Evidence uncertainties as presented in clinical guidelines: a survey

1. Introduction

The purpose of this report is to outline the third project in Cochrane Oral Health's priority setting process. We wanted to consider current evidence uncertainties, and gather data on where systematic reviews may be required. Clinical guidelines were chosen as the mechanism for exploring these uncertainties. We previously conducted an exercise to explore the evidence base and the primary research that is available, (see https://oralhealth.cochrane.org/sites/oralhealth.cochrane.org/files/public/uploads/cochrane_oral_health_priority_setting_developments_in_the_evidence_base.pdf) for information. This was a "bottom-up" exercise, looking at the evidence that exists, however the current analysis takes a top-down approach, looking at what is required by a specific group of stakeholders (i.e. guideline developers) rather than what is available.

Systematic reviews have been seen as completing the circle, or bridging the gap between primary research and the creation of clinical practice guidelines (MAGIC, 2018). Policy makers and guideline developers are key stakeholders in Cochrane reviews, according to the *Strategy to 2020* (Cochrane, 2015). The methods of guideline developers vary, but generally they look to high quality systematic reviews as the first level of evidence considered in terms of recommending good practice to clinicians, and they will sometimes undertake a systematic review if one does not already exist (Shekelle, 1999). An indication from a guideline document or a consensus statement that evidence is lacking, or that high quality research is not available is a cue to develop new topics for a systematic review, and can also reinforce the importance of an existing review topic. The lack of evidence may even act as a stimulus for the commission of research projects and targeted funding (Yaffe, et al, 2012). The questions that guideline developers still feel they have to answer are a good indicator of where the gaps may be in systematic review evidence and also in primary research. The identification of these gaps, or evidence uncertainties, are key to understanding oral health priority setting. It is important to both understand these uncertainties across Cochrane Oral Health's scope, and to map whether the Group's existing systematic reviews could potentially answer these questions.

The uncertainties have been explored by a survey and content analysis of clinical guidelines, published between 2005 and 2018.

2. Methods

Search strategies were developed in twelve key topic areas in oral health. These were areas considered to be "active" in terms of the number of clinical trials registered over the past three years, according to the survey of the evidence base that we undertook previously (see https://oralhealth.cochrane.org/sites/oralhealth.cochrane.org/files/public/uploads/cochrane_oral_health_priority_setting_developments_in_the_evidence_base.pdf) .

The topic areas were:

- Periodontal disease
- Oral cancer
- Partial / full edentulousness
- Caries management
- Malocclusion
- Gingivitis
- Temporomandibular joint disorder
- Oral mucositis
- Root canal therapy
- Impacted / unerupted teeth
- Wisdom tooth extraction
- Traumatised teeth

MEDLINE, Google Scholar and the National Institute of Health and Care Excellence (NICE) databases were searched in 2018. In the case of MEDLINE, subject searches were undertaken, and linked to the Canadian Agency for Drugs and Technology in Health (CADTH) filter for identifying guidelines and consensus statements (CADTH, 2019). In Google Scholar where the search interface is less advanced, keyword searches were limited by introducing "recommendation", "guideline" or "consensus" into the title search. The NICE database search was limited to guidance documents. The search results were then screened using the Cochrane Register of Studies software, and any results that were not guidance documents were discarded, along with duplicates. However, commentaries on guidelines were retained in order to follow up the primary guideline document reference.

The searches were limited to more current guidance; any guidelines or consensus statements published before 2005 were not examined. This is because the vast majority of Cochrane Oral Health's reviews were published or updated after this date, and may already have answered any uncertainties in guidelines published before 2005. Any guidelines that had cited Cochrane Oral Health's reviews over the research period were also examined. These citations were drawn from the data at held at the editorial base, which was comprised of citation results from Web of Science and Google Scholar, combined with data provided by information specialists at the UK Cochrane Centre.

The resulting list of guidelines and consensus statements was examined by retrieving the full text document. In some cases, the document had to be omitted because it was not available. Evidence uncertainties were explored in three ways:

- If the guideline had graded evidence as to level of quality according to research design, the topics that were based on levels of evidence below that of randomised clinical trial were extrapolated;
- If the guideline had set out future directions for research, these were compiled if they were related to oral health interventions, diagnoses or prognosis;
- If the guideline neither set out future directions for research or graded evidence, the guideline was examined for phrases such as "insufficient evidence" or "low-quality evidence" or "poor quality evidence", or "research" or "trial".

