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Tests to detect and inform the diagnosis of caries

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Tests to detect and inform the diagnosis of caries (Protocol)

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[Diagnostic Test Accuracy Protocol]

Tests to detect and inform the diagnosis of caries

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ABSTRACT

This is a protocol for a Cochrane Review (Diagnostic test accuracy). The objectives are as follows:

- To undertake a series of Cochrane Reviews to establish the diagnostic accuracy of index tests for the detection and diagnosis of dental caries. We propose a new review for each identified method for the detection and diagnosis of coronal caries in children and adults (five reviews in total); and one new review of the comparative accuracy of the identified methods, used alone or in combination.

    - Review 1. Visual or visual-tactile examination according to detailed criteria.
    - Review 2. Radiography.
    - Review 3. Fluorescence.
    - Review 4. Electrical conductance.
    - Review 5. Fibre-optic transillumination.
    - Review 6. Comparative accuracy review which will bring together the results of these reviews in a review of the comparative accuracy of the identified methods. Additional statistical analyses will be undertaken using the extracted data from all eligible studies that have evaluated one or more methods.

- To undertake a series of Cochrane Reviews to establish the diagnostic accuracy of index tests for the detection and diagnosis of root dental caries, in adults. We propose the following new diagnostic test accuracy (DTA) review.

    - Review 7. Diagnostic tests for root caries in adults.

A single review for root caries will be completed due to a smaller volume of studies identified through a scoping search. The scoping search was completed during the grant application (January 2017) and interrogated MEDLINE only, in combination with existing

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systematic reviews of DTA for caries there is an anticipation that the visual, radiography and fluorescence reviews will each include over 100 studies (Bader 2002; Bader 2004; Gimenez 2013; Gimenez 2015; Schwendicke 2015).

Where sufficient studies are available, each individual review (numbers 1 to 5) will include evaluation of comparative accuracy of different index test methods/approaches, for example visual to evaluate differences between measurement indices i.e. ICDAS, Nyvad, ERK and other caries detection indices.

Aligned to the objectives listed above, the specific research questions answered through the suite of systematic reviews will include.

- What is the diagnostic test accuracy of different tests for different purposes (detection or diagnosis), in different roles (adjunct to visual examination or independent test), in different populations (children: primary/mixed dentition, adolescents: immature permanent dentition, or adults: mature permanent dentition), and when tested against different reference standards.

    - What is the diagnostic test accuracy of each of the index tests compared to an appropriate reference standard for detecting and diagnosing initial stage decay on the occlusal and approximal tooth surfaces?

    - Do measures of sensitivity and specificity for single tests differ from the sensitivity and specificity of tests used in combination? Is there a benefit to using more than one index test as opposed to a single test?

    - What is the potential value of each index test at different positions in the clinical pathway? For example, 'disease-free' individuals could be 'screened out' on the basis of a clinical examination, whilst those with a suspicion of disease would receive an x-ray.

- What is the comparative diagnostic test accuracy of the different index tests?

BACKGROUND

Cochrane Oral Health (COH) is undertaking a number of Cochrane Reviews of diagnostic test accuracy (DTA) on the detection and diagnosis of dental caries. The suite of systematic reviews forms part of a National Institute for Health Research (NIHR) Cochrane Programme Grant Scheme and will involve collaboration with the Complex Reviews Support Unit. The reviews will follow standard Cochrane DTA methodology and will be differentiated according to the index test under evaluation. This generic protocol will serve as the basis for the suite of systematic reviews.

Caries is an entire disease process, which can be stabilised and sometimes reversed if diagnosed and treated early on in the disease process (Fejerskov 2015; Pitts 2009). In some Scandinavian countries programs are in place which nearly eradicate caries, but this is continuous day-to-day work and has not been replicated in other populations (Pitts 2017). Despite this the 2015 Global Burden of Disease study identified dental caries as the most prevalent, preventable condition worldwide (Feigin 2016; Kassebaum 2015), affecting 60% to 90% of children and the majority of adults of the world's population (Petersen 2005). Furthermore, the global incidence of untreated caries was reported to be 2.4 billion in 2010 (Feigin 2016; Kassebaum 2015; World Health Organization 2017) and despite a reduction in caries in some industrialised countries, the global incidence of caries has increased by 14% in the 5 years to 2015 to over half a billion people (Feigin 2016). In the UK, the primary reason for childhood (aged 5 years to 9 years) hospital admissions is for the extraction of teeth (Public Health England 2014). Longitudinal studies have shown that those who experience caries early in childhood will have an increased risk of severe caries in later life, the trajectory of disease will be of increased severity (Broadbent 2008; Hall-Scullin 2017).

Untreated caries can lead to episodes of severe pain and infection, often requiring treatment with antibiotics. Dental anxiety, resulting from the failure to treat caries and the subsequent need for more invasive management, can adversely affect a person's future willingness to visit their dentist, leading to a downward spiral of oral disease (Milsom 2003; Thomson 2000). If left to progress, treatment options are limited to restoration or extraction, requiring repeated visits to a dental surgery or even to a hospital (Featherstone 2004; Fejerskov 2015; Kidd 2004).

The cost of treating caries is high. In the UK alone, the National Health Service (NHS) spends around GBP half a billion every year in treating the disease. Hidden costs also exist, and the related productivity losses are high, estimated at USD 27 billion globally in 2010 (Listl 2015).

Caries detection and diagnosis will usually be undertaken at a rou-

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tine dental examination, by a general dental practitioner, in patients who are presenting asymptomatically. However, caries detection can additionally be employed in secondary care settings, school or community screening projects and epidemiology or research studies (Braga 2009; Jones 2017). The traditional method of detecting dental caries in clinical practice is a visual-tactile examination often with supporting radiographic investigations. This combination of methods is believed to be successful at detecting caries that has progressed into dentine and reached a threshold where restoration is necessary (Kidd 2004). The detection of caries earlier in the disease continuum could lead to stabilisation of disease or even possible remineralization of the tooth surface, thus preventing the patient from entering a lifelong cycle of restoration (Pitts 2017). However, early caries is difficult to detect visually, and the use of radiographs provides limited ability to detect small changes in dental enamel (Ismail 2007).

Detection and diagnosis at the initial (non-cavitated) and moderate (enamel cavitation) levels of caries is fundamental in achieving the promotion of oral health and prevention of oral disease (Fejerskov 2015; Ismail 2013). A wide variety of treatment options are available under NHS care at these different thresholds of disease, ranging from minimally invasive treatments (e.g. sealing the affected surface of the tooth, or 'infiltrating' the softer demineralised tissue with resins) for initial caries, through to step-wise caries removal and restoration for extensive lesions.

