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Cytological diagnoses associated with non-invasive follicular thyroid neoplasms with papillary-like nuclear features, (NIFTP) according to the Bethesda System for Reporting Thyroid Cytopathology: a systematic review and meta-analysis.

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Abstract

Background.

The recent introduction of non-invasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) in the WHO classification of thyroid tumors has significantly modified the risk of malignancy of cytological diagnoses. In fact, while this tumor was previously classified as a carcinoma (the encapsulated, non-invasive form follicular variant of papillary thyroid carcinoma), it is now considered a neoplasm with low malignant potential. Given that the cytological features of NIFTP are not specific and overlap with other pathologic entities, there is no specific cytological diagnostic category for NIFTP. To obtain more robust information about the cytological findings associated with NIFTP, we systematically reviewed published articles and carried out a meta-analysis of the data.

Research Design and Methods.

The review was conducted according to Prisma guidelines. A comprehensive literature search of the PubMed/MEDLINE and Scopus databases was conducted using a combination of terms “non-invasive”, “encapsulated”, “follicular variant”, “NIFTP” and “thyroid cancer”. The search was updated until June 2018, and references of the retrieved articles were also screened. Only original articles reporting the classification of histologically proven NIFTPs with cytological findings according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) were eligible for inclusion.

Results.

The literature search revealed 117 articles, of which 15 were included in the study. All studies were retrospective. A total number of 915 NIFTP cases were retrieved. The incidence of cases cytologically classified according to TBSRTC was as follows: non-diagnostic 3%, benign 10%, atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) 30%, follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN) 21%, suspicious for malignancy 24%, and malignant 8%. Mild heterogeneity between the studies was found. Publication bias was absent.

Conclusions.

This meta-analysis shows that the cytological diagnoses associated with NIFTP by fine-needle aspiration cytology includes a wide spectrum of findings. The majority of cases are cytologically indeterminate and the remainders may be read as non-diagnostic, benign or malignant. In order to develop an accurate presurgical diagnosis of these cases, further cytological and/or molecular characteristics need to be identified.

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Introduction

The recently reviewed version of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has introduced a modification into each diagnostic category (DC) concerning the risk of malignancy (ROM) (1). In the first edition of TBSRTC, which has received worldwide recognition, each DC had an associated ROM and suggestions were made as to the management and the success rate of treatment of each category (2). In the current edition of the TBSRTC, each DC is associated with two different ROMs: one that takes into consideration the non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) as a carcinoma and the other that considers NIFTP as a tumor with low malignant potential (1, 2). The downgrading of the non-invasive encapsulated follicular variant of papillary thyroid carcinoma (non-invasive E-FV-PTC, aka NIFTP) into a tumor with low malignant potential and the deletion of the term carcinoma in its definition, has also forced the committee in charge of the revised version of TBSRTC to downgrade the ROM (2, 3). It needs to be emphasized that the diagnosis of NIFTP requires excision of the lesion and surgical pathology, as a complete histopathological evaluation of the tumor capsule, tumor content and search for vascular invasion can only be carry out with histological evaluation (3). For this reason, TBSRTC does not comprise a specific DC for NIFTP and preliminary data have shown that these tumors are associated with a spectrum of cytological findings, from benign to indeterminate (i.e. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS) and Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/SFN)), and from Suspicious for Malignancy (SM) to Malignant (M) (4, 5). Overall, these studies indicate that NIFTP is difficult to distinguish from the non-invasive E-FV-PTC and the infiltrative form of FV-PTC (I-FV-PTC). A predominant microfollicular pattern in the absence of nuclear atypia is mostly associated with a benign diagnosis on histology (either hyperplastic nodule or follicular adenoma) whilst the presence of microcalcifications and papillary structures showing typical nuclear features of PTC with more than 2-3 intra nuclear pseudoinclusions (INI) are mostly associated with a classical variant of PTC (CV-PTC) (6). Identification of the cytological diagnosis under which a NIFTP is most frequently classified, could help better defining the management strategies for the patient preoperatively. Here we aimed to

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systematically review the literature on the cytological features of NIFTP to obtain more robust evidence on this topic. Then, based on the retrieved data, we attempted to perform a meta-analysis on the prevalence of NIFTP in the different DCs of TBSRTC.

Material and Methods

Conduct of review

This present systematic review was conducted according to Prisma guidelines [view Supplementary Table 1].

Search strategy

A comprehensive literature search was conducted using the online databases of Pubmed/MEDLINE and Scopus by searching papers reporting NIFTP cases, using a combination of the terms “non-invasive”, “encapsulated”, “follicular variant”, “NIFTP” and “thyroid cancer” to find articles with data on the classification of fine-needle aspiration cytology (FNAC) samples as NIFTP, according to TBSRTC. This allowed identifying a large number of studies that reported histologically proven NIFTP, and which contained information on the presurgical cytological specimens. A beginning date limit was not used. The search was updated until June 8th, 2018 and no language restrictions were used. To try to expand the search, references of the retrieved articles were also screened to identify additional studies.

Study selection

Only original articles reporting NIFTP cases with a histological assessment and a classification of their FNAC samples were initially considered as eligible for inclusion. The main exclusion criteria were articles with overlapping patient or nodule data and case reports; in addition, papers reporting only some TBSRTC categories were excluded because these results did not allow us to know the distribution of NIFTP among the six categories of TBSRTC and calculate the incidence of each cytological class. Two researchers (MB, PT) independently reviewed titles and abstracts of the retrieved articles, applying the selection criteria; then, all authors independently reviewed the full-text of the remaining articles to determine their final inclusion.

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Data extraction

For each included study, the following information was extracted independently by two investigators (MB, PT) in a piloted form: 1) study data (authors, year of publication and country of origin); 2) number of cases of NIFTP evaluated; and 3) distribution of NIFTP within TBSRTC categories. Data were cross-checked, and any discrepancies were discussed and mutually solved.

Study quality assessment

The risk of bias of included studies was assessed independently by two reviewers (MB, PT) through the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for the following aspects: patient selection; index test; reference standard; flow and timing. Risk of bias and concerns about applicability were rated as low, high and unclear risk.

Statistical analysis

A proportion meta-analysis calculation was used to obtain the pooled rate of NIFTP assessed in TBSRTC categories. For statistical pooling of data, the DerSimonian and Laird method (random-effects model) was used (7). In this model, pooled data represent weighted averages related to the sample sizes of studies. Pooled data were presented with 95% confidence intervals (95% CI) and displayed using a forest plot. I-square index was used to quantify the heterogeneity among the studies, and significant heterogeneity was defined as an I-square value > 50%. Egger's test was carried out to evaluate the possible presence of a significant publication bias. Statistical analyses were performed using the StatsDirect statistical software version (StatsDirect Ltd; Altrincham, UK).

Results

Eligible articles

The comprehensive literature search identified 117 articles. An initial review of the titles and abstracts excluded 98 articles. A further four articles were excluded because they reported only NIFTP cases which were either FN/SFN or SM on FNAC (8, 9) or did not include the whole spectrum of the Bethesda system categories (6, 10); hence, it was not

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possible to calculate the rate of NIFTP within the overall diagnostic categories of FNAC. In the end, fifteen articles (4, 5, 11-23) were included in the study [see Supplemental Figure 1].

Qualitative analysis (systematic review)

Included studies were published by authors from the USA, Canada, Europe and Asia. The majority of these studies reported series of histologically proven NIFTP in which the cytological diagnoses were retrospectively reviewed for the publication; other studies reported NIFTP nodules in which the possibility of a NIFTP lesion had been suggested on cytological evaluation and was then confirmed on histopathology. Only two papers used liquid based cytology. Data on the cytological assessments could be clearly identified in all these manuscripts and the true percentage of each FNAC category was calculated. Table 1 details the main publication characteristics and findings of the included studies. Quality assessment of the studies is reported in Table 2.

