adopting these approaches is often in the identification of system components, and accurately estimating causes and effects (and uncertainties). There are few examples of the use of these analytical tools in systematic syntheses.
CONSIDERATIONS OF BIAS AND RELEVANCE

It is always important to consider the extent to which (1) The findings from each study have internal validity, particularly for non-randomised studies which are typically at higher risk of bias. (2) Studies may have been conducted but not reported because of unexciting findings. (3) Each study is applicable to the purposes of the review, that is, has external validity (or ‘directness’), in the language of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.83 At minimum, internal and external validity should be examined and reported, and the risk of publication bias assessed, and these can be achieved through the GRADE framework.10 With sufficient studies, information collected might be used in meta-regression analyses to evaluate empirically whether studies with and without specific sources of bias or indirectness differ in their results.

CONCLUSION

Our review of quantitative synthesis methods for evaluating the effects of complex interventions has outlined many possible approaches that might be considered by those collating evidence in support of guideline development. We have described three broad categories: (1) Non-quantitative methods, including tabulation, narrative and graphical approaches. (2) Standard meta-analysis methods, including meta-regression to investigate study-level moderators of effect. (3) More advanced synthesis methods, in which models allow exploration of intervention components, investigation of both moderators and mediators, examination of mechanisms, and exploration of complexities of the system.

The choice among these approaches will depend on the purpose of the synthesis, the similarity of the studies included in the review, the level of detail available from the studies, the nature of the results reported in the studies, the expertise of the synthesis team, and the resources available. Clearly the advanced methods require more expertise and resources than the simpler methods. Furthermore, they require a greater level of detail and typically a sizeable evidence base. We therefore expect them to be used seldomly; our aim here is largely to articulate what they can achieve so that they reviews, but they may be useful when the focus of analysis is on understanding the causes of complexity in a given system rather than on the impact of an intervention.

Box 3 Example of a mathematical modelling approach for soft drinks industry levy

Briggs et al examined the potential impact of a soft drinks levy in the UK, considering possible different types of response to the levy by industry.80 Various scenarios were posited, with effects on health outcomes informed by empirical data from randomised trials and cohort studies of association between sugar intake and body weight, diabetes and dental caries. Figure 4 provides a simple characterisation of how the empirical data were fed into the model. Inputs into the model included levels of consumption of various types of drinks (by age and sex), volume of drinks sales, and baseline levels of obesity, diabetes and dental caries (by age and sex). The authors concluded that health gains would be greatest if industry reacted by reformulating their products to include less sugar.

It may be desirable to learn about a specific setting, intervention type or outcome measure more directly than others. For example, to inform a decision for a low-income setting, emphasis should be placed on results of studies performed in low-income countries. One option is to restrict the synthesis to these studies. An alternative is to model the dependence of an intervention’s effect on some feature(s) related to the income setting, and extract predictions from the model that are most relevant to the setting of interest. This latter approach makes fuller use of available data, but relies on stronger assumptions.

Often, however, the accumulated studies are too few or too disparate to draw conclusions about the impact of bias or relevance. On rare occasions, syntheses might implement formal adjustments of individual study results for likely biases. Such adjustments may be made by imposing prior distributions to depict the magnitude and direction of any biases believed to exist.84 85 The choice of a prior distribution may be informed by formal assessments of risk of bias, by expert judgement, or possibly by empirical data from meta-epidemiological studies of biases in randomised and/or non-randomised studies.86 For example, Wolf et al implemented a prior distribution based on findings of a meta-epidemiological study87 to adjust for lack of blinding in studies of interventions to improve quality of point-of-use water sources in low-income and middle-income settings.88 Unfortunately, empirical evidence of bias is mostly limited to clinical trials, is weak for trials of public health and social care interventions, and is largely non-existent for non-randomised studies.

Figure 4 Simplified version of the conceptual model used by Briggs et al (adapted from Briggs et al80).

Soft drinks levy

Possible industry responses

Change in sugar intake

Meta-analysis of randomised trials

Meta-analysis of cohort studies

Cohort study

Body weight

Diabetes

Dental caries
can be adopted when they are appropriate. Notably, the choice among these approaches will also depend on the extent to which guideline developers and users at global, national or local levels understand and are willing to base their decisions on different methods. Where possible, it will thus be important to involve concerned stakeholders during the early stages of the systematic review process to ensure the relevance of its findings.

Complexity is common in the evaluation of public health interventions at individual, organisational or community levels. To help systematic review and guideline development teams decide how to address this complexity in syntheses of quantitative evidence, we summarise considerations and methods in tables 1 and 2. We close with the important remark that quantitative synthesis is not always a desirable feature of a systematic review. Whereas some sophisticated methods are available to deal with a variety of complex problems, on many occasions—perhaps even the majority in practice—the studies may be too different from each other, too weak in design or have data too sparse, for statistical methods to provide insight beyond a commentary on what evidence has been identified.

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### Contributors

JPTH co-led the project, conceived the paper, led discussions and wrote the first draft. JAL-L undertook analyses, contributed to discussions and contributed to writing the manuscript. BJJ drafted material on mechanisms, contributed to discussions and contributed extensively to writing the manuscript. SRD screened and categorised the results of the literature searches, collated examples and contributed to discussions. SD undertook searches to identify relevant literature and contributed to discussions. JMG contributed to discussions and commented critically on drafts. LAM undertook analyses, contributed to discussions and commented critically on drafts. THMM contributed examples, contributed to discussions and commented critically on drafts. EAR and JT contributed to discussions and commented critically on drafts. DMC co-led the project, contributed to discussions and contributed extensive parts of the paper. All authors approved the final version of the manuscript.

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