With advances in technology over the last 2 decades, alternative methods of detection have become available, such as advancements in radiography and the development of fluorescence, transillumination and electrical conductance devices. These could potentially aid or replace the detection and diagnosis of caries at an early stage of decay. This would afford the patient the opportunity of a less invasive treatment with less destruction of tooth tissue and potentially result in a reduced cost of care to the patient and to healthcare services.

Target condition being diagnosed

Caries is an entire disease process, which can be arrested and sometimes reversed if diagnosed early enough (Fejerskov 2015; Pitts 2009). The term dental caries is used to describe the mechanisms and symptoms of the breakdown of the tooth surface which result from an imbalance in the activity within the biofilm (or dental plaque) within the oral cavity (Kidd 2016). This imbalance is especially related to pH levels which are readily affected by the consumption of sugar, which increases the acidity. Disease progression can be moderated by the influx of fluoride through toothpaste and other available fluoride sources. However, the levels of sugar consumption observed in many populations will often outweigh the benefits of fluoride (Hse 2015). Ultimately, carious lesions may develop and destroy the structure of the tooth.

The most common surfaces for caries to manifest are on the biting (occlusal) surface or the tooth surface which faces an adjacent tooth (approximal surfaces); although smooth-surfaces on the flat exterior of teeth can be affected. The severity of disease is defined by the depth of erosion of the tooth's structure and whether the lesion is active or arrested. Caries presenting at levels into tooth enamel have potential to be stabilised or even reversed, whereas the progression of carious lesions into the dentine and pulp of the tooth will require restoration (Bakhshandeh 2018; Kidd 2004).
Assessment of disease severity traditionally used in epidemiological and research studies has employed some variant of the DMFT (decayed, missing and filled teeth) scale. Within the D (decayed) component there are four clinically detectable thresholds applied as indicators for diagnosis and treatment planning, often labelled as D1, D2, D3 and D4 (Anaise 1984) (Additional Table 1). Typically the D3 threshold has been used to determine the presence of caries (Pitts 1988; Shoaib 2009).
These four categories have formed the basis for expanded indices such as the International Caries Detection and Assessment System (ICDAS) (Ekstrand 2007; Ismail 2007). Other available systems include: the Nyvad system (Nyvad 1999); Ekstrand-Ricketts-Kidd (ERK) system (Ekstrand 1997); British Association for the Study of Community Dentistry (BASCD) (Pitts 1997); and the Dundee Selectable Threshold Method for caries diagnosis (DSTM) (Fyffe 2000). The ICDAS and DSTM systems both provide the opportunity to investigate initial caries (into enamel) which may confer benefits for preventative or non-operative treatment.

Treatment of caries

There are many varied treatment options available to the dental clinician, dependent on the thresholds of observed disease. Initial caries can be treated without surgical intervention using preventive and remineralising approaches such as plaque control, dietary advice, and application of fluoride (Kidd 2016). Minimally invasive treatments for initial caries are available, such as sealing the affected surface of the tooth, or 'infiltrating' the softer demineralised tissue with resins. High-risk patients with severe caries may require step-wise caries removal and restoration of extensive lesions.
A caries management pathway, informed by diagnostic information, can be beneficial in guiding the clinician towards prevention or a treatment plan. One recently developed care pathway is the International Caries Classification and Management System (ICCMS) (Ismail 2015). The system presents three forms of management in the care pathway:

1. when dentition is sound the clinician proceeds with preventative strategies to prevent sound surfaces from developing caries;
2. non-invasive treatment of the lesion to arrest the decay process and encourage remineralization, preventing initial lesions from progressing to cavitated decay; and

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3. management of more severe caries through excavation and restoration or potentially extraction.

At the core of this care pathway is the ability to detect early caries accurately and optimise the preventative strategies. The detection and diagnosis of early caries remain challenging, and the likelihood of undiagnosed early disease is high (Ekstrand 1997). In such instances, the opportunity for preventing initial lesions from progressing to cavitated decay, or even reversing the disease process, is missed, and disease progresses to cavitated decay where restoration is required (Ekstrand 1998).

Index test(s)

The cornerstone of caries detection is a visual and tactile dental examination, and the ability of clinicians to accurately detect disease in this way has been researched for over half a century (Backer Dirks 1951). A range of tests exist which may be suitable at different stages of the care pathway, in particular focusing on the detection and diagnosis of disease (Bloemendal 2004; Fyffe 2000). Reviews will be completed for each of the following index tests.

- Visual or visual-tactile examination.
- Radiography.
- Fluorescence.
- Electrical conductance.
- Fibre-optic transillumination.

For more information about index tests see Additional Table 2.

If included numbers of studies are low in either electrical conductance or fibre-optic transillumination then a combined review assessing a broad group of novel technologies will be introduced. Where combinations of index tests are used they will be included if the diagnostic information can be isolated from the other tests. If sufficient numbers of combined tests are included then subgroups will be created of these combined tests (e.g. visual and radiograph combined). Other novel devices or methods may exist but have not been widely reported such as topical dyes, photographic methods and scanning. These will be added to the review if studies are found within the searches; this may be an additional review combining all of these novel tests in what is likely to be a narrative rather than statistical synthesis.

Clinical pathway

The process proceeding from a dental patient attending for a routine examination and a caries assessment being undertaken potentially has four intertwined stages: screening, detection, diagnosis and treatment planning. If the presenting patient is seemingly asymptomatic then this could be viewed as a screening exercise as the clinician is seeking to establish who probably has caries and who is healthy (Wilson 1968), however patients are likely to present with some level of caries as the established scales (for example ICDAS) are sensitive enough to detect any changes in the enamel of the tooth's surface. As confirmed by a survey of the English population reporting a mean number of carious teeth in dentate adults to be 0.8 (Adult Dental Health Survey 2009). Therefore, detection is a more reasonable description of this initial examination, this is where the clinician aims to establish the true presence or absence of disease. Since caries is a dynamic process the pure detection of the disease at one time point is not sufficient to inform the future care of the patient, additionally the depth and severity of demineralisation, allied to a decision on the caries activity levels, must be combined to reach a diagnosis (Ismail 2004; Nyvad 1997). This diagnosis then feeds into a caries management pathway once the patient's history, personal oral care and risk factors have been considered. A comprehensive methodology has been developed titled the International Caries Classification and Management System (ICCMS™) which aims to address the need for guidance when diagnosing caries and then following a decision-making process to use preventative measures and minimise invasive treatment (Ismail 2015).

Figure 1 presents the key elements of the ICCMS process and these reviews could inform the process at 'Keystone 3' where diagnosis is an indefinable component.

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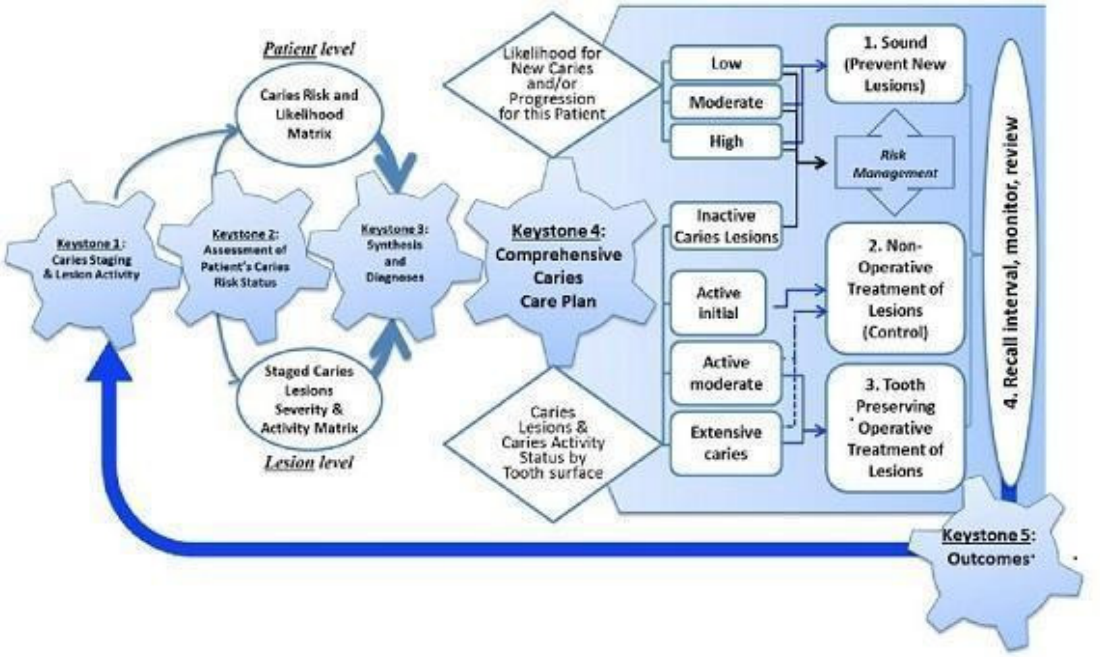
Figure 1. Keystones of the International Caries Classification and Management System (ICCMS™). Copyright© 2018 Ismail AI, Pitts NB, Tellez M. The International Caries Classification and Management System (ICCMS™) an example of a caries management pathway. BMC Oral Health 2015 15(Suppl 1):S9: reproduced with permission.



Role of index test

Given that a visual-tactile inspection is the cornerstone of a clinical examination it is unlikely that any of the index tests under evaluation would be used as a complete replacement for the detection and diagnosis of initial decay. Supplementing the visual-tactile examination with an index test could aid in the detection of initial decay. The index tests could also have a triage role in assisting the general dentist to more accurately assess signs of uncertain clinical significance. The information from caries detection (including assessment of severity of disease) will be an integral part of diagnosis, which additionally incorporates patient risk factors and treatment planning protocols.

Rationale

Despite technological advancement, the usual method of caries detection is currently based upon information from visual-tactile clinical examination with or without radiographs. There have been a number of systematic reviews conducted in this area, commencing with an extensive review of in vitro studies investigating visual, radiographic, fibre-optic, electrical conductance and fluorescence in primary and permanent dentition, which focused on histological reference standards only and grouped studies according to index test, disease threshold (enamel or dentinal lesions) and tooth surfaces (occlusal or proximal); a meta-analysis was not undertaken and the authors graded the quality of the available evidence as low (Bader 2002). 2 years later the same authors published a review focusing on laser fluorescence devices with a large increase in available studies being evident in the intervening years, it was still not possible to perform a meta-analysis and the authors raised concerns over the laser fluorescence devices' propensity for increasing specificity as sensitivity improved (Bader 2004). These two reviews predate the development of meta-analysis methods for DTA reviews recommended in the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (Deeks 2013). More recently two reviews have been completed which investigated fluorescence and visual techniques, these included primary and permanent dentition, occlusal and proximal surfaces, and accepted histological, operative, visual and radiographs as the reference standard (Gimenez 2013; Gimenez 2015). There are two further recent reviews which investigate methods for detecting secondary caries and radiographic techniques (Brouwer 2016; Schwendicke 2015), the former reports a lack of evidence on secondary caries detection while the latter reports conclusive evidence for radiographs potential for diagnosing dentinal lesions.

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There is potential for improvement in some areas of these systematic reviews. We aim to build upon existing research in this area by: expanding the search strategy to capture all relevant evidence, applying appropriate hierarchical analysis, and assessing the body of evidence using GRADE (Hsu 2011) to facilitate the production of evidence summaries and evidence to decision criteria.

OBJECTIVES

- To undertake a series of Cochrane Reviews to establish the diagnostic accuracy of index tests for the detection and diagnosis of dental caries. We propose a new review for each identified method for the detection and diagnosis of coronal caries in children and adults (five reviews in total); and one new review of the comparative accuracy of the identified methods, used alone or in combination.

    - Review 1. Visual or visual-tactile examination according to detailed criteria.
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Aligned to the objectives listed above, the specific research questions answered through the suite of systematic reviews will include.

- What is the diagnostic test accuracy of different tests for different purposes (detection or diagnosis), in different roles (adjunct to visual examination or independent test), in different populations (children: primary/mixed dentition, adolescents: immature permanent dentition, or adults: mature permanent dentition), and when tested against different reference standards.

    - What is the diagnostic test accuracy of each of the index tests compared to an appropriate reference standard for detecting and diagnosing initial stage decay on the occlusal and approximal tooth surfaces?
    - Do measures of sensitivity and specificity for single tests differ from the sensitivity and specificity of tests used in combination? Is there a benefit to using more than one index test as opposed to a single test?
    - What is the potential value of each index test at different positions in the clinical pathway? For example, 'disease-free' individuals could be 'screened out' on the basis of a clinical examination, whilst those with a suspicion of disease would receive an x-ray.

- What is the comparative diagnostic test accuracy of the different index tests?

Secondary objectives

Areas of potential heterogeneity will be investigated.

- In vitro or in vivo studies which affect the applicability of the results as the laboratory-based studies will not incur the difficulties of examining dentition within the oral cavity.
- Tooth surface being reported (occlusal, proximal or smooth surface).
- Consideration of point measurement devices versus imaging or surface assessment devices (this is relevant to fluorescence, electrical conductance and fibre-optic transillumination and may be investigated in the comparative accuracy review).
- Participants or teeth with previously applied restorations (secondary caries) and pit and fissure sealants.
- Prevalence of caries, particularly relevant to in vitro designs, a higher prevalence may have a significant effect on the ability to detect and diagnose caries.

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• Recruited population - children: primary/mixed dentition, adolescents: immature permanent dentition, or adults: mature permanent dentition.

