**Systematic review of the effectiveness and cost-effectiveness of 'HealOzone' for the treatment of occlusal pit/fissure caries and root caries.**
(There is no CIC information contained in this assessment report)

**Produced by**
Aberdeen Health Technology Assessment Group[1]
Institute of Applied Health Sciences
University of Aberdeen

Dental Health Services Research Unit[2]
The MacKenzie Building
Kirsty Semple Way
Dundee DD2 4BF

Authors:
**Miram Brazzelli[1]**
Lynda McKenzie[1]
Shona Fielding[1]
Cynthia Fraser[1]
Jan Clarkson[2]
Mary Kilonzo[1]
Norman Waugh[1]

Correspondence to:
**Miriam Brazzelli**
c/o Health Services Research Unit
University of Aberdeen
Polwarth Building
Foresterhill
Aberdeen AB25 2ZD

Date completed: 22nd November 2004
Expiry Date:

## About the “Home Unit”

The Aberdeen Health Technology Assessment Group is part of the Institute of Applied Health Sciences (IAHS). The Institute of Applied Health Sciences within the College of Medicine and Life Sciences of the University of Aberdeen is made up of discrete but methodologically related research groups. The HTA Group is drawn mainly from the Health Services Research Unit, the Department of Public Health, and the Health Economics Research Unit.

The HTA Group carries out independent health technology assessments (TARs) for the UK HTA Programme, which commissions TARs for the National Institute for Clinical Excellence (NICE) and other bodies, such as the National Screening Committee. In addition, a joint venture between the Health Services Research Unit at Aberdeen and the Medical Care Research Unit at Sheffield University forms the Review Body for Interventional Procedures Programme (ReBIP) within NICE. ReBIP undertakes systematic reviews and, where appropriate, establishes UK registries to collect and analyse data on the efficacy and safety of selected procedures.

TARs completed by the Aberdeen HTA Group to date include:

*Metal on metal hip resurfacing arthroplasty*
*Endoscopic inguinal hernia repair*
*Tension-free vaginal tape for urinary incontinence*
*Home versus hospital haemodialysis in end-stage renal failure*
*Literature searching for HTA reports*
*Myocardial perfusion scintigraphy for angina and myocardial infarction*
*Autologous chondrocyte implantation in the knee*

Members of the Aberdeen HTA group have contributed to other recent TARs , including;

*Pegylated interferon for hepatitis C*
*Immediate angiography for myocardial infarction (in press)*

*Continuous subcutaneous insulin infusion in diabetes*

and are currently involved in:

*CT screening for lung cancer and heart disease*
*Inhaled insulin in diabetes*

## Contribution of authors

Miriam Brazzelli and Shona Fielding completed the review of effectiveness. Lynda McKenzie conducted the review of economic evaluations. Lynda McKenzie and Mary Kilonzo conducted the economic evaluation. Cynthia Fraser developed and ran the search strategies. Norman Waugh provided oversight and contributed to drafting the review. Jan Clarkson provided clinical advice and commented on the draft review.

## Conflict of Interest

None.


## Source of funding

This report was commissioned by the NHS R&D HTA Programme.


## Relationship of reviewer(s) with sponsors

None of the reviewers has any pecuniary relationship with sponsors.

# Summary


## Background

Dental caries is a chronic disease caused by the localized and progressive demineralisation of the hard tissues of the coronal and root surfaces of the teeth. Caries location, development, and progression depend upon a range of environmental, social, and genetic factors and vary greatly amongst individuals.

Despite the decline in the prevalence of dental caries observed in the industrialised countries during the past few decades as a consequence of the increased availability of fluoride-delivery products and improved oral hygiene, dental caries is still a common disease experienced by almost 80% of children by the age of 18 and by almost 90% of adults.

The current management of early non-cavitated occlusal and root caries, and cavitated root caries, which are still accessible to cleaning, is usually based on non-operative preventive strategies that include information on oral hygiene, dietary advice, use of topically applied fluorides, and application of sealants. For cavitated occlusal caries and cavitated root caries that are not easily accessible to cleaning restorative interventions are adopted (drilling and filling).

HealOzone has been recently proposed as a novