Detection Methods for Early Caries Diagnosis: A Systematic Review and Meta-Analysis

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Keywords

Caries detection · Early caries · Incipient caries · Permanent teeth · Primary teeth

Abstract

The aim was to appraise the evidence on the performance of various means for the detection of incipient caries *in vivo*. Five databases of published and unpublished research were searched for studies from January 2000 to October 2019. Search terms included “early caries” and “caries detection.” Inclusion criteria involved diagnostic test accuracy studies for early caries detection in permanent and primary teeth. A risk-of-bias assessment was performed using the QUADAS-2 tool. We performed the study selection, data extraction, and risk-of-bias assessment in duplicate. The review protocol was *a priori* registered in the Open Science Framework. Of the initially 22,964 search results, 51 articles were included. For permanent teeth, when histologic examination was considered as the reference for occlusal surfaces, the sensitivity (Se) range appeared high for the DIAGNOdent Pen (DD Pen) at 0.81–0.89, followed by ICDAS-II at 0.62–1, DIAGNOdent (DD) at 0.48–1, and bitewing radiography (BW) at 0–0.29. The corresponding specificity (Sp) range was: DD Pen 0.71–0.8,

ICDAS-II 0.5–0.84, DD 0.54–1, and BW 0.96–1. When operative intervention served as the reference for occlusal surfaces, again, the DD means valued the most promising results on Se: DD 0.7–0.96 and DD Pen 0.55–0.90, followed by ICDAS-II 0.25–0.93, and BW 0–0.83. The Sp range was: DD 0.54–1, DD Pen 0.71–1, ICDAS-II 0.44–1, and BW 0.6–1. For approximal surfaces, the Se was: BW 0.75–0.83, DD Pen 0.6, and ICDAS-II 0.54; the Sp was: BW 0.6–0.9, DD Pen 0.2, and ICDAS-II 1. For primary teeth, under the reference of histologic assessment, the Se range for occlusal surfaces was: DD 0.55–1, DD Pen 0.63–1, ICDAS-II 0.42–1, and BW 0.31–0.96; the respective Sp was: DD 0.5–1, DD Pen 0.44–1, ICDAS-II 0.61–1, and BW 0.79–0.98. For approximal surfaces, the Se range was: DD Pen 0.58–0.63, ICDAS-II 0.42–0.55, and BW 0.14–0.71. The corresponding Sp range was: DD Pen 0.85–0.87, ICDAS-II 0.73–0.93, and BW 0.79–0.98. Se and Sp values varied, due to the heterogeneity regarding the setting of individual studies. Evidently, robust conclusions cannot be drawn, and different diagnostic means should be used as adjuncts to clinical examination. In permanent teeth, visual examination may be enhanced by DD on occlusal surfaces and BW on approximal surfaces. In primary teeth, DD Pen may serve as a supplementary tool across all surfaces. © 2021 S. Karger AG, Basel

Introduction

Caries prevalence has been declining over the last decades [Jones et al., 2017]. However, the burden of the disease is still profoundly evident and impacting, as it afflicts most people to some extent, despite the growing awareness on the benefits of oral hygiene and the use of fluoride, especially regarding specific types of teeth and surfaces [Ekstrand and Qvist 2015]. Still, in 2015, >10% of the world's population has been affected by dental caries, underpinning the pervasiveness of this disease across all age groups, and substantiating its pronounced social impact [Vos et al., 2016]. Caries may not only account for decayed teeth, but also for days of pain, sleepless nights, and time lost from school and work [Goodwin et al., 2015; Kassebaum et al., 2015].

An important factor contributing to the high prevalence is that caries may progress undetected in the initial stages and later develop into cavities. Therefore, research in the field, should be focused on the early and accurate detection of incipient caries. Conditional to this, caries prevalence and its socio-economic cost might be subsequently reduced and, concurrently, the basic principle of minimally invasive dentistry would be reinforced.

The most common diagnostic tools for caries are clinical examination and radiography [Gomez 2015; Lino et al., 2015; Diniz et al., 2016; Lenzi et al., 2016]. Nevertheless, these methods are not without shortcomings. First, monitoring caries progression by direct visual examination is particularly challenging, due to the low reproducibility [Hintze et al., 1998]. Dentists are not able to reliably determine the subtle visual and tactile differences between active and inactive enamel lesions from a single clinical examination [Ekstrand et al., 2005], as caries is a dynamic and fluctuating process involving demineralization and remineralization over a period of time [Fejerskov 1997]. Furthermore, radiography may underestimate the depth of the carious lesion and present a very low sensitivity rate, especially in the detection of incipient caries [Souza et al., 2013; Menem et al., 2017]. Last, the clinical criteria for caries classification vary across different systems.

Considering the above, new diagnostic tools with different characteristics have attained increased interest in the dental industry in the recent years, effectively contributing to early caries detection. These methods have been generally reported to present high sensitivity (Se) and good reproducibility but demonstrate low specificity (Sp) and some are affected by potential confounding factors [Gomez, 2015]. The National Institutes of Health (NIH)

Consensus Development Conference on Diagnosis and Management of Dental Caries through Life in 2001 reached the conclusion that the evidence base for the currently applicable methods for the detection and activity assessment of non-cavitated carious lesions was not adequate to substantiate any formal recommendation to adopt them [Bader et al., 2002].

There is ambiguity regarding the net effectiveness of diagnostic methods, as conventional ones are more specific than sensitive, while newer methods are considered more sensitive than specific [Gimenez et al., 2015]. In this context, the subtle balance between Se and Sp of each diagnostic method might influence the selected treatment option and clinical decisions, and leading, potentially, to misclassification followed by subsequent over-treatment or under-treatment [Zaidi et al., 2016].

Heterogeneity, unconfirmed data, and subjectivity according to diagnostic tools in the current published research all fuel future initiatives to comprehensively assess the existing evidence in the field. Systematic reviews and meta-analyses comprise the most powerful research tools to identify and rate the best available data. The aim of this timely systematic review of diagnostic test accuracy was to compare all in vivo studies, by referring to the accuracy of the diagnostic means available to clinicians and frame future perspectives on the most efficient methods for early caries detection in the permanent and primary dentition.

Materials and Methods

Protocol

The aim of this review was to answer the question: "What is the accuracy of different diagnostic tools for early caries detection in primary and permanent teeth, as reported through visual examination, radiography, fluorescence, ultrasonic detection, infrared spectroscopy, and others, compared against reference standards for caries detection (histological, microscopic, and operative procedures) regardless of the type of teeth, dentition and age of the patient population?"

The protocol of the Cochrane Collaboration (2014; The Nordic Cochrane Centre, Copenhagen, Denmark) was followed in this review with Review Manager (RevMan v5.3.). The reporting scheme of the review was aligned to the recommendations of the latest PRISMA statement for diagnostic tests accuracy studies [McInnes et al., 2018] and the PICO framework [Schardt et al., 2007]. The review protocol was a priori registered in the Open Science Framework (DOI 10.17605/OSF.IO/X9UWY).

Search Strategy

An electronic search was conducted of published and unpublished literature, independently and by two investigators (P.F. and E.O.). The main formal databases utilized in this study were MED-

LINE (via PubMed) and Scopus. Filters were used to ensure that the date range was 2000/01/01–2019/10/25 for MEDLINE and 2000–2019 for Scopus. Reports in the “grey literature,” defined as theses, dissertations, product reports, and unpublished studies via ClinicalTrials.com, Open Grey, and the ISRCTN registry, were also included. The date range for these search engines was 2000/01/01–2019/02/21. A hand search was also conducted of the articles retrieved for full-text evaluation for any additional potential for inclusion.

The main keywords that we used were: “caries diagnosis,” “incipient caries,” “caries detection,” “early caries diagnosis,” “technological devices for caries diagnosis,” and “caries diagnosis methods.”

Eligibility Criteria

Study Design. Clinical (in vivo) studies referring to the accuracy of different (any) diagnostic tools for the evaluation of caries.

Type of Teeth. No restriction. Studies referring to primary/permanent teeth were included.

Index Tests. Visual, visual/tactile examination, radiography, laser fluorescence, fibre-optic trans-illumination (FOTI), near-infrared spectroscopy (NIR), ultra-sonic caries detector (USD), optical coherence tomography (OCT), and electrical conductance (EC) were assessed.

Target Condition. Any study investigating caries.

Inclusion Criteria. Only studies reporting on Se and Sp values were included.

Exclusion Criteria. Studies not reporting on specific diagnostic methods and that were not in vivo studies were excluded. Animal studies were excluded. Studies that were not written in the English language were not considered.

Study Selection

Studies gathered from the databases were cross-checked to exclude duplicates. Titles and abstracts were evaluated separately by two reviewers (P.F. and E.O.), according to the study’s main topics, with further exploration of the full text. Each reviewer forwarded the studies for inclusion or exclusion, according to the eligibility criteria ($\kappa = 0.93$). Discrepancies were discussed among reviewers until a consensus was confirmed. A third reviewer (C.R.) was consulted when needed.

Data Collection Process

Data were extracted and recorded in a standard form (Zotero v5.0.47, Corp. for Digital Scholarship, and the Roy Rosenzweig Center for History and New Media). This form included specific characteristics of the study (type, title, authors, abstract, publication, volume, issue, pages, date, series, series title, series text, journal abbreviation, language, DOI, URL, ISSN, short title, mean of access, archive, location in the archive, library catalogue, call number, date added, date modified). Data were extracted by two of the reviewers (P.F. and E.O.) and re-examined by another reviewer (C.R.). Inconsistencies were discussed until a consensus was reached.

Quality Assessment of Accuracy Studies

The methodological quality of the studies was determined by means of the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool [Whiting et al., 2011]. Four domains were considered to determine the risk of bias and level of concern according to the applicability of the studies:

- 1 Patient selection: studies with a non-random or non-consecutive sample of patients, with the inclusion of entire cases of cavitated lesions or exclusion of cases difficult to diagnose, were judged as having a high risk of bias concerning the patient selection. This was also the case for case-control studies.
- 2 Index test: when a threshold was not reported and when diagnostic methods were interpreted with knowledge of the results of the reference standard, the index test domain was classified as being high-risk.
- 3 Reference standard: when reference standards were performed without knowledge of the index test results, the domain reference standard was classified as having a low risk of bias. All studies in which one of the index tests was also the reference standard were excluded. Moreover, studies that did not report a reference standard were excluded a priori.
- 4 Flow and timing: when the reference standard was not used for all samples, or if not all samples were included in the analysis, the flow and time domain was classified as having a high risk of bias. Furthermore, when a long period had elapsed (i.e., >1 month) between the index test and the reference standard, the flow and time domain was classified as high-risk because this situation could have resulted in changes in the lesion. The same applied if the interval was not reported.

Concerns about the applicability of the studies were determined as follows:

- 1 Patient selection: studies implemented with the inclusion of only cavitated lesions and studies with a small sample size (<20 lesions) were characterized as having a high concern regarding applicability.
- 2 Index test: when the index test implementation was different from the review question, a high concern was documented for the specific study.
- 3 Reference standard: when the gold standard demonstrated the presence of carious lesions in the enamel and/or dentin by histological/microscopic analysis and/or hardness measurement, the concern related to applicability was characterized as low. Studies assessing the validation of the target condition by radiographic analysis or that used hard-tissue removal (drilling) and/or clinical examination (visual-tactile) as their gold standard scored as being of high concern regarding applicability.

Summary Measures and Data Synthesis

Studies were analyzed and evaluated regarding content validity. Those that met the highest number of criteria needed were judged as having greater content validity. Finally, a qualitative and quantitative analysis of the study outcomes was performed.

Quantitative syntheses of the studies’ findings were performed, if applicable, and after exploring heterogeneity levels across individual reports. Random-effects meta-analyses were conducted to account for within- and between-study heterogeneity as well as for correlation between the Se and Sp estimates. The model fits a 2-level mixed regression approach, with independent binomial distributions for the true-positives and true-negatives, and a bivariate approach for the log odds ratio transforms for Se and Sp between studies. Summary estimates of Se and Sp and diagnostic odds ratio (DOR) with respective confidence interval (CI) and hierarchical summary receiver operating characteristic (HSROC) curves (as curvilinear lines passing through the summary points) were planned, to be presented for all applicable comparisons. Pooled estimates were presented if ≥ 4 studies were deemed eligible for a

Fig. 1. PRISMA flowchart.

single comparison. Authors were contacted to request data if not all available information was provided within the published document.

Additional Analyses

Meta-regression analytical techniques were planned for the assessment of the effect of tooth type (permanent or primary) on the pooled estimate. In addition, sensitivity analyses were planned, with the exclusion of high risk-of-bias studies from the syntheses if both high and lower risk-of-bias studies were included, to isolate and explore the effect of the high risk-of-bias studies. Publication bias was planned to be examined through standard funnel plots if >10 studies were included in the quantitative syntheses.

Results

Descriptive Findings and Quality Assessment

After electronic database and hand-searching, out of a total of 10,368 unique records screened, 271 studies were left for a full-text assessment according to the eligibility

Fig. 2. Proportion of studies with low, high, or unclear risk of bias (%).

Fig. 3. Proportion of studies with low, high, or unclear concerns regarding applicability (%).

criteria. Out of these, 51 were finally included and 5 were eligible for the quantitative syntheses overall (Fig. 1). A customized e-mail was sent to the corresponding authors of 27 studies deemed eligible for data request, but only 5 [Heinrich-Weltzien et al., 2002; Reis et al., 2006; Abalos et al., 2009; Diniz et al., 2012; Tassoker et al., 2020] provided relevant additional data. Study characteristics and qualitative data are presented in detail in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000516084).

Almost half of the included studies (22/51) were published between 2015 and 2019; the breakdown of the rest, regarding the year of publication was: 14/51 were published between 2010 and 2014, 12/51 in 2005–2009, and only a fraction of 3/51 between 2000 and 2004.

Results of the risk-of-bias assessment and applicability appear in Figures 2 and 3. Generally, of the 51 included articles, 43 can be classified as having a high risk of bias, 2 a low risk of bias and 6 an unclear risk of bias. Sixty per cent of the included studies presented a low risk of bias

according to flow and timing as well as according to the index test domain. In addition, more than two-thirds (60%) of the studies were characterized as having a high risk of bias regarding the reference standard, and another 2/3 were also considered to have an unclear risk of bias when referring to the patient selection domain. Almost all the included studies were characterized as having a low risk of concern regarding applicability in the reference standard, index test, and patient selection domains. The global risk of bias and the overall applicability concerns of the studies appear in Table 1.

Visual Criteria

Visual criteria were evaluated in 35 studies. ICDAS-II was the most common method for visual examination, with a total of 14 studies (40.0%) assessing its effectiveness as a diagnostic tool. Ekstrand's criteria were assessed in 10 studies and Nyvad's criteria in 4.

The sample sizes reported were in the considerably wide range of 25–4,112 teeth. On average, there were two examiners per study, with only a few studies utilizing a different number. Various reference standards were used for validation, with histological examination and operative intervention being, by far, the most used, with application in 15 and 14 studies, respectively. The Se scores of visual methods ranged from 0.04 to 1 and the Sp scores from 0.44 to 1. Area under the ROC curve data (Az) ranged from 0.56 to 0.99 (Tables 2, 3; online suppl. Tables 2–4).

Radiography

Intraoral bitewing radiography (BW) was evaluated in 28 studies. The range of the sample sizes was the same as the respective range of studies evaluating visual criteria (25–4,112 teeth) since some studies simultaneously investigated radiography and visual examination as different index tests.

On average, there were two examiners per study. Histological examination and operative intervention were again the most used reference standards in 11 (39.3%) and 10 studies (35.7%), respectively. Se ranged from 0 to 0.96, Sp from 0.6 to 1, and Az from 0.51 to 0.95 (Tables 2, 3; online suppl. Tables 2–4).

DIAGNOdent 2095

The first-generation DIAGNOdent laser fluorescence device (DD), also known as DIAGNOdent 2095, was evaluated in 18 studies. Sample sizes ranged from 30 to 433 teeth. However, this range was considerably smaller than the corresponding ranges for visual methods and intraoral radiographs. On average, there were two examiners per study. Like the previous methods, operative inter-

Table 1. Risk-of-bias applicability concerns

Study	Risk of bias	Applicability concerns
Bizhang et al., 2016	high	low
Kim et al., 2017	high	low
Jablonski-Momeni et al., 2014	high	low
Goel et al., 2009	high	low
Reis et al., 2006	high	low
Chan et al., 2018	high	low
Abalos et al., 2009	high	low
Bahrololoomi et al., 2015	high	low
Bozdemir et al., 2013	high	low
Chu et al., 2010	high	low
Costa et al., 2008	high	low
Heinrich-Weltzien et al., 2002	high	unclear
Kavvadia and Lagouvardos, 2008	high	low
Krause et al., 2007	high	low
Lussi et al., 2001	high	low
Matalon et al., 2007	high	low
Melo et al., 2015	high	low
Ozkan and Guzel, 2017	high	low
Huth et al., 2008	high	low
Kavvadia et al., 2018	high	low
Huth et al., 2010	high	low
Ribeiro et al., 2015	high	low
Newman et al., 2009	high	low
Barberia et al., 2008	high	low
Błażejewska et al., 2016	high	low
de Souza et al., 2018	high	low
Holtzman et al., 2015	high	low
Jung et al., 2018	high	low
Mortensen et al., 2018	high	low
Rechmann et al., 2012	high	low
Theocharopoulou et al., 2015	high	low
Akbari et al., 2012	high	low
Baelum et al., 2012	high	low
Bussaneli et al., 2015	high	low
Coutinho et al., 2014	high	low
Novaes et al., 2009	high	low
Zeitouny et al., 2014	high	low
Braga et al., 2010	high	low
Cinar et al., 2013	unclear	low
Diniz et al., 2012	low	low
Freitas et al., 2016	high	low
Kockanat et al., 2017	high	low
Kucukyilmaz et al., 2015	unclear	low
Simon et al., 2016	high	low
Singh et al., 2016	unclear	low
Subka et al., 2019	unclear	low
Tassoker et al., 2020	high	low
Teo et al., 2014	unclear	low
Castilho et al., 2016	low	low
Angnes et al., 2005	unclear	low
Rocha et al., 2003	unclear	low