METHODS

Criteria for considering studies for this review

Types of studies

For all reviews we will consider diagnostic accuracy study designs that are:

• studies with a single set of inclusion criteria that compare a diagnostic test with a reference standard. We will include prospective studies that evaluate the diagnostic accuracy of single index tests, and studies that directly compare two or more index tests;

• studies that evaluate test combinations alone or in comparison to a single test or other test combinations;

• randomised controlled trials (RCTs) of the diagnostic test accuracy of one or more index tests in comparison, or versus a no test option;

• 'case-control' type accuracy studies where different sets of criteria are used to recruit those with or without the target condition, although prone to bias some innovative tests may be identifiable through this design only and this may provide an opportunity to report them, these studies will not be included in the primary analysis;

• studies reporting at both the patient and tooth or tooth surface level will all be included, however only those reporting at the tooth surface level will be included in the primary analysis.

In vitro and in vivo studies will be considered for all reviews. In vitro studies occur where teeth have been extracted prior to the study's commencement, commonly for orthodontic purposes, and their caries status is still to be determined. The index test can then be performed, albeit in a scenario which is not representative of the typical clinical setting, this will often be followed by a reference standard of histology. In vivo studies recruit apparently healthy participants and conduct index tests and reference standards with the teeth in the oral cavity, without extraction of the teeth and therefore histology would not be undertaken.

Studies will not be included where:

• artificially created carious lesions are used in the testing procedure;

• an index test is used during the excavation of dental caries to ascertain the optimum depth of excavation.

Participants

Presenting participants should be seemingly asymptomatic for dental caries, seemingly asymptomatic patients may still have early caries which are undetected at the point of recruitment. Studies will be excluded where they consciously recruit participants with caries into dentine or those that are referred to secondary care for restorative treatment as there is a likelihood that advanced caries (into dentine or pulp) will be present and readily detectable without the need for the index tests presented here. Furthermore studies that are unclear on the level of caries present in the selected participants but report a prevalence of caries into dentine that is greater than 50% will also be excluded.

Children, adolescent and adult patients will all be included in each review, except for the root caries review (adults only), this will allow for analysis of the diagnostic test accuracy of index tests for primary, mixed and permanent dentition.

Index tests

• Visual or visual-tactile examination according to detailed criteria and indices (e.g. Ekstrand, ICDAS), the tactile label infers the use of a probe which although discouraged may be used in studies.

• Radiography - to include all intra and extraoral methods, furthermore both conventional film and digital imaging modalities will be assessed.

• Fluorescence - incorporating a spectrum of devices from laser-based detection to quantitative light-induced fluorescence (QLF), covering devices which behave as an adjunct and require an operator judgement and those which generate a conclusion via a software algorithm.

• Electrical conductance - widely used for root caries but also investigated for coronal caries.

• Fibre-optic transillumination - incorporated white light scattering and near infrared.

• Any new, innovative test that does not fit within the other criteria.

These index tests must be completed on intact teeth and could be used as an adjunct or replacement for aspects of the current examination e.g. digital radiography to replace conventional radiography. The intention is to assess the index tests in isolation where possible otherwise the result of one index test may influence another, however where multiple index tests are used as a combined index test these will be reported separately.

Variation may exist within each index test according to examiner training and experience, where multiple examiners are reported then the first set of reported results will be selected.

Target conditions

• Coronal caries: initial stage decay, defined as initial or incipient caries or non-cavitated lesions. Specifically where there

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is a detectable change in enamel evident which has not progressed into dentine; on i) occlusal and ii) approximal surfaces.

- Initial caries adjacent to existing restorations on i) occlusal and ii) approximal surfaces.
- Root caries (adults only): non-cavitated decay.

Reference standards

A number of different reference standards have been used in primary diagnostic test accuracy (DTA) studies. The only way of achieving a true diagnosis of caries presence and levels is to extract and section the tooth and perform a histological assessment (Downer 1975; Kidd 2004). It would not be ethically reasonable to undertake on a healthy population in clinical (in vivo) studies, whilst acceptable and widely used in in vitro studies conducted on previously extracted teeth. The only scenario where histology can be a viable scenario for studies undertaken in a primary or secondary care setting would be where a tooth has been identified as requiring extraction (ideally for a non-caries reason, such as orthodontic extraction) and the index test could be applied prior to extraction, followed by the reference standard of histology. This would bring into question the study's external validity.

Alternatives available are operative exploration, where a clinician removes caries with a dental burr (drill) in preparation for a restoration and reports the depth of decay. This technique would be acceptable as a reference standard for patients with caries requiring restoration, but would not be ethical for caries-free patients and a different reference standard would be required, such as a visual, fluorescence or radiographic tests. Some primary studies have employed a composite reference standard based on the results of information from multiple sources.

The optimum reference standard will be histology. Operative exploration will be an acceptable reference standard with the understanding that in vivo studies will require a separate reference standard for sites not requiring treatment and verification bias would therefore be introduced. The index tests listed may be used as reference standards, however, it is important to understand the limitations of such an approach when interpreting the performance of the index test relative to the imperfect reference standard and this will be reflected in the quality assessment. A period of up to 3 months between index test as a reference standard is acceptable.

Search methods for identification of studies

For the planned reviews on the detection and diagnosis of caries, separate search strategies will be developed for MEDLINE Ovid and Embase Ovid, according to the guidance provided in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* (de Vet 2008).

Electronic searches

The searches will be undertaken without restrictions on language or date of publication, and will not be limited by study design filters in order to ensure the literature search is as comprehensive as possible. Searches will combine controlled vocabulary searching with text word searches. Search strategies will consist of search terms for the condition (caries) and the reference test (as appropriate). Medical Subject Headings (MeSH) have already been identified; these include tooth demineralisation, dental radiography, and oral diagnosis. These terms will be repeated across the search strategies, and then the appropriate index tests will be added to the search. MeSH for the index tests will include: electrodiagnosis, fluorescence, lasers, fibre optic technology, optical fibres, subtraction technique, and digital radiography. We will search the reference lists of included papers and previously published systematic reviews for additional publications not identified in the electronic searches. Examples of search strategies can be found in Appendix 1; Appendix 2 and Appendix 3.

The searches will be managed through Cochrane Register of Studies, to ensure efficient de-duplication of the search results.

Searching other resources

Unpublished data will be sought via searches of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/), which includes trial data from the European Union, the UK, Australia, China, the Netherlands, Brazil, India and Korea.

Data collection and analysis

Selection of studies

Two review authors will independently screen and assess the results of all searches for inclusion. Any disagreements will be resolved through discussion and, where necessary, consultation with a clinical or methodological member of the team. During the screening process, studies eligible for all reviews will be identified for inclusion. Studies that meet the criteria but do not report the data in the format of a 2 x 2 contingency table will be eligible for inclusion. In such instances the study authors will be contacted and the required data requested. An adapted PRISMA flowchart will be used to report the study selection process (McInnes 2018). Once agreement for inclusion is reached, the studies will be categorised according to their index test, tooth surface and age (adult or child).

