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The use of systematic reviews in HTA

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Abstract

Basically the Health Technology Assessment (HTA) is based on the scientific method and aims to produce information used in the field of health policy choices that need to be effective, efficient and safe. For this reason they Systematic Reviews (SR) and Meta-Analysis (MA) are generally used.
Typically, a single evaluation, even if resulting from an appropriate experimental study, can hardly be considered sufficient to help in make decisions on a health intervention mainly for statistical considerations (sample size is rather limited). Furthermore, if there were more primary studies, the results would not completely be in agreement with each other or may be dissimilar as they would be drawn from different social and economic backgrounds and thus are only partially comparable.
The SR and MA consolidate existing relevant search results in order to resolve any inconsistency or ambiguity between the existing studies and produce results that are obvious or significant results in individual studies. Often, when one decides to conduct an HTA, evidence of efficacy are lacking both quantitatively and qualitatively and / or the application contexts are often very dissimilar. Even in this case, the SR and MA do not generate new data but can produce new knowledge from existing evidence. Also the use of RS and MA to assess the availability or lack of sufficient evidence (for example on the efficacy of an intervention / treatment) or to indicate the need to conduct further studies and to generate new evidence pointing out which aspects should be taken into consideration.

Keywords: *systematic review, meta-analysis, health technology assessment*

The need for evidence of effectiveness in Public Health

The Public Health operators, similarly to what happens in clinical practice, when they have to make a decisions or develop health policy programs, they should always refer to the practice of 'Evidence Based Medicine (EBM), meaning by the Anglo-Saxon term "evidence facts", data or scientific knowledge that can be used to make decisions, solve problems or orienting action with appropriateness in the allocation of resources.

Considering that they are becoming more and more limited, it is very important to be able to use them properly. The main strategy used in HTA is essentially aimed at the search for evidence of the effectiveness of medical acts and their critical and systematic formulation. *(Buckley 2014)*

Basically the health technology assessment is based on the scientific method and aims to produce information used in the field of health policy choices that need to be effective, efficient and safe.
For this reason they Systematic Reviews (SR) and

Meta-Analysis (MA) are generally used.

The systematic review of the literature and meta-analysis are instruments of secondary research or synthesis (also called "complementary methods") which, through the research and the analysis
of the scientific literature, involve the combination of data and the integration of results of
several clinical research studies that deals with the same subject – including the primary research
studies - and share the same exposure and the same goal (result, impact, outcome).

More specifically, the aim of SR and MA is to summarize in an efficient way information and data from primary research tools, critically evaluating and expressing in a comprehensive and transparent way the information gleaned from experimental or observational studies of a specific medical intervention or on a therapeutic efficiency strategy. Then these data turn into summary findings (report) in order to provide the reader with a concise but comprehensive state of research on which he can base policies and clinical decisions.

Generally, for many matters treated in the HTA assessments there is no single definitive primary study be made of whether a technology is better than another in a particular clinical situation. Typically, a single evaluation, even if resulting from an appropriate experimental study, can hardly be considered sufficient to help make decisions on a health intervention mainly for statistical considerations (as generally speaking in the trials the sample size is rather limited). Furthermore, if there were more primary studies, the results would not completely be in agreement with each other or may be dissimilar as they would be drawn from different social and economic backgrounds and thus are only partially comparable.

The SR and MA consolidate existing relevant search results in order to resolve any inconsistency or ambiguity between the existing studies and produce results that are obvious or significant results in individual studies.

Often, when one decides to conduct an HTA, evidence of efficacy are lacking both quantitatively and qualitatively and / or the application contexts are often very dissimilar.
Even in this case, the SR and MA do not generate new data but can produce new knowledge from existing evidence. Also the use of RS and MA to assess the availability or lack of sufficient evidence (for example on the efficacy of an intervention / treatment) or to indicate the need to conduct further studies and to generate new evidence pointing out which aspects should be taken into consideration.

The collection of evidence relating to a particular technology is very important to carry out a synthesis whether it be qualitative or quantitative: primary studies are to be taken into account, and the search of literature is readily available due to it being published on specific databases, periodicals or in documents of producers organizations (**Tab. 1-2**).