Quantitative analysis (meta-analysis)

Overall, the included articles reported 915 histologically proven NIFTP lesions for which a preopertiave FNAC was available. The pooled rate of each FNA category is shown in Figure 1 and details of the results are reported in Table 3. In all Bethesda categories there was mild heterogeneity between the studies, while publication bias was always absent. The most prevalent cytological category was AUS/FLUS (30%). Because the large majority of cases were classified as Bethesda III, IV or V, we considered these three classes for sub-analysis; the pooled rate of NIFTP with a presurgical cytology diagnosis in class III-IV was 52% (95% CI from 42 to 62), with heterogeneity (I2 88%, 95% CI from 82 to 91) and without publication bias (P = 0.32); the pooled rate of NIFTP with a cytology diagnosis in III-IV-V was 78% (95% CI from 71 to 84) with heterogeneity (I2 80%, 95% CI from 66 to 86) and no publication bias (P = 0.21). Subsequently, to resolve the heterogeneity between the studies, we analyzed the pooled results from those studies with a larger series of NIFTP; there were 7 studies with 50 or more cases reporting 729 NIFTP (4, 5, 13, 16, 18, 22, 23) and these articles were chosen for this sub-analysis. The pooled results were quite similar to those summarized above: non diagnostic FNAC 4%, benign 13%, AUS/FLUS 27%, FN/SFN

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24%, suspicious for malignancy 22% and malignant 9%. There was mild heterogeneity in all these results, however publication bias was only present in non-diagnostic FNAC. In addition, the pooled prevalence of FNAC classified as III-IV was 51%, and the pooled prevalence of cases classified as III-IV-V was 74%.

Discussion

NIFTP is a recently described entity among thyroid tumors (3) which is considered to have an indolent behavior. Therefore, these cases are considered similar to low malignant potential lesions that need a simple lobectomy (without subsequent radioiodine therapy) and then clinical follow-up (3). Alternatively, performing a total thyroidectomy is also a consideration (24). Thus, detecting these tumors before surgery would have a significant impact for the management of patients in clinical practice. To date, while FNAC diagnosis is pivotal in identifying benign and malignant thyroid nodules, it does not have the ability to confidentially predict a NIFTP lesion. Several retrospective data have been reported, but there is no clear evidence that there is a way to predict the presence of a NIFTP cytologically (25). The present study was specifically undertaken to provide more robust information on the cytological TBSRTC categories associated with NIFTP in the currently available literature (references in Table 1). Fifteen relevant studies were retrieved and 915 cases of NIFTP were described in these papers. The most important result was that, using FNAC, three in four NIFTP were read as AUS/FLUS or FN/SFN (Figure 2) or SM, only 8% were classified as malignant, and a non-negligible number of cases were cytologically benign (10%) or not adequate for diagnosis (3%). These findings were confirmed when meta-analysis was performed only on those papers with a larger series of cases.

First and foremost, the introduction of the NIFTP concept has perturbed the cytopathology community. The low malignant potential of resected encapsulated, non-invasive E-FV-PTC, has been known for years. The change in name (with the disappearance of the term, “carcinoma”) and the downgrading of this entity to a low potential malignant lesion that requires simple lobectomy, has prompted cytopathologists to investigate whether this tumor might be detected in FNAC samples in order to guide the subsequent surgical treatment and tailor the management of patients. As shown in our study, a significant

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proportion of NIFTP was classified as cytologically indeterminate into the AUS/FLUS DC. AUS/FLUS DC is a problematic and heterogeneous category, comprising cases that present diagnostic difficulties due to poorly preserved, poorly fixed or poorly stained specimens (26) or comprising paucicellular specimens with mild atypia, either architectural (microfollicular structures) or cytological (nuclear atypia), that are qualitatively and quantitatively insufficient to place the FNAC either into the FN/SFN DC or in the SM or M diagnostic categories (26). The incidence of cases placed into the AUS/FLUS category should not be superior to 10% according to the new version of TBSRTC in order to maintain a high diagnostic accuracy of thyroid FNAC. However, as shown by our study in which NIFTP lesions were found to be most commonly associated with AUS/FLUS diagnoses, we assume that there may be an increase in AUS/FLUS cases in the future, which may be higher than the recommended 10% (1). Moreover, since NIFTP is ultimately a histological diagnosis and hence a surgical disease, limited surgery (lobectomy) is recommended for these cases to confirm the cytological suspicion. In the USA, pre-surgical triage can also be done by carrying out molecular tests for indeterminate FNA results, thus refining the role of cytology. However, the fact that the majority of NIFTP cases in our meta-analysis (30%) are placed in to the AUS/FLUS DC, reflects the diagnostic difficulties related to NIFTP: since atypical nuclear changes in NIFTP are subtle (beyond that of a benign aspirate but insufficient to warrant a suspicious for malignancy diagnosis), most cases fall in this category, as suggested also by Strickland et al. (1, 2, 8). In addition, according to our present study, a non-negligible rate of NIFTP were cytologically classified as benign (10%). Unfortunately, we do not know if the benign diagnoses were due to the cytopathologist missing slight nuclear atypia or whether they were not missed but considered to be of reactive nature, or whether there was a problem related to the sampling (i.e. normal thyroid instead of the lesion). Since NIFTP are lesions of low malignant potential, these missed diagnoses would probably not have any impact on quality of life of these patients, but a long follow-up is needed to confirm this assumption. Eight percent of all reported NIFTP cases were diagnosed as malignant. Considering that the 2015 ATA guidelines suggests both lobectomy and total thyroidectomy as treatment options for low-risk PTC, there should not be any important medico-legal issues related to this “false positive” diagnosis (24, 25).