The uncertainties that were mentioned as needing further exploration by the guidelines were inputted into an Excel spreadsheet for each topic area, and coded by theme, type of review (eg prevention/treatment/diagnosis etc), the population and the condition.

3. Results

The search for potential clinical guidelines yielded a total of 569 records from three databases (MEDLINE, Google Scholar and Web of Science) after the removal of duplicates. Cochrane Oral Health had obtained 68 further guidelines citing their reviews by monitoring the literature, giving a total of 637. Of these, 112 were rejected as not relevant (i.e. not in Cochrane Oral Health's scope), not available or accessible, or on obtaining the full text, were not actually guidelines. This left 525 guidelines for analysis. The most represented clinical topics in the guidelines were preventing and treating caries (75 guidelines), oral cancer (70 guidelines), periodontal disease (55 guidelines) and the efficacy of dental implants (43 guidelines).

36% (191) of the guidelines listed no recommendations for future research, and did not comment on evidence gaps or areas where evidence was poor quality or lacking. This means that almost two-thirds of the clinical guidelines that were in Cochrane Oral Health's scope found areas where the evidence could be improved. 685 uncertainties were found in total from the 334 guidelines that had found gaps in the evidence.

3.1 Diagnosis of oral diseases

Eighteen of the uncertainties were about diagnosis of oral diseases. Almost half (7 out of 18) were about diagnosis of oral or head and neck cancers, covering the efficacy of diagnostic tests including imaging techniques. Three of the uncertainties were about the accuracy of tests for diagnosis of dental caries, and three were about diagnosis of temporomandibular joint disorders. The other five uncertainties in this category were about diagnosing taste abnormalities, imaging techniques for diagnosing malocclusions, imaging techniques for diagnosis of sialorrhea, diagnosis of dental neglect in children and establishing thresholds for intervention, and the biological markers for diagnosing peri-implant diseases for those people who have dental implants to replace missing teeth.

3.2 Oral health and its links to other health conditions

Thirty-eight uncertainties were about the links between oral health and other health conditions. The vast majority of these (29 out of 38) were about periodontal disease in particular. The links between periodontal disease and heart disease were most important to establish, 11 uncertainties were related to this. Nine uncertainties related to periodontal disease and diabetes, and whether improved periodontal health can help to keep diabetes controlled. Seven were about whether periodontal treatment can lead to better outcomes in pregnancy.

There were another nine uncertainties in this category. Three of these were about the links between good oral hygiene and the prevention of complications in the critically ill. The other six were split between oral care and pneumonia in nursing home residents, oral health as a predictor for physical frailty in the elderly, establishing a link between oral health and child maltreatment, whether oral health can predict or control dementia, whether there was a link between stress and oral ulcers and finally, whether temporomandibular joint disorders can cause migraines to develop.

3.3 Prevalence of oral disease

Only four of the uncertainties were about the prevalence of oral diseases, and all four were on different topics: the prevalence of human papilloma virus (HPV) in disadvantaged women, the presence of premalignancies or oral tumours in different populations with different baseline

risks, the prevalence of medication-related osteonecrosis of the jawbones in people undergoing tooth extractions, and trends in the prevalence of periodontal disease. However, establishing prevalence is not within the remit of Cochrane Oral Health, and so these topics were not relevant to this prioritisation process.

3.4 Prevention of oral disease

Almost one third of the uncertainties (212 out of 685) related to the prevention of oral diseases and disorders. Almost half of these (93 out of 212) were about preventing caries, and over one third of these concerned fluoride, including which mode of delivery was most effective, the effectiveness of types of fluoride (e.g. stannous, sodium or silver diamine) and the use of fluoride in certain high risk groups (e.g. the elderly, and those with autoimmune diseases like Sjogren's syndrome). The efficacy of behavioural interventions to prevent caries and the use of dental sealants were other areas where guideline developers thought research was most lacking.

Prevention of oral diseases generally was another area of concern, with 49 uncertainties identified from the guidelines. Twelve of these concerned methods of oral health promotion, and ten were about toothbrushing and the correct method, duration and amount of toothpaste to prevent oral diseases. Behavioural interventions were also an area of uncertainty in the general prevention of oral diseases, and another cited area was recall intervals and how often to visit the dentist.

Preventing oral mucositis in cancer patients was a further area of uncertainty. Lasers, growth factors and different antimicrobials and surface protectants were all interventions that were considered to need further research. Oral cancer screening to prevent oral lesions becoming cancerous, preventing medication related osteonecrosis of the jaws and preventing periodontal disease were less prominent, but also significant areas of prevention where evidence was lacking.