Table 2. Overall ranges of the basic diagnostic methods

Diagnostic technique	Studies, <i>n</i>	Sensitivity	Specificity	AUC of ROC value
Visual examination methods	35	0.04–1	0.44–1	0.56–0.99
Bitewing radiography	28	0–0.96	0.6–1	0.51–0.95
DIAGNOdent	18	0.43–1	0.5–1	0.55–0.94
DIAGNOdent Pen	20	0.16–1	0.2–1	0.4–0.95
VistaProof	4	0.26–0.92	0.41–0.98	0.66–0.97
CarieScan Pro	5	0.3–0.92	0–0.97	0.47–0.97
SoproLife	4	0.86–0.98	0.55–0.96	0.89–0.98

Table 3. Ranges of the basic diagnostic methods according to the type of surface and dentition (note that studies with mixed dentition do not appear in this table)

Diagnostic technique			Studies, <i>n</i>	Sensitivity	Specificity	AUC of ROC value
Visual examination methods	occlusal	primary	8	0.42–1	0.51–1	0.77–0.98
		permanent	17	0.25–1	0.44–1	0.56–0.96
	approximal	primary	4	0.05–0.96	0.73–1	0.58–0.95
		permanent	5	0.04–0.81	0.83–1	0.77–0.99
Bitewing radiography	occlusal	primary	6	0.14–0.96	0.78–0.99	0.64–0.95
		permanent	11	0–0.93	0.6–1	0.51–0.74
	approximal	primary	8	0.14–0.96	0.62–1	0.58–0.92
		permanent	3	0.15–0.83	0.6–0.99	0.71
DIAGNOdent	occlusal	primary	3	0.43–1	0.5–1	not available
		permanent	15	0.48–1	0.54–1	0.55–0.94
	approximal	primary	0			
		permanent	0			
DIAGNOdent Pen	occlusal	primary	3	0.63–1	0.44–1	0.66–0.95
		permanent	7	0.6–0.97	0.54–0.85	0.67–0.92
	approximal	primary	5	0.16–0.97	0.68–1	0.57–0.92
		permanent	3	0.6–0.88	0.2–0.98	0.4–0.9
VistaProof	occlusal	permanent	1	0.32–0.78	0.64–0.85	0.65–0.84
		permanent	1			
CarieScan Pro	occlusal	primary	3	0.72–0.91	0–0.92	0.47–0.92
		permanent	2	0.3–0.92	0.75–0.97	0.973
SoproLife	occlusal	primary	1	0.86–0.98	0.92–0.96	0.94–0.98
		permanent	2	0.93–0.95	0.55–0.88	0.89

vention and histological validation were the most used reference standards, in 8 and 8 studies, respectively. Se of the DD ranged from 0.48 to 1, Sp from 0.5 to 1, and Az from 0.55 to 0.94. Finally, there was an apparent heterogeneity in the calibration cut-off points of the device (Tables 2, 3; online suppl. Tables 2–4).

DIAGNOdent Pen

The second-generation DIAGNOdent laser fluorescence device, better known as the DIAGNOdent Pen (DD Pen) was assessed in 20 studies. The number of teeth under evaluation ranged from 37 to 621, and again, two examiners per study were reported on average. Various reference

Fig. 4. Forest plot regarding ICDAS-II at D1 histological level.

standards were used for validation, with histological validation and operative intervention being used in 6 and 6 studies, respectively. Others included BW, computed microtomography, and visual examination (in some cases after the removal of orthodontic brackets or the use of elastic orthodontic separators) and were also relatively evenly represented. Se of the DD Pen ranged from 0.16 to 1 and Sp from 0.2 to 1. While these ranges are broadly similar to corresponding ranges of the DD, there were some differences. Az for the DD Pen ranged from 0.4 to 0.95. Again, there was a variety of cut-off points used for the calibration of the device (Tables 2, 3; online suppl. Tables 2–4).

CarieScan Pro

The CarieScan Pro device was evaluated in 5 studies, with a considerably smaller number of teeth assessed, namely, 25–120 across studies, but similarly reporting duplicate examination screenings, as per the number of investigators involved. Histological validation was used as the reference standard in 3 studies and operative intervention in 1. Se of the CarieScan Pro device ranged from 0.72 to 0.91, Sp from 0 to 0.92, and Az from 0.47 to 0.92 (Tables 2, 3; online suppl. Tables 2–4).

VistaProof

The VistaProof fluorescence camera was evaluated in 4 studies, with the number of teeth assessed at 32–619, again aligning with duplicate examination schemes. Histological validation was used as the reference standard in 1 study and, similarly, the operative intervention was used as the reference standard in another. Se of the VistaProof fluorescence camera ranged from 0.26 to 0.92 and Sp from 0.41 to 0.98; Az was available in only 1 study and stood at 0.66–0.97 (Tables 2, 3; online suppl. Tables 2–4).