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Undoubtedly, awareness of the NIFTP and the vast number of articles that have been written concerning the cytopathological features of the NIFTP, suggest that, on routine cytology, this entity had an impact on cytopathologists, who now pay more attention (at least the authors of the present paper) to subtle nuclear atypias. In the future, as data on prospective evaluations of cytology findings and NIFTP histologies become available, cytopathologists may place less cases into the SM and M categories (reserved only for very suspicious or clear cut cases of PTC, as suggested by the revised version of TBSRTC), but this will result in an increase in AUS/FLUS diagnoses (1). When dealing with nuclear atypia, cytopathologists have the possibility of a NIFTP in mind and they would like to avoid a false positive diagnosis. This perspective change will also affect the manner in which NIFTP will be diagnosed in the future. In our opinion, a diagnosis of “malignant” by cytology will be reduced in frequency, as only clear-cut cases of PTC will be cytologically classified (9).

Limitations and strengths of the present review have to be discussed. Almost all studies included in the review were retrospective and the authors reviewed FNAC samples of NIFTP specifically for the publications; this study design could introduce a bias. We found that NIFTP may be associated with all cytological categories (from I to VI of TBSRTC). Therefore, we must consider that there is a selection bias in almost all included studies because NIFTP was searched for at histology and some other cases whose lesion was cytologically classified as non-diagnostic, benign or indeterminate by FNAC may not have undergone surgery. Consequently, the incidence of NIFTP cytologically classified as Bethesda I to IV might be higher than we found; on the contrary, the percentage of NIFTP read as malignant, when using FNAC, could be overestimated. As further evidence, this finding was present particularly in those articles with a small sample size.

In conclusion, the present meta-analysis shows that the diagnosis of NIFTP by FNAC remains a significant challenge. In fact, the majority of these cases are cytologically assessed as indeterminate and the others may be read as non-diagnostic, benign or malignant. Further cytological investigations are needed in order to develop a tailored management of these cases.

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Author Disclosure Statement

The authors have nothing to disclose.

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Table 1. Main characteristics of the included studies.

First author [ref]	Year	Journal	Country	Single/ multi-institute study	FNAC classification of cases	NIFTP cases (n)
Strickland [5]	2015	Thyroid	USA	Single	During clinical practice	85
Canberk [13]	2016	Acta Cytol	Turkey	Single	Retrospective	94
Strickland [12]	2016	Thyroid	USA	Single	During clinical practice	8
Ibrahim [14]	2016	Am J Clin Pathol	USA	Single	Retrospective	23
Bizzarro [15]	2016	Cancer Cytopatol	Italy	Single	Retrospective	37
Faquin [4]	2016	Cancer Cytopatol	USA, Switzerland	Multi	Retrospective	173
Zhao [16]	2017	Cancer Cytopatol	USA	Single	Retrospective	50
Hahn [11]	2017	Clin Endocrinol	Korea	Multi	Retrospective	35
Mito [17]	2017	Cancer Cytopatol	USA	Single	Retrospective	29