The finding of new evidence should not be omitted and research can be undertaken on more specialized databases or even using the registers of clinical trials, reference lists and Internet search engines such as "google scholar" (for research of so-called "grey literature"), so as to expand the search beyond the most important biomedical bibliographic databases (PubMed, Scopus, Embase, and others).

A manual search of the magazines could also be made, or the search for conference proceedings, or to enable direct contact with the authors and/or sponsor in order to obtain a more complete and unbiased identification of relevant clinical trials and other studies (consistent with the predefined inclusion criteria).
(**Table 1 and Table 2**: Database to search for primary studies and some data bases for research of unpublished studies. **Table 3**: Database to search for systematic reviews).

Table 1 Database to search for primary studies

Database	Body	Website	Notes
Medline	National Library of Medicine (USA)	www.ncbi.nlm.nih.gov/pubmed/	Free
CINAHL	EBSCO	EBSCO www.ebscohost.com	Paid
EMBASE	Elsevier	www.embase.com	Paid
Cochrane Central Register of Controlled Trials	The Cochrane Collaboration	www.mrw.interscience.wiley.	Paid
TRIP Database	TRIP Database Ltd	www.tripdatabase.com/	Paid
PsycINFO/PscyLIT	American Psychological Association	www.apa.org/psycinfo/	Free
Sociological Abstract	ProQuest e CSA	www.csa.com/factsheets/	Paid
ERIC	Educational Resources	www.eric.ed.gov	Free
Web of science	Institute of Scientific Information	www.thomsonreuters.com/	Paid
Econlit	American Economic Association	www.econlit.org	Paid
ESDS Qualidata	UK Data Archive	www.esds.ac.uk/qualidata/	Free

Table 2. Some database for research of unpublished studies

Database	Body	Web site	Notes
The National Research	The National Research	www.nihr.ac.uk/	Free
Healthy People 2010 Information Access Project	U.S. Department of Health and Human Service	www.wonder.cdc.gov	Free
CHID	Agenzie Federali US	www.cehn.org/archives	Free
Dissertation Abstracts	Ann Arbor	www.library.dialog.com/	Paid
Conference Papers Index	ProQuest-CSA	www.csa.com/factsheets/	Paid
Googlescholar.com	Google	www.scholar.google.it/	Free

Table 3. Databases to search for systematic reviews

Database	Body	Website	Notes
Cochrane Database of Systematic review	The Cochrane Collaboration	www.cochrane.org/reviews	Paid
Database of Abstracts of Reviews of Effects (DARE)	Centre for review and dissemination University of York - NHS	www.crd.york.ac.uk/crdweb	Free
Health Technology Assessment Database (HTA)	Centre for review and dissemination University of York - NHS	www.crd.york.ac.uk/crdweb	Free
NHS Economic Evaluation Database	Centre for review and dissemination University of York - NHS	www.crd.york.ac.uk/crdweb	Free
The Campbell Library	The Campbell Collaboration	www.campbellcollaboration.org/	Free
Database of promoting health effectiveness reviews (DoPHER)	EPPI-Centre	www.eppi.ioe.ac.uk/cms/	Free
Health Evidence	Public Health Agency of Canada	http//:health-evidence.ca/	Free

The secondary research, conducted in a systematic and organized, aims to make the HTA report "researched" - by identifying and selecting the studies which are worth a scientifically treatment - and "refined" - minimizing the effects of those with low-quality value, of little relevance and reliability of data – so that they can be presented to the stakeholders to make decisions about the technology to be discussed.

The systematic review minimizes the effects of low-quality scientific production (and with little relevance and reliability) and it makes up for the lack of time and resources needed to face a study from scratch (if there is already a large production and availability of studies) .

Systematic reviews differ from traditional narrative reviews of literature because they provide for a crucial author's influence in the selection of studies (often because they fit in with the author's ideas) in the critical evaluation of these studies and in the summary of the results.

In fact, systematic reviews follow standard protocols whose key elements are: a) the completeness of the research studies (by clearly defining the objective, the databases consulted for the search, selection criteria, inclusion and exclusion of studies) ; b) the quality of the included studies (following validated standard instruments and recognized in the scientific literature); c) the possibility to quantitatively summarize the results through meta-analysis.

This allows, first of all, the control of the distortions and the minimization of the risk of error (bias) but also the reproducibility of the review with the obtaining of the same synthetic data as well as the possibility to check the data of third (and therefore also the veracity) or the possibility to reproduce at alater stage a data update.

It is well known that there are certain biases that are inherent in some studies in the literature, such as the qualitative / narrative biases and the same non-systematic literature reviews and editorials. On this evidence, then, it is given greater emphasis to the production of well-designed studies that provide quantitative results and making use of well-documented and validated methods.
The use of explicit and systematic methods limits bias (systematic errors) and reduces random effects, providing then more reliable results from which it possible to draw conclusions and make decisions.

An example of systematic review (including also the meta-analysis) that follows a clear and reproducible synthetic protocol was published by Saulle et al. on the magazine "Oral Dis." 2014 Jun 24. doi: 10.1111/odi.12269. titled "Human papillomavirus and cancerous diseases of the head and neck: a systematic review and meta-analysis.". R Saulle, L Semyonov, A Mannocci, A Careri, F Saburri, L Ottolenghi, F Guerra, G La Torre.

Limitation of SR and MA

Even systematic reviews that meet the most rigorous selection and inclusion criteria of the studies may reflect the bias of publication.
The validity and applicability of the results from the supplementary methods is restricted by any limitations of the included primary studies, where the highest grade is reserved for the RCTs (Randomized Controlled Trials), the lowest one in terms of descriptive studies (case series) or studies reporting the opinions of experts (see chapter "The epidemiological method" and "evidence based medicine").

The health research, as well as in other fields, often they made compromise between wanting to rely on the highest quality of evidence and the need to obtain useful results when the high-quality evidence is scarce or non-existent. For example: in law, there is a principle in which the same evidence that is essential in a case could be ignored in another one because in the second case there is a best available proof. The synthesis of the best evidence extends this principle to the practice of systematic review.
The concept of RCT as the only reliable source of evidence proof has also been passed by the Cochrane Collaboration (http://www.ph.cochrane.org/Files/PHRG_FAQ_Sept07.pdf): when it was not possible to implement randomized trial, it is necessary to consider as robust evidence, in order to guide decision-making processes, including those resulting from studies traditionally considered of lower rank (Lyles 2007; Ogilvie 2005).

In taking health policy decisions, the use of the best evidence that is available should not be precluded even by designs plans of not very high quality. Where there is little or no high-quality evidence may be necessary to find the lower-quality evidence, provided by documenting potential forms of bias that may follow such evidence.

Critical evaluation of evidence of effectiveness

The critical evaluation of each research paper is a critical step for the proper use of knowledge in the practice of public health. The model proposed by Sackett, referring to the assessment of knowledge published in the literature, is based on the three cornerstones of the Evidence Based Medicine and they are a) the judgment on the study or review of studies quality (internal validity); b) on the intervention effect size (importance) and c) on its applicability to the local situation (generalizability or external validity) (Sackett 2000).

Once the documents of interest have been identified, it is necessary to assess the quality and validity in the light of the methodological rigor with which they were produced and evaluate his credibility (see chapter "The assessment of methodological quality of studies").
The internal validity (efficacy) depends on the type of design and quality in its operation and in the analysis performed. The external validity: (generalizability or effectiveness) depends on the representativeness of the sample and the context in which it was done the study compared to the actual population that will be applied. Some factors that may limit the external validity of the results are for example the study of the population in the strict sense (i.e.: the age, the presence / absence of comorbidities, the restriction to particular study setting), the selection of outcome measures , the compared not appropriate therapies or insufficient duration of follow-up. The factors affecting the quality of the evidence are: the presence of study limitations for each included work, the variability or heterogeneity of the results according to the reference population, the type of intervention or outcomes considered and publication bias (studies which seem to have a certain effect tend to be published and the ones in which the interventions have no effect are left out).

If we try to adapt the fundamental questions of EBM to the practice of public health we can formulate a series of questions according to the following scheme:

- Is this study / review valid?
- Has this valuable study / review an impact on the population and is ti worthy of consideration for the decision maker?

- Is this study / review valid and relevant to the decision-maker , applicable to the context (social, political, organizational, etc.) which the recommendation is addresses?