SoproLife

The SoproLife fluorescence camera as a diagnostic modality was assessed in 4 studies. Sample sizes ranged between 37 and 433 teeth, and the examination procedure was done in triplicate. Histological validation was used as the

reference standard in 1 study and visual examination (ICDAS-II) for the rest. Se of the SoproLife fluorescence camera ranged from 0.86 to 0.98, Sp from 0.55 to 0.96, and Az from 0.89 to 0.98 (Tables 2, 3; online suppl. Tables 2–4).

Miscellaneous Methods

Various diagnostic modalities, including OCT, NIR, quantitative light-induced fluorescence (QLF), and modifications and combinations of the methods described above, were evaluated in 19 studies. Representation of these methods was sparse with none of them being assessed in >2 studies. There was a broad range of sample sizes (25–1,160 teeth), as expected when considering the heterogeneity of the diagnostic tools (online suppl. Table 5).

Effect of Index Test, Meta-Analyses, Additional Analyses

Out of the 51 articles included in the qualitative analysis, 5 were included in the quantitative synthesis, following the appraisal of the heterogeneity of study conditions and settings. All the studies included in the quantitative synthesis examined permanent teeth. A pooled estimate, resulting from formal statistical analysis was only possible for the DD, due to the low number of studies included for the other comparisons (i.e., <4). For all studies included in the quantitative synthesis, the reference standard adopted was either histological examination or operative intervention, the surfaces were occlusal, and the dentition was permanent.

ICDAS-II Visual System

Two studies investigating the diagnostic performance of ICDAS-II at the D1 histological level were included in the quantitative synthesis (Fig. 4; online suppl. Fig. 1). Diniz et al. [2012] reported Se of 0.93 (95% CI: 0.86, 0.97) and Sp of 0.60 (95% CI: 0.15, 0.95). In a more recent study [Tassoker et al., 2020], the corresponding values stood at 0.86 (95% CI: 0.76, 0.93) and 0.85 (95% CI: 0.55, 0.98), respectively.

Ekstrand's Visual System

Three studies examined the diagnostic performance of Ekstrand's visual criteria at the D3 histological level and

Fig. 5. Forest plot regarding Ekstrand's system at D3 histological level.

Fig. 6. Forest plot regarding DIAGNOdent at D3 histological level.

Fig. 7. HSROC curve regarding DIAGNOdent at D3 histological level.

they were synthesized (Fig. 5; online suppl. Fig. 2). Abalos et al. [2009] showed Se of 0.93 (95% CI: 0.82, 0.98) and Sp of 0.88 (95% CI: 0.75, 0.95), while Reis et al. [2006] reported 0.72 (95% CI: 0.53–0.86) and 0.84 (95% CI: 0.77, 0.89), respectively. Furthermore, Heinrich-Weltzien et al. [2002] estimated a considerably lower Se of 0.25 (95% CI: 0.19, 0.31), while the Sp was at similar levels to the other 2 studies, i.e., 1.00 (95% CI: 0.86, 1.00).

DIAGNOdent 2095

Four studies [Heinrich-Weltzien et al., 2002; Reis et al., 2006; Abalos et al., 2009; Diniz et al., 2012] reported on the diagnostic performance of DD at the D3 histological level and were included in the meta-analysis. The breakdown of individual studies for both Se and Sp is presented in Figure 6. The HSROC curve is also presented, while the summary estimate for Se was 0.86 (95% CI: 0.75, 0.92), while the Sp values were lower at 0.68 (95% CI: 0.54, 0.79) (Fig. 7). The overall DOR, as a single measure for diagnostic effectiveness and performance of DD was 13.0 (95% CI: 5.25, 32.10), revealing 13 times higher odds for DD being positive in identifying true caries, compared to being positive when no true caries exist.

DD Pen

Two studies exploring the diagnostic performance of DD Pen at the D1 histological level were included (Fig. 8;

Fig. 8. Forest plot regarding DIAGNOdent Pen at D1 histological level.

online suppl. Fig. 3). Diniz et al. [2012] reported Se 0.67 (95% CI: 0.57, 0.76) and Sp of 1 (95% CI: 0.9, 1), while the recent study of Tassoker et al. [2020] calculated respective values of 0.81 (95% CI: 0.70–0.89) and 0.77 (95% CI: 0.46, 0.95).

No additional analysis, sensitivity analysis, or exploration for publication bias could be performed due to the paucity of studies included in the quantitative synthesis.