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Bychkov [18]	2018	Pathology	Thailand, India, Taiwan, Japan Korea	Multi	Retrospective	59
Diaz del Arco [19]	2018	Acta Cytol	Spain	Single	Retrospective	6
Mahajan [20]	2018	Cytopathol	India	Single	Retrospective	23
Kim [21]	2018	J Pathol Transl Med	Korea	Single	Retrospective	25
Mainthia [22]	2018	Surgery	USA	Single	Retrospective	149
Lastra [23]	2018	JASC	USA	Multi	During clinical practice	119
TOT						915

Legend – All data refer to NIFTP with a proven histological diagnosis. All studies reported conventional cytological examinations of smears except two studies [5,15] which used liquid-based cytology.

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Table 2. Quality assessment of the studies according to QUADAS-2.

	Risk of bias				Feasibility		
First author [ref]	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Strickland [5]	L	L	L	L	L	L	L
Canberk [13]	L	H	L	H	L	L	L
Strickland [12]	L	L	L	L	L	L	L
Ibrahim [14]	L	U	L	L	L	L	L
Bizzarro [15]	L	H	L	H	L	L	L
Faquin [4]	L	L	L	L	L	L	L
Zhao [16]	L	H	L	H	L	L	L
Hahn [11]	L	H	L	H	L	L	L
Mito [17]	L	L	L	L	L	L	L
Bychkov [18]	L	H	L	H	L	L	L
Diaz del Arco [19]	L	H	L	H	L	L	L
Mahajan [20]	L	L	L	L	L	L	L
Kim [21]	L	H	L	H	L	L	L
Mainthia [22]	L	H	L	H	L	L	L
Lastra [23]	L	L	L	L	L	L	L

Legend – L, low risk of bias; H, high risk of bias, U, unclear risk of bias.

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Table 3. Proportion of NIFTP in the cytological classes of Bethesda system.

Bethesda category	Pooled rate (95% CI)	Consistency – I2 (95% CI)	Publication bias
Non diagnostic	3% (2 to 6)	62% (23 to 67)	P = 0.08
Benign	10% (7 to 14)	69% (41 to 81)	P = 0.27
AUS/FLUS	30% (23 to 38)	81% (68 to 87)	P = 0.41
FN/SFN	21% (16 to 27)	71% (45 to 82)	P = 0.92
Suspicious for malignancy	24% (18 to 31)	79% (64 to 86)	P = 0.07
Malignant	8% (5 to 11)	57% (11 to 75)	P = 0.11

Legend – Absence of heterogeneity was set at I2 <50%. Publication bias was analysed using the Egger test: a significant test identified the presence of publication bias.

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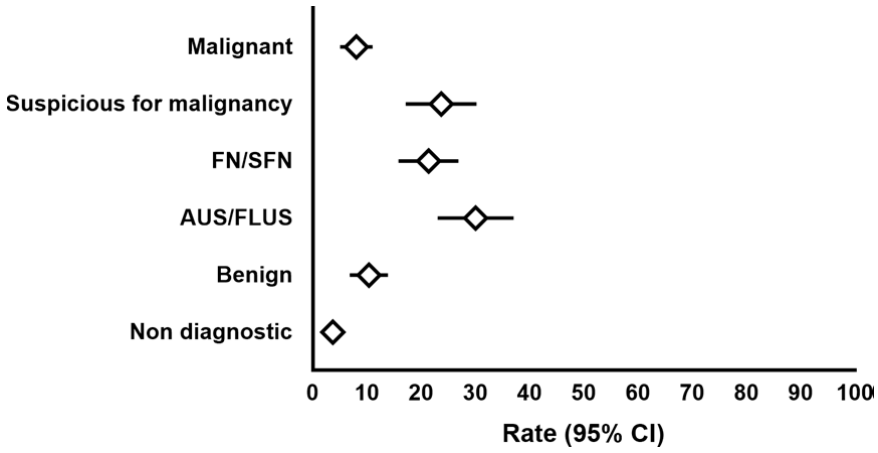

Fig 1. Forest plot of the pooled rate (95% CI) of non-invasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) in the six diagnostic categories of the Bethesda system (random effect).