Phases of the systematic review

The RS is a well-structured evaluation process that consists of several steps, mostly standardized.
After reviewing the individual studies found in the literature, an evaluation team must then assess, integrate, summarize and consolidate the available relevant results.
Basically, the main steps of a systematic review are the following ones:
1. To specify the objective of the systematic review of the literature
2. To define a structured protocol review (for this purpose it is appropriate to use an appropriate format as "PICOTS") so that it is explicit, impartial, and reproducible, including:
    - definition of inclusion and exclusion criteria for the literature search and selection, including the type of publication, the designs of the studies to include / exclude, the considered outcomes etc.
    - declaration of bibliographic databases that will be consulted (or other sources)
    - definition of search / logic terms for each database to be examined by specifying the keywords
    - declaration of the methods that will be used for the review (for example, number of reviewers who evaluate in parallel and independently of each retrieved study).
    - intention to conduct a meta-analysis (if feasible and if it is appropriate to perform it) specifying the methods that will be used to combine data and perform a pooled analysis
    - to record or to publish the study protocol, as appropriate (i.e. on database PROSPEROUS - see details below)
3. To carry out an extensive search of the literature
    - identify the relevant documents to the question by consulting the various databases following the methods listed in the protocol
4. To select the relevant material to the question (according to the inclusion and exclusion criteria defined in the initial phase) documenting all research sources and methods used
5. To review the search results and compare them with the inclusion / exclusion criteria
    - To report back the included and excluded studies (for example, using a flow chart)
    - To identify and exclude studies repeatedly found in various search engines
    - To compile and provide lists of included and excluded studies (with the reasons for this)
    - To assess potential sources of publication bias
6. To extract data from each study included in the review
    - In keeping with the study protocol of the systematic review
    - To include the characteristics of the model "PICOTS"
    - To present the extracted data in the form of tables
7. To evaluate the quality of the studies for each work included in the review
    - To evaluate the quality of the document for each study at least in duplicate and independently between operators. (See below for the assessment of study quality tools).
    - To consider the potential conflicts of interest
8. To carry out meta-analysis (if specified in the protocol and whether it is methodologically feasible based on the characteristics of the primary data obtained from the review)
9. To evaluate the quality (or strength) of the cumulative body of scientific evidence obtained from data of the individual studies.
    - To evaluate the risks of having bias, the relevance of the scientific evidence, the consistency of the results through the available evidence, and accuracy in reporting the results.
    - To assign a level of evidence of the resulting tests
10. To present the results / conclusions / recommendations:

    - To present the results linking the various studies included in the review / results that are explicitly test evidence from studies included
    - To take into account the quality of included studies
    - Present findings clearly to allow a critical evaluation and a possible reply to the systematic review

The interpretation of the tests implies a classification

process of studies finally to confer to each of them a weight and the resulting opportunity to include them or not in the summary. For 'results' refers to the conclusions that have been reached at the end of the study, for 'recommendations' means the recommendations, the advice that emerge from the results that can be formulated as a public health strategies, or as a clinical-organizational guidelines or practical guidelines.

12. Synthesis and consolidation of evidence and data (quantitative)

- for example make meta-analysis

13. To conduct a sensitivity analysis of the systematic review results

- To consider the publication bias and the plausible changes in the assumptions and estimates of results or other parameters taken into account.
- To perform also analyzes (for example, subgroup analysis and meta-regression) for a better understanding of the heterogeneity of the effects

14. To describe the limits including the actual / potential conflicts of interest and the process biases

- The report or the final report (or synthetic) must contain the number of selected studies, excluded studies and reasons for exclusion, a first evaluation of the quality of the included studies, a summary of findings, a preliminary conclusion to answer the question.Take them into account for the totality of the included studies and throughout the systematic review process
- To describe whether there are any gaps in evidence defining a future research agenda to cover any gaps on the subject.

15. To spread (for example, publish) and disseminate the results obtained.

Based on these methods, structured reports qualitative (systematic review) and / or quantitative (meta-analysis) can be built.

Often the terms SR and MA are used as synonyms, while, in a definitely more correct, the two tools define the MA as the statistic component (quantitative analysis) of an SR (qualitative analysis).