Data extraction and management

Two review authors will extract data independently and in duplicate. A piloted study data extraction form based on the review

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inclusion criteria will be developed and applied to eligible studies. Disagreements will be resolved through discussion by the review team. Where data have been reported for occlusal and approximal surfaces we will extract data separately for the different surfaces. Study authors will be contacted to obtain relevant data missing from the full paper.

We will record the following data for each study:

- sample characteristics (age, sex, socioeconomic status, risk factors where stated, number of patients/carious lesions, lesion location);
- setting (country, disease prevalence, type of facility);
- the type of index test(s) used (category, name, conditions (i.e. clean/dried teeth), positivity threshold);
- study information (design, reference standard, case definition, training and calibration of personnel);
- study results (true positive, true negative, false positive, false negative, any equivocal results, withdrawal).

Assessment of methodological quality

QUADAS-2 will be used to assess the applicability and risk of bias of the primary diagnostic studies over the four domains of participant selection, index test, reference standard, and flow and timing (Whiting 2011). 'Review specific' descriptions of how the QUADAS-2 items will be implemented to accompany the checklist (Additional Table 3).

A 'Risk of bias' judgement ('high', 'low' or 'unclear') will be made for each domain. If the answers to all signalling questions within a domain are judged as 'yes' (indicating low risk of bias for each question) then the domain will be judged to be at low risk of bias. If any signalling question is judged as 'no', indicating a high risk of bias, the domain will be scored as at high risk of bias. This will be followed by a judgement about concerns regarding applicability for the participant selection, index test and reference standard domains. Results of the assessment of methodological quality will also be presented graphically.

Participant selection domain (1)

The selection of patients will have a fundamental effect on an index test's ability to detect caries. The full range of potential disease stages and patient age ranges need to be investigated to form a complete appraisal of the test's potential to correctly classify disease.

Studies may choose to focus on one particular surface (occlusal/approximal) or stage of disease (caries into dentine/enamel) or particular age group (children/adults). However it is vital that within the chosen population all participants meeting the eligibility criteria should be provided with the opportunity to take part. Inappropriate exclusion may lead to an over or under estimation of the test's ability to detect disease, thus affecting the internal validity of the study.

Within in vitro studies the selection of teeth should be described and prevalence of each stage of disease reported, this will inform the applicability of this test to a wider population. All in vivo studies will be affected by spectrum of patient, tooth surface and disease stage and their applicability influenced by the prevalence of staging of the disease present in the selected patients.

Study results should be reported at a tooth or surface level, as apposed to patient level, which has the potential for the index test and reference standard to be reporting on different sites within the same mouth.

Index test domain (2)

The nature of the index tests and the visual presentation of the disease means that it should be feasible to ensure that the index test is conducted prior to the reference standard. The visual, fluorescence, fibre optic and radiography tests should be completed before the extraction of a tooth for any histological analysis, or before in situ excavation of a tooth is undertaken. To minimise potential for bias, separate examiners should be utilised for index test and reference standard. The threshold of disease positive and negative should be presented prior to analysis and be reflective of the participants recruited to the study. For example, in studies investigating asymptomatic patients at a screening level, then early stages of disease may be of importance and thresholds of caries into enamel of greater relevance than caries into dentine or pulp. With the subjective nature of many of the index tests there may be potential for information bias unless different examiners have been applied for each of the thresholds interpreted within the studies. For example if the decision is border-line between caries into enamel and dentine, the interpretation of the first threshold would influence the decision made on the second threshold. It is unlikely that studies will have utilised multiple index test examiners or where they have it is probable that they each score all of the thresholds and are included for validation of the test. However, the inclusion of a question here will allow the identification of studies that have achieved this and inform the future discussions.

Reference standard domain (3)

The reference standard must be completed by an examiner different to the index test, as the subjectivity of a histological examination could be compromised by knowledge of the index test results. For in vivo studies this would have greater relevance where the reference test is a visual, radiograph or fluorescence test; and in particular where excavation by a clinician is used. These standards could be applied immediately after the classification of disease at index test level and if not separated by using a different examiner then bias will be introduced. Time delays between index test and reference standard should be under 1 month for in vivo studies.

Each participating tooth or patient should be exposed to the same reference test. This is possible in the in vitro setting as each selected

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tooth can have a histological assessment applied. However, it is unlikely in the clinical setting as it would be unethical for healthy teeth to be extracted or excavated for investigation. The reason for specific teeth chosen for reference tests should be reported.
A 3-month follow-up could be used as a reference standard as any early lesions present at the initial examination would be evident after 3 months but it is unlikely that new lesions would be presenting by this stage. This follow-up examination should be completed without knowledge of the index test results.

Flow and timing domain (4)

The index test should be conducted prior to the reference standard (unless a case-control type study). If the reference standard used is visual, radiographic or excavation then there should be less than 1 month between index test and reference standard. Caries is a slow growing disease so minimal changes should be experienced within this time frame.

Comparative domain

If any comparative test studies are identified and included then a comparative domain will be added to the QUADAS-2 checklist. These would include either:

- direct within-person comparison (two or more index tests compared in each individual and in one study);
- within-study between-person (RCTs).

Selection bias needs to be considered regarding selection of teeth or participants for inclusion in between-person comparison studies (RCTs), i.e. were the same participant selection criteria used for those allocated to each test? Further considerations for studies where index tests have been compared, either direct within-person or between-person comparisons, would be the ordering of index tests and the blinding of examiners to prior or subsequent index tests. For between-person comparison studies (RCTs) there must be a maximum time delay between tests of 3 months, to ensure that the disease has not progressed and invalidated the comparison.

Statistical analysis and data synthesis

Individual test reviews

For each index test, estimates of diagnostic accuracy will be expressed as sensitivity and specificity with 95% confidence intervals. This information will be displayed as coupled forest plots, and plotted as summary receiver operating characteristic (ROC) plots, displaying the sensitivity-specificity points for each study.
Hierarchical models will be used for data synthesis. The data will be extracted for the primary outcome of early caries (caries limited to dental enamel which has not progressed into dentine), this consistent threshold will be possible to apply across the visual, radiograph and transillumination reviews therefore a meta-analysis will be conducted to combine the results of studies for each index test using the hierarchical bivariate or hierarchical summary ROC (HSROC) approach to estimate the expected values of sensitivity and specificity (Macaskill 2010; Reitsma 2005). Where a common threshold is difficult to apply, which is anticipated in the fluorescence and electrical conductance reviews as the devices often provide a numeric output on a continuous scale and are often interpreted at different thresholds, a summary curve using a HSROC model (Rutter 2001) will be applied. Review Manager 5 (Review Manager 2014), the NLMIXED procedure in SAS and the meqrlogit command in Stata 14 (Stata 14) will be used to undertake the analyses.
We will present estimates of sensitivity and specificity as summary operating points with confidence and prediction regions on SROC plots with 95% confidence regions. Results will be reported separately for primary and secondary caries within each review.