3.5 Prognosis and risk factors

Uncertainties relating to prognosis and risk factors for oral disease accounted for 51 of the 685 uncertainties. Sixteen were about risk and dental caries, primarily about developing adequate risk assessment tools. Nine were about the prognosis and risk in the development of oral cancer, concerns here included the role of alcohol, the risk of recurrence and the likelihood of oral lichen planus becoming oral cancer. Eight were around establishing the risk factors for periimplantitis, in particular the role of confounding factors including smoking. Five were about the risk factors involved in periodontal disease, with a consensus that evidence is generally lacking this area; and five were about the prognosis and development of osteonecrosis of the jaws.

3.6 Treatment of oral disease

Uncertainties about how to treat oral disease accounted for over half of the total, 362 out of 685. Seventy-one of these were about how to treat missing teeth or edentulousness, particularly in terms of dental implants. The most frequently mentioned uncertainties here were to do with types of materials for implant manufacture, the best type of implant placement technique, and establishing the factors for implant failure. Fifty-three uncertainties were about treating dental caries, and the type of restoration material was the most frequently mentioned uncertainty. The

removal of caries was also a topic that required more research, with micro-invasive interventions such as the Hall Technique featuring in this category.

Forty-five uncertainties were around treating periodontal disease, particularly around surgical techniques and the management of tissue, and regeneration techniques such as guided tissue regeneration and platelet rich plasma. The best regime of antimicrobials and the effectiveness of supportive therapy were also mentioned in this category. Forty-one uncertainties were about treating oral cancer, most of these were around the efficacy of chemotherapy treatments, or chemotherapy combined with radiotherapy. Uncertainties around surgical treatment for oral cancer included the efficacy of transrobotic surgery, types of reconstruction technique, and which type dressing materials promoted healing.

Twenty four related to general oral surgical procedures, and almost half of these were about which type of anaesthesia to use or how best to deliver it to patients (eg injection techniques or type of mask). Other topics in this category included whether antibiotic prophylaxis was useful for people with particular conditions or prosthetic joints, and three guideline developers stated that there was a lack of research generally on oral surgical procedures, particularly relating to rehabilitation and quality of life. Eighteen uncertainties were around root canal treatment, which type of surgical treatment is most effective and how it compares to non-surgical treatment. The next most mentioned uncertainty in this category was what type of filling material to use in the tooth.

Seventeen treatment uncertainties were about treatment of facial pain or temporomandibular joint disorders. Five of these were about the efficacy of alternative medicines, such as herbal therapies and acupuncture. Again, surgical procedures featured in this category, with uncertainties including the efficacy of the gamma knife, and the Gasserian ganglion percutaneous technique. Two guideline developers stated that there was uncertainty in all treatments for this condition.

Fourteen treatment uncertainties related to treatment of medication-induced osteonecrosis of the jaw bones. There was a consensus among guideline developers that research in this area is generally lacking, but specific areas that were mentioned included the efficacy of drug holidays to give the patient a break from medication causing the condition, the use of lasers for treatment, and the use of prosthetics such as implants. Hyperbaric oxygen and platelet-rich plasma were other treatments mentioned in this category.

Twelve uncertainties were around treating traumatised teeth. The type of surgical procedure to use was again the most mentioned uncertainty in this category. Other uncertainties were about raising the profile of out-of-hours services, the use of antibiotics to reduce revascularisation in immature teeth, reducing inflammation using corticosteroids and the long term effects of replanting a tooth

4. Discussion

It is clear that guideline developers believe that there is still much uncertainty around oral diseases and disorders. 685 uncertainties were identified over a 14 year period. Treatment and prevention are particular areas of concern. In terms of treatment, dental implants are a particularly hot topic, followed by treatment of caries, periodontal diseases, and oral cancer. Caries prevention remains at the forefront of prevention guidelines, followed by the prevention of general oral disease and the prevention of oral conditions (such as oral mucositis) in people undergoing cancer treatment.

This information is useful, but the next stage needs to be a mapping exercise, to see which of the identified uncertainties are already covered by a Cochrane systematic review. Are there gaps in

the evidence that Cochrane needs to be bridging? Incorporation of this knowledge into an evidence map will show which of Cochrane Oral Health's existing topics are priorities that are relevant to guideline developers, and where there might be new topics that should be registered in the future.

5. References

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