The "Picots-SD" model

A useful approach that allows to properly structure the question is "Picots framework "(see, for example, Counsell 1997), built by the Cochrane Collaboration approach and partly modified to the peculiarities of the Lines of Public Health Guide. Under this approach, each question should within it contain at least the following components:

- POPULATION. Examples: condition or severity of disease / stage, comorbidities, risk factors, demographic factors
- INTERVENTION. Examples: the type of technology, system / dose / frequency, the technique / method of administration
- COMPARATOR. Examples: that answers the question " are there alternative actions, compared to participate in the subject of our question "? Examples: placebo, usual / standards care, active control
- OUTCOMES. Examples: morbidity, mortality, quality of life, adverse events.
- TIMING. Examples: duration / follow-up intervals
- SETTING. It means the context in which the intervention is practiced. Examples: inpatient, specialties, home care
- STUDY DESIGN. Examples: RCT, observational studies
- RECIPIENTS. They are those to whom the recommendations are addressed which arising from a given question.

Often in evidence questions the reduced model or the "PICO" is used, which provides only the elements: Population, Intervention, Comparator, Outcomes.

Evaluation of systematic reviews

Once the studies were sourced, screened and included, these should be subjected to a quality assessment and therefore must be evaluated critically (for this purpose see chapter 7).

Tools "Reporting" of systematic reviews and meta-analysis

In addition to tools for assessing the methodological quality of systematic reviews, there are tools designed to improve the "reporting" of systematic reviews and meta-analysis, including the "PRISMA Statement," which stands for "Preferred Reporting Items for Systematic Reviews and Meta-Analyses " (Liberati A. 2009).

The Prisma Statement consists of a small number of essential evidence-based recommendations for writing systematic reviews which replaces the previous one and now obsolete checklist QUORUM (http://www.prisma-statement.org/statement.htm).

PRISMA acts as a support / guide the authors in conducting systematic reviews and meta-analysis it could in any case be used also for the critical evaluation of these documents; It differs from other checklist because in

detail assesses the various sections that compose a review, starting with the title of the same, analyzing the abstract, introduction, methods, results and the part relating to the discussion; Finally, ask the authors to provide information on the methods used to finance the production of the document (Moher 2009 Liberati 2009).
It is a check list with 27 items, and can also be used as a guide for the "critical appraisal" of a meta-analysis. (**Table 6**).

PRISMA also recommended the production of a flow chart outlining the studies selection process from the database search until the inclusion in the SR / MA. In a systematic review document will be drawn up, the methodology must be reported according to Prisma Statement. (Please refer to the systematic review - conducted by Saul et al - presented at the end of the chapter, which serves as a practical example for conducting and reporting of SR and MA).

Software and support systems

Various software packages are available for the conduct of systematic reviews and specifically the management of references (examples are: EndNote, Reference Manager, and RefWorks).
A resource to avoid cases of duplication and minimize publication bias in systematic reviews is the database "Prospero", an international free registry recording of systematic reviews protocols on health topics and social care. *(Booth 2013).*

The purpose of the recording of systematic reviews is also to ensure transparency in the review process by providing a complete list of systematic reviews and protocols at an early stage with a permanent record of the original protocol of each systematic review even if not published.

As such, the comparison of this register with all the results reported in systematic reviews will be able to reveal any differences between the methods of the results of the protocol recorded with those that are shown in the final analysis. Founded in 2011, Prospero is managed by the Centre for Reviews and Dissemination and is funded by the National Institute for Health Research UK *(Booth 2013).*

Meta-analysis

It is a quantitative assessment - as well as a systematic summary, organized and structured on an issue of interest - which can be carried out as a systematic review and that achieves a unique fact of synthesis and a quantitative estimate of overall effect of a particular technology, or other variable (treatment, diagnostic method, etc.) on a defined outcomes *(Borenstein 2009).*

Specifically the MA refers to a group of statistical methods that allow the combination of data ("pooling") from multiple independent studies, conducted on the same subject, generating a single data conclusive quantitative synthesis that responds to a specific question.
This combination can produce a stronger and more rigorous evidence and conclusion to that which can be provided instead of any individual study (Laird 1990; Normand 1999; Thacker 1988).