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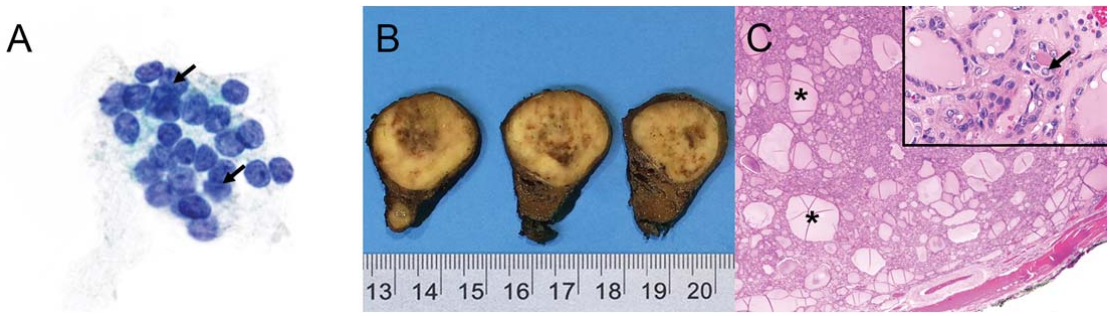

Fig 2. Cytohistological correlation in a case of NIFTP in a 35-year old female with a 2.2 cm nodule evaluated by ultrasound-guided thyroid fine-needle aspiration. (A) Clusters of microfollicular structures presented nuclear superposition, enlargement and scattered grooves (arrows) (Liquid-based cytological specimen, Papanicolaou staining, 400x). The final cytopathological diagnosis was that of follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN). (B) Grossly, the nodule showed a whitish appearance and was well circumscribed and (C) did not show microscopic signs of capsular or vascular invasion. It was predominantly comprised of microfollicular structures mixed with more cystic follicles (asterisks), at high power magnification atypical nuclei were evident (clearing of the chromatin) and only a single nuclear pseudoinclusion (arrow) was detected. The final histopathological diagnosis was that of NIFTP.

Supplementary Table 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
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.	NA
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.	4

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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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
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).	4
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.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
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.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
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.	5

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Section/topic	#	Checklist item	Reported on page #
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).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
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.	5-6
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.	5-6
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).	5-6
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.	5-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5-6

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
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).	6-9
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).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
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.	None

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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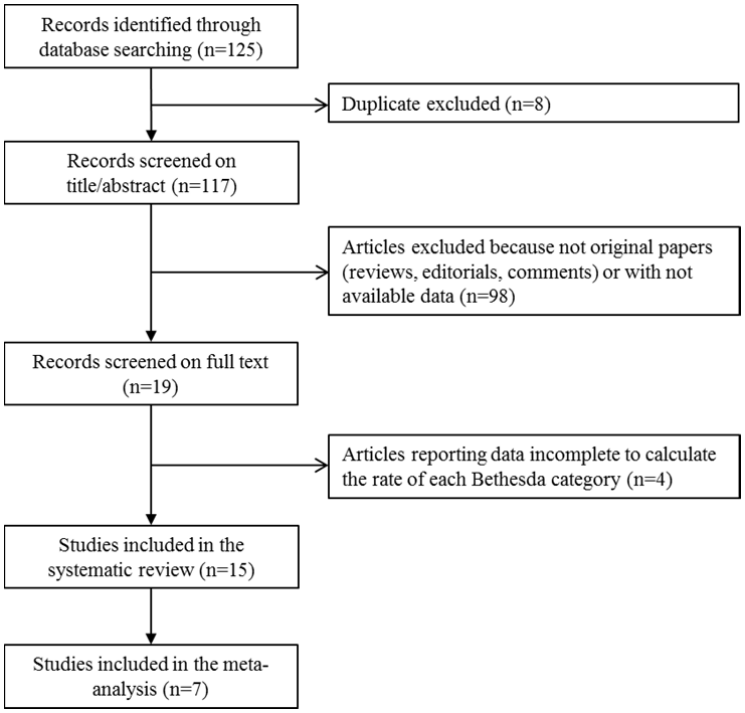

Supplementary Figure 1 : Flow chart of the search for eligible studies.