Discussion

Summary of the Evidence

Visual examination for the detection of caries is the most common diagnostic method, mainly due to its cost-effectiveness. Even though the ranges reported in this study appear relatively wide, most studies suggest moderate-to-high Se and Sp values. Regarding the Se of visual methods for the occlusal surfaces of permanent teeth, the study by Heinrich Weltzien et al. [2002] constitutes a significant outlier at only 0.25, and the second-lowest Se value was 0.54. According to their study, visual examination could not correctly identify all occlusal caries and a considerable amount remained undetected. BW, as a supplement to visual examination, is one of the oldest methods for caries detection. Most of the included studies indicated a low Se in the detection of incipient caries as well as in most occlusal lesions without signs of cavitation. Conversely, high Sp values were reported across all types of surfaces and dentitions, thus indicating the potential of this well-established tool to streamline and correctly classify non- carious surfaces.

The DD is one of the most thoroughly studied devices in the contemporary scientific literature. The original DD can only be used on occlusal surfaces. The Se and Sp values in the individual studies ranged from moderate to high in both permanent and primary teeth. The original DD has been superseded by the DD Pen, a more compact and updated version. The latter may be used for the detection of approximal carious lesions, unlike its predecessor. In terms

of Se, several studies [Diniz et al., 2012, Cinar et al., 2013, Kucukyilmaz et al., 2015, Kockanat and Unal, 2017] report a modest increase in occlusal caries detection compared to with the original DD. On the other hand, Sp values seemed to be similar or even slightly lower than the corresponding values obtained with the original DD which is still in use. For approximal lesions, the Se values for permanent teeth and the Sp values for primary teeth were fairly high. However, the Se values for primary teeth and the Sp values for permanent teeth varied across studies.

The VistaProof fluorescence camera appears to have moderate-to-high Sp on buccal and occlusal surfaces. Highly variable Se values for occlusal lesions, in conjunction with the very limited number of studies assessing VistaProof in a clinical setting, preclude any further conclusion or speculation regarding this tool. A similar picture is formulated for the CariesScan Pro device, thus, imposing further uncertainty for clinical practice decision-making based on the existing evidence. The Soprolife fluorescence camera appears promising for both permanent and primary dentition, firstly, regarding its potential to correctly identify occlusal carious lesions, and secondly, as it does not seem to considerably lag where Sp is concerned. Further assessment of this tool would be useful. The QLF system was assessed in only 2 of the studies included in this review, although it is a diagnostic device that is relatively well-studied in the scientific literature, mostly in an in vitro setting. To date, it appears that the QLF system has been studied with sound emphasis on its technical aspects rather than its diagnostic validity in a clinical setting. This is possibly one of the main reasons why the QLF system appears under-represented in this review. Additional, well-designed clinical trials for the performance of QLF are necessary to provide clinically relevant information.

Findings in Context

Previous systematic reviews in the field of diagnostic tools for early caries detection do exist. Gomez et al. [2013] found a large variation and lack of consistency regarding Se and Sp values across the analytical tools exam-

ined in both in vitro and in vivo studies with no distinction between the DD and DD Pen. However, since the publication of their report, new original studies have been published, to timely substantiate an update in the search for existing evidence, with our systematic review identifying a surplus of approximately 24 in vivo (clinical) studies. Other reviews have appeared recently in the literature, but with a scope to provide evidence for a limited number of specific analytical techniques and lacking a clear discrimination between updated tools such as the DD Pen and its predecessor, or between different types of tooth surfaces, or considering only certain specific reference standards [Iranzo-Cortés et al., 2019].

The studies contributing to this review present, in many cases, considerably variable results. This pertains largely to the heterogeneity inherent in the different methodologies followed in the individual studies, and subsequently reflects the overall heterogeneity in the results of meta-analyses. This is endemic to medical research [Alba et al., 2016; Rhodes et al., 2018]. A recent report on orthodontic meta-analyses from Cochrane and non-Cochrane reviews, revealed that more than one-third of the reviews presented substantial levels of heterogeneity [Koletsis et al., 2018]. Speculations in this respect may relate to different cut-off points or different techniques for the interpretation of the diagnostic methods. Moreover, the assessment of carious lesions of various stages across clinical studies might also be liable for the considerable heterogeneity present in the results of this study. Differences in the experimental design of the included studies, especially in the reference standards used, could clearly have affected the outcomes. Clearly, more randomized controlled trials, with comparable protocols, experimental designs, and outcomes, are to be welcomed and valued.

Finding the ideal early caries diagnostic method appears a somewhat utopian notion, in view of the considerable variation in Se and Sp values and lack of Az values in many studies. A dynamic equilibrium of the false-positive and false-negative rates in diagnosis should be anticipated as the most effective means. Generally, on occlusal surfaces, the performance of visual methods and the DIAGNOdent devices appears similar, with BW lagging behind. On approximal surfaces of primary teeth, the DD Pen appears to be more valid than BW, with the added benefit of not emitting ionizing radiation.