Comparative accuracy review

We will carry out a comparative analysis using the mada, HSROC and mvmeta packages in R, to compare the outcomes of different tests in a single analysis. Our general approach will be to employ a hierarchical model with the different index tests indicated using a covariate term, however an estimation of summary curves and comparison of curves will be used for tests that have numerical outputs on a continuous scale. Formal model comparisons will be undertaken using a likelihood ratio test to determine the statistical significance of adding (or removing) the covariates for sensitivity or specificity or both of the different index tests to the hierarchical model.
We will base our test comparisons on all available studies that have evaluated one or more tests, either direct within-person or between-person comparisons, this should maximise the number of studies available for analysis. These estimates will then be entered into Review Manager 5 (Review Manager 2014) with the summary operating points, confidence and prediction regions of the different index tests displayed on the summary ROC plot.
Where sufficient numbers of studies of within-person comparisons exist (i.e. data from all patients receiving all index tests) the results of these studies will be evaluated separately in an ancillary analysis and reported alongside results from the between-person comparison of all studies.
The hierarchical meta-regression approach currently advocated by the Cochrane Methods Screening and Diagnostic Tests group remains the most accessible method of synthesis of information from multiple index tests. Recent methodological research has proposed a 'network meta-analysis' approach (e.g. Menten 2015), usually implemented within a Bayesian framework. We will explore the feasibility of using a 'network meta-analysis approach' to investigate point estimates rather than comparisons of accuracy based on

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curves; this will account for the bivariate nature of the data, extend to more than two index tests and sensibly account for within- and between-study variability.

Investigations of heterogeneity

A range of sources of heterogeneity will potentially occur in each of the reviews, they will be considered in the individual reviews. An initial inspection of the clinical and methodological characteristics of the included studies, coupled forest plots and summary ROC plots will form the basis of the assessment of heterogeneity. More formally, meta-regression analyses will be carried out to explore possible sources of heterogeneity, where sufficient numbers of studies allow. Formal model comparisons will be undertaken using a likelihood ratio Chi^2 statistic to determine the statistical significance of adding one or more potential sources of heterogeneity (covariates) to the hierarchical model. Where substantial heterogeneity is observed then this will be clearly articulated in the 'Summary of findings' tables to aid interpretation of the results. The sources of heterogeneity will probably include.

Population characteristics

- Children or adults; the detection of disease in the different dentition of children or adolescents will affect the stage at which the disease is identified and treatment options which would be considered.
- In vitro or in vivo studies; many laboratory-based studies will be included and the clinical relevance of these requires consideration.
- Selection of tooth surface under investigation and whether this is reported at the patient, tooth or surface level.
- Participants or teeth with previously applied pit and fissure sealants.
- Prevalence of caries.

Index test characteristics

- Different methods of administration of each index test (e.g. film and digital radiology, or different types of fluorescence devices) (see Additional Table 2).

Reference standard characteristic

- Reference standard used: histology, excavation or usage of visual or radiograph techniques which may cause a reduction to sensitivity and specificity as less cases are identified as test positive.

Sensitivity analyses

Where a sufficient number of studies investigate the same index test, the following sensitivity analyses will be performed to assess the impact on summary estimates of restricting the analyses according to the following criteria:

- studies that are 'unclear' on their inclusion criteria for caries threshold, the 'unclear' label identifies poorly reported studies that give insufficient description on the participant inclusion criteria;
- studies with a high prevalence of dentine caries (i.e. greater than 50%);
- where a low risk of bias exists for an index test;
- where a low risk of bias exists for a reference standard.

Assessment of reporting bias

Methods currently available to assess reporting or publication bias for diagnostic studies may lead to uncertainty and misleading results from funnel plots (Deeks 2005; Leeflang 2008), therefore we will not perform reporting bias tests in the reviews.

Presentation of main results

We aim to develop a 'Summary of findings' table for each index test and for the main target conditions following GRADE methods (Atkins 2004; Hsu 2011), and using the GRADEPro online tool (www.guidelinedevelopment.org). To enhance readability and understanding, we will re-present test accuracy results in natural frequencies to indicate numbers of false positives and false negatives. The quality of the body of evidence will be assessed with reference to the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, and the risk of publication bias; these will be considered narratively where statistical methods are not available. We will categorise the quality of the body of evidence for each of the main accuracy measures, for each comparison as high, moderate, low or very low.

We will consider the following additional guidance for the comparative accuracy review for the detection and diagnosis of caries (Gopalakrishna 2014):

- for a between-person comparison of two or more index tests, an initial assessment of quality of the test accuracy for each index test will be followed by an assessment of the quality of the comparison;
- when making the comparative assessment, the judgement for each GRADE domain (e.g. risk of bias, indirectness, etc.) will be recorded as the lower of the two judgements for that domain for each index test compared with its reference standard; and
- the overall quality of evidence (for a between-person comparison of two or more index tests) will be further downgraded by one level for indirectness.

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Should updated GRADE DTA specific guidance become available during the course of the research then this will be used to construct the 'Summary of findings' tables.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Classification of levels of caries levels

DMFT classification	Definition (Pitts 2001)
0	Sound (non-diseased)
D1	Non-cavitated yet clinically detectable enamel lesions with intact surfaces
D2	Cavitated lesion penetrating the enamel or shadowing
D3	Cavity progressing past the enamel-dentine junction into dentine
D4	Cavity progressing into pulp

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Table 2. Index tests for caries