The meta-analysis purposes include:

- To encourage the systematic organization of evidence
- To increase the statistical power of the primary endpoint
- To improve the accuracy of the estimate of the effectiveness of a treatment, through the simultaneous analysis of more trials
- To provide quantitative estimates of the effects (e.g, odds ratios or effect sizes)
- To study subgroups of patients in the different studies (sensitivity analysis)
- To increase the general applicability (external validity) of the results
- To study the presence of heterogeneity between clinical trials
- To resolve uncertainty when reports do not agree on the result
- To evaluate the amount of variability between studies
- To identify the characteristics of group practices to particularly effective treatments
- To draw attention to the strengths and weaknesses of a body of research in a particular area
- To identify the needs for a new collection of primary data

The meta-analysis is typically used for arguments in the literature that have no definitive conclusions, including the arguments for which the studies derive dissimilar results. It is useful for example when there is uncertainty in the assessment of effectiveness of a treatment, or because the results of the individual studies are not unique, or because the individual studies are performed on a few patients and therefore are unreliable. In MA, the combination of data from multiple independent studies decreases the imprecision of the results of the individual studies. The overall result is then expressed with the same measures of association used for individual studies (relative risk, odds ratio, etc.).
The basic steps in the meta-analysis are the following ones:

1. To specify the problem of interest / Definition of a goal.
2. To specify the criteria for inclusion and exclusion of studies (for example, type and quality).
3. To identify and acquire all studies meeting the inclusion criteria (to make sure that research is exhaustive).
4. To classify the characteristics and results of the studies included in the meta-analysis: must take into account clinical factors (patient characteristics, study setting and methods of processing; other), the methodological characteristics (sample size), or statistics (heterogeneity, pooling) of the primary results.
5. To statistically combine the results of studies (pooling analysis) - if they are similar in clinical characteristics and without significant heterogeneity - using the common variables and perform sensitivity analyzes.
6. To present the results.

Evaluating a meta-analysis should lead to a single conclusion from two alternatives:

a. the studies are too heterogeneous (for patient characteristics, treatment modalities, for endpoints, for results) and therefore would be arbitrary to reach a combined measure of their results;
b. the studies are sufficiently similar to each other and allow an overall measure of effectiveness of the treatment, more precise and reproducible than that of each analyzed trials.

The meta-analysis can be restricted by publication bias of RCTs or other primary studies included in the meta-analysis, by selection bias of existing studies, by the poor quality of primary studies, from an unexplained heterogeneity (or insufficient comparability) and bias interpretation of results (Borenstein 2009; Nordmann 2012).

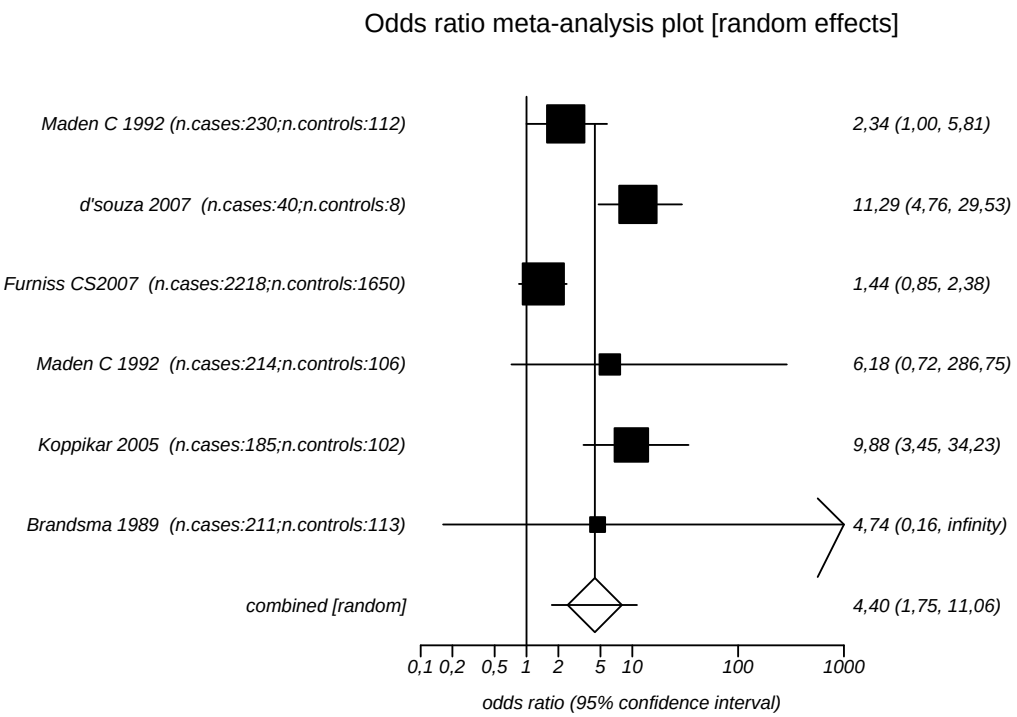
Some of the techniques used for statistical combination of the results are: analysis pooling data, the effect size, the method based on the weighting of the variance, Mantel-Haenszel, the Peto Peto method, DerSimonian and Laird.