Strengths and Limitations

To the best of our knowledge, this is, to date, the first comprehensive systematic review and meta-analysis of

clinical trials assessing all available diagnostic methods. Previous studies on this topic typically included in vitro studies in their analysis, thus making the findings potentially less clinically relevant. A comprehensive assessment of all available diagnostic means for non-cavitated carious lesions was performed, based on a concise literature search of all the published and unpublished literature recorded in 5 databases. The protocol of this review was a priori registered and followed a pre-defined methodology, one that safeguarded against selective reporting and considerable deviations from the original design [Fleming et al., 2015; Koufatzidou et al., 2019].

On the other hand, some limitations do exist. More than 60% of the included studies were characterized as having a high risk of bias regarding the reference standard, which can be attributed to the strict eligibility criteria used. Specifically, we judged studies as having a low risk of bias only when histological examination (considered the gold standard) was reported as the reference standard. However, it should be noted that a reference standard such as histology applied to ex vivo studies can only be performed in clinical studies to a relatively small subset of teeth that can be extracted and processed in the laboratory. This brings a non-negligible source of bias, i.e., the selection of teeth (and patients) where extraction is scheduled for specific treatments (third molars, deciduous teeth prior to natural shedding, and periodontal or orthodontic patients) to comply with ethical considerations. Operative intervention through drilling to identify the carious lesions was also considered a valid reference standard and, in fact, a close counterpart of histologic examination for the quantitative synthesis. It was the second most frequent validation method after histological examination and was used in 13 studies, with publication dates scattered over a wide time range. As a result, there have been different definitions for the term “early” or “incipient” caries over the years as well as various approaches for the management of these lesions. It should also be noted that teeth with obvious cavities were not included and, in this way, teeth with clinically important lesions were not taken into consideration, as per the reviews’ aims, so false-negatives do exist. For instance, an occlusal carious lesion classified as IC-DAS 3 is characterized as “early,” but in some cases the appropriate management is operative intervention (e.g., fissurotomy, enameloplasty, etc.). Consequently, a proportion, at least, of early carious lesions do fit the aim of our study and present themselves as an “operative intervention” reference standard.

In addition, approximately two-thirds of the included studies were considered to have an unclear risk of bias

in the domain of patient selection. This percentage agrees with the findings of another systematic review and meta-analysis that also used the QUADAS-2 tool [Iranzo-Cortés et al., 2019]. As previously discussed, the clear heterogeneity between individual study reports did not allow for many studies to be mathematically synthesized and the results to benefit the precision of the summary effect. On similar grounds, predefined additional analyses or publication bias effects could not be formally explored.

The fact that only 5 studies could be included in the meta-analysis due to the scarcity of data, despite considerable efforts to retrieve the necessary data from the authors, is also an important limitation of this study. Concerning the personal communication with the authors, 27 individualized messages were sent for providing data. Eighteen authors did not answer, even after reminders were sent twice after a pre-specified time interval of 2 and then a further 4 weeks. Four responded but they did not provide the data needed, even after specific queries and reminders, 2 replied that they no longer had access to the data, 1 had gone into retirement, and another provided a different dataset from the one we requested. All conversations were recorded in a standardized format but cannot be accessed due to the GDPR policy.

Conclusions

Although many diagnostic methods have emerged and studied thoroughly in recent years, robust conclusions cannot be drawn regarding their definite effectiveness. The results of this systematic review and meta-analysis reveal a considerable variation in the Se and Sp values detected, due to the heterogeneity in the experimental settings of individual studies.

However, based on the results of this report, clinical considerations may be framed in terms of the most-valued diagnostic use of the existing tools, per tooth and surface:

- Visual examination remains the method of choice across all types of surfaces and dentitions, irrespective of the visual criteria used.
- In permanent teeth, visual examination may be supplemented by DD for the diagnosis of occlusal caries. When examining approximal surfaces, visual examination may be enhanced by BW.
- In primary teeth, visual examination may be supplemented with the DD Pen for the diagnosis of occlusal lesions. For approximal surfaces, the DD Pen may also be used as an adjunct to visual examination.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.F. drafted the protocol, searched for trials, obtained full texts, inserted data into Zotero, evaluated trials to include, extracted data from trials, entered data into Review Manager, communicated with authors, carried out the analysis, and drafted the final review. E.O. drafted the protocol, searched for trials, obtained full texts, entered data into Zotero, evaluated trials to include, extracted data from trials, carried out the analysis, and drafted the final review. D.K. drafted the protocol, entered data into Review Manager, carried out the analysis, interpreted the analysis, and drafted the final review. C.R. drafted the protocol, developed a search strategy, selected which trials to include, and drafted the final review.

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