Test	Characteristics	Intended use in clinical pathway	Other information
Visual or visual-tactile examination	Identifying caries according to their visual appearance, aided by a dental mirror and probe, on clean and dry teeth	The fundamental step in the detection of caries, but limited in the diagnosis of early lesions. All patients presenting to a dental clinician will receive a visual examination	**Advantages:** completed and interpreted quickly with minimal invasion and little cost except clinician training and time **Disadvantages:** early caries are difficult to observe visually, depth and severity of lesions cannot be assessed, approximal lesions cannot be seen
Radiography	Bite-wing radiology is the most commonly used method. Others include: subtraction radiographs which provides a semi-automated method for monitoring progression of lesions (Ellwood 1997; Wenzel 2000) and cone beam computed technology (CBCT) which provides a 3-dimensional image which appears to offer great potential for diagnosis with increased levels of radiation (Horner 2009)	Widely used as an adjunct to aid detection and in particular to inform the clinician of the depth and severity of lesion (Wenzel 1995; Whaites 2013) Relevant on occlusal surfaces but also in approximal location which are otherwise difficult to assess visually	**Advantages:** radiographs aid the detection of caries and are shown to be more sensitive than visual examination on approximal and occlusal lesions (Wenzel 2004) **Disadvantages:** limitations exist when detecting early caries in enamel surfaces. There is a small but real risk over patient exposure to ionizing radiation, which has to be balanced with the patient's age, caries risk and time since previous radiograph (Pitts 2017) . Digital radiographic methods have shown benefits for patients with the speed in which they can be viewed and for the ability to manipulate images for increased clarity (Wenzel 2006)
Fluorescence	The breakdown of enamel alters the characteristics of its structure, when exposed to light-inducing fluorescence diseased teeth respond differently to sound teeth. There is potential for mineral loss to be quantified and used to aid the diagnostic decision and treatment pathway (Angmar-Månsson 2001; Matos 2011). Fluorescence is typically divided into laser fluorescence and light fluorescence (i.e. Diagnodent type devices and QLF type devices)	Potential to aid the clinician in identifying early caries which may not be possible with a visual examination alone. Quantitative light-induced fluorescence (QLF) emits either green or red light and may ascertain whether the lesion is active or arrested	**Advantages:** the potential to identify changes in tooth characteristics that are otherwise unobservable in a visual-tactile examination **Disadvantages:** uncertainty of the reliability of devices and the ability to detect disease and health

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Table 2. Index tests for caries (*Continued*)

Fibre-optic transillumination	Fibre-optic transillumination (FOTI) uses a light emitted from a hand held device which when placed directly onto the tooth illuminates the tooth (Pretty 2006). Any demineralisation should appear as shadows in the tooth due to the disruption of the tooth's structure due to caries	An adjunct to the visual examination, particularly useful for identifying detecting approximal caries, with its strength being in identifying early caries in enamel and dentine (Davies 2001). A further advancement with fibre-optic techniques combines this with a camera to capture an image which may or may not be linked to software for analysis, Digital Imaging FOTI (DIFOTI)	**Advantages:** the potential to identify changes in tooth characteristics that are otherwise unobservable in a visual-tactile examination **Disadvantages:** uncertainty of the reliability of devices and the ability to detect disease and health
Electrical conductance	The demineralisation of the tooth is reported to have an effect on the tooth's electrical conductance. This is measured by placing a probe on the tooth which measures any potentially higher conductivity which occurs due to carious lesions being filled with saliva (Tam 2001)	An adjunct to the visual examination	**Advantages:** the potential to identify changes in tooth characteristics that are otherwise unobservable in a visual-tactile examination **Disadvantages:** uncertainty of the reliability of devices and the ability to detect disease and health. Particularly due to the necessity to place the probe in an identical location for a reproducible result

Table 3. QUADAS-2 tool

Item	Response (delete as required)
Participant selection - Risk of bias	
1) Was a consecutive or random sample of participants or teeth used?	**Yes** - where teeth or participants were selected consecutively or allocated to the study via a randomisation process **No** - if study described another method of sampling **Unclear** - if participant sampling is not described
2) Was a case-control design avoided?	**Yes** - if case-control clearly not used **No** - if study described as case-control or describes sampling specific numbers of participants with particular diagnoses **Unclear** - if not clearly described
3) Did the study avoid inappropriate exclusions (e.g. inclusion of caries into dentine)?	**Yes** - if the study clearly reports that included participants or teeth were apparently healthy or caries into dentine were excluded **No** - if lesions were included that showed caries into dentine or exclusions that might affect test accuracy (e.g. teeth with no caries)

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Table 3. QUADAS-2 tool (*Continued*)

	Unclear - if not clearly reported
Could the selection of participants have introduced bias?	
If answers to all of questions 1) and 2) and 3) was Yes	**Risk is Low**
If answers to any of questions 1) and 2) and 3) was No	**Risk is High**
If answers to any of questions 1) and 2) and 3) was Unclear	**Risk is Unclear**
Participant selection - Concerns regarding applicability	
1) Does the study report results for participants or teeth selected by apparent health or suspected early caries (i.e. studies do not recruit patients who are known to have advanced caries into dentine)?	**Yes** - if a group of participants or teeth has been included which is apparently healthy or indicative of early caries **No** - if a group of participants or teeth has been included which is suspected of advanced caries **Unclear** - if insufficient details are provided to determine the spectrum of participants or teeth
2) Did the study report data on a per-patient rather than on a tooth or surface basis?	**Yes** - if the analysis was reported on a surface or tooth basis **No** - if the analysis was reported on a per-patient basis **Unclear** - if it is not possible to assess whether data are presented on a per-patient or per-tooth basis
3) Did the study avoid an in vitro setting which required the usage of extracted teeth?	**Yes** - if the participants were recruited prior to tooth extraction **No** - if previously extracted teeth were used in the analysis **Unclear** - if it was not possible to assess the source and method of recruiting of included participants/teeth
Is there concern that the included participants or teeth do not match the review question?	
If answers to all of questions 1) and 2) and 3) was Yes	**Risk is Low**
If answers to any of questions 1) and 2) and 3) was No	**Risk is High**
If answers to any of questions 1) and 2) and 3) was Unclear	**Risk is Unclear**
Index test - Risk of bias (to be completed per test evaluated)	
1) Was the index test result interpreted without knowledge of the results of the reference standard?	**Yes** - if the index test described is always conducted and interpreted prior to the reference standard result, or for retrospective studies interpreted without prior knowledge of the reference standard **No** - if index test described as interpreted in knowledge of reference standard result **Unclear** - if index test blinding is not described

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Table 3. QUADAS-2 tool (*Continued*)

2) Was the diagnostic threshold at which the test was considered positive prespecified?	**Yes** - if threshold was prespecified (i.e. prior to analysing the study results) **No** - if threshold was not prespecified **Unclear** - if not possible to tell whether or not diagnostic threshold was prespecified
For visual and radiograph tests only: 3) For studies reporting the accuracy of multiple diagnostic thresholds for the same index test or multiple index tests, was each threshold or index test interpreted without knowledge of the results of the others?	**Yes** - if thresholds or index tests were selected prospectively and each was interpreted by a different clinician or interpreter, or if study implements a retrospective (or no) cut-off (i.e. look for deepest/most severe lesion first) **No** - if study states reported by same reader **Unclear** - if no mention of number of readers for each threshold or if prespecification of threshold not reported **N/A** - multiple diagnostic thresholds not reported for the same index test
Could the conduct or interpretation of the index test have introduced bias?	
For visual and radiographic studies item 3) to be added	
If answers to all of questions 1) and 2) was Yes	**Risk is Low**
If answers to any of questions 1) and 2) was No	**Risk is High**
If answers to any of questions 1) and 2) was Unclear	**Risk is Unclear**
Index test - Concerns regarding applicability	
1) Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	**Yes** - if the criteria for detection or diagnosis of the target disorder were reported in sufficient detail to allow replication **No** - if the criteria for detection or diagnosis of the target disorder were not reported in sufficient detail to allow replication **Unclear** - if some but not sufficient information on criteria for diagnosis to allow replication were provided
2) Was the test interpretation carried out by an experienced examiner?	**Yes** - if the test clearly reported that the test was interpreted by an experienced examiner **No** - if the test was not interpreted by an experienced examiner **Unclear** - if the experience of the examiner(s) was not reported in sufficient detail to judge or if examiners described as 'Expert' with no further detail given
Is there concern that the included participants do not match the review question?	
If the answer to question 1) and 2) was Yes	**Concern is Low**
If the answer to question 1) and 2) was No	**Concern is High**

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Table 3. QUADAS-2 tool (*Continued*)

If the answer to question 1) and 2) was Unclear	**Concern is Unclear**
Reference standard - Risk of bias	
1) Is the reference standard likely to correctly classify the target condition?	**Yes** - if all teeth or surfaces underwent a histological or excavation reference standard **No** - if a final diagnosis for any participant or tooth was reached without the histological or excavation reference standards **Unclear** - if the method of final diagnosis was not reported
2) Were the reference standard results interpreted without knowledge of the results of the index test?	**Yes** - if the reference standard examiner was described as blinded to the index test result **No** - if the reference standard examiner was described as having knowledge of the index test result **Unclear** - if blinded reference standard interpretation was not clearly reported
Could the reference standard, its conduct, or its interpretation have introduced bias?	
If answers to questions 1) and 2) was Yes	**Risk is Low**
If the answer to question 1) and 2) was No	**Concern is High**
If the answer to question 1) and 2) was Unclear	**Concern is Unclear**
Reference standard - Concerns regarding applicability	
1) Does the study use the same definition of disease positive as the prescribed in the review question?	**Yes** - same definition of disease positive used, or teeth can be disaggregated and regrouped according to review definition **No** - some teeth cannot be disaggregated **Unclear** - definition of disease positive not clearly reported
Flow and timing - Risk of bias	
1) Was there an appropriate interval between index test and reference standard (in vivo studies less than 3 months, in vitro no limit but must be stored appropriately)?	**Yes** - if study reports index and reference standard had a suitable interval or storage method **No** - if study reports greater than 3-month interval between index and reference standard or inappropriate storage of extracted teeth prior to reverence standard **Unclear** - if study does not report interval or storage methods between index and histological reference standard
2) Did all participants receive the same reference standard?	**Yes** - if all participants underwent the same reference standard **No** - if more than 1 reference standard was used **Unclear** - if not clearly reported

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Table 3. QUADAS-2 tool (*Continued*)

3) Were all participants included in the analysis?	**Yes** - if all participants were included in the analysis **No** - if some participants were excluded from the analysis **Unclear** - if not clearly reported
If answers to questions 1) and 2) and 3) was Yes	**Risk is Low**
If answers to any one of questions 1) or 2) or 3) was No	**Risk is High**
If answers to any one of questions 1) or 2) or 3) was Unclear	**Risk is Unclear**

APPENDICES

Appendix 1. Search strategy - visual

MEDLINE Ovid:
1. exp Tooth demineralization/
2. (teeth adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or remineral$)).mp.
3. (tooth adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or remineral$)).mp.
4. (dental adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or remineral$)).mp.
5. (enamel adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or remineral$)).mp.
6. (dentin adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or remineral$)).mp.
7. (root adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or remineral$)).mp.
8. Dental caries activity tests/
9. or/1-8
10. Physical examination/
11. ((visual or tactile) adj3 (exam$ or inspect$)).mp.
12. ((caries or “dental decay” or “tooth decay” or carious) adj3 (diagnos$ or detect$ or check$ or assess$)).mp.
13. ((diagnos$ or detect$) adj3 method).mp.
14. (“assessment system” or ICDAS or “Dundee Selectable Threshold” or “WHO criteria” or “World health organization criteria” or “Universal Visual Scoring System” or ERK).mp.
15. or/10-14
16. 9 and 15

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Appendix 2. Search strategy - fluorescence

MEDLINE Ovid:
1. exp Tooth demineralization/
2. (teeth adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
3. (tooth adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
4. (dental adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
5. (enamel adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
6. (dentin$ adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
7. (root adj5 (cavit$ or caries or carious or decay$ or lesion$ or deminerali$ or reminerali$)).mp.
8. or/1-7
9. Fluorescence/
10. exp Lasers/
11. fluorescen$.mp.
12. (QLF or DiagnoDENT).mp.
13. ((ultraviolet$ or light$ or laser$) adj5 (detect$ or diagnos$)).mp.
14. (quantitative adj (light$ or laser$)).mp.
15. or/9-14
16. 8 and 15

Appendix 3. Search strategy - radiographs

MEDLINE Ovid:
1. Dental caries/
2. (caries or carious).mp.
3. (teeth adj5 (cavit$ or decay$ or lesion$ or deminerali$ or reminerali$ or fissure$)).mp.
4. (tooth adj5 (cavit$ or decay$ or lesion$ or deminerali$ or reminerali$ or fissure$)).mp.
5. (dental adj5 (cavit$ or decay$ or lesion$ or deminerali$ or reminerali$ or fissure$)).mp.
6. (enamel adj5 (cavit$ or decay$ or lesion$ or deminerali$ or reminerali$ or fissure$)).mp.
7. (dentin$ adj5 (cavit$ or decay$ or lesion$ or deminerali$ or reminerali$ or fissure$)).mp.
8. or/1-7
9. exp radiography, dental/
10. ((dental or oral or teeth or tooth or mouth or caries) adj5 (x-ray$ or xray$ or radiograph$ or radiology or bitewing$ or tomograph$)).mp.
11. "bitewing radiograph$".mp.
12. ((diagnos$ or detect$) and caries and radiograph$).mp.
13. 9 or 10 or 11 or 12
14. 8 and 13

CONTRIBUTIONS OF AUTHORS

All review authors collaborated in the conception of the review purpose and design.

Drafting the protocol: Richard Macey and Tanya Walsh.

Developing the search strategy: Tanya Walsh and Richard Macey.

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DECLARATIONS OF INTEREST

Richard Macey: none known.

Tanya Walsh: none known. I am an Editor with Cochrane Oral Health.

Philip Riley: none known. I am a salaried member of the Cochrane Oral Health editorial team.

Anne-Marie Glenny: none known. I am Deputy Co-ordinating Editor of Cochrane Oral Health.

Helen V Worthington: none know. I am Co-ordinating Editor of Cochrane Oral Health.

Janet E Clarkson: none known. I am Co-ordinating Editor of Cochrane Oral Health.

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