The opportunity to make any of these techniques to a group of studies depends on the comparability and on the characteristics of the individual studies, the type of variables used, from assumptions about the uniformity of treatment effects, and other factors (Eddy 1992 ; Laird 1990; Normand 1999). The various meta-analysis techniques have specific rules relating to the inclusion of certain types of studies, and the combination of the results. Some meta-analytic techniques "adjust" the results of the individual studies to try to take account of differences in study design and bias related to their internal and external validity.

Meta-analysis is a very explicit and precise method where the bias can be minimized by maintaining a systematic approach (as reported by RS) (Egger 2001). Than the less stringent methods of combination evidence, meta-analysis can take much longer and require statistical and methodological expertise.
Several computer software packages are available to conduct a meta-analysis such as: Comprehensive Meta-analysis (CMA), OpenMeta [analysts], and RevMan.

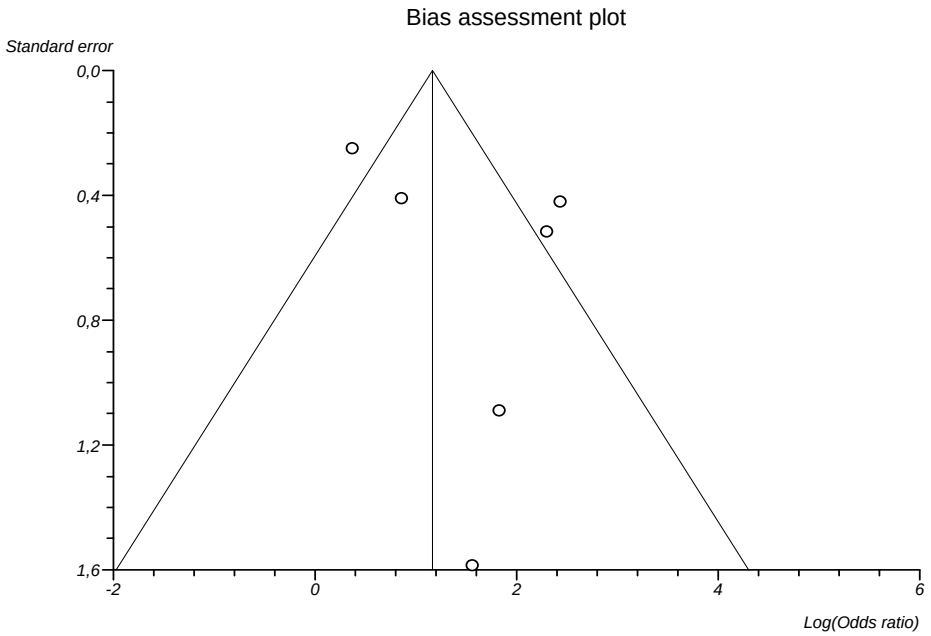
HOW TO REPRESENT THE RESULTS OF META- ANALYSIS

Figure 1. Forrest plot of the studies selected for anatomic site: oral cavity



The combined Odds Ratio (OR) analysis resulted by all the studies examined the risk in "Oral cavity"

Figure 2. Funnel plot of the studies selected for anatomic site: Oral cavity



The bias assessment plot analysis resulted by all the studies examined the risk in "Oral cavity"

Tabella 6. PRISMA 2009 Checklist PRISMA "Preferred Items for Reporting of Systematic Reviews and Meta-analisys". Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche P, et al. The Prisma Group (Moja L). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6.

TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary	13	State the principal summary measures (e.g., risk ratio, difference in means).	

measures			
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	**15**	**Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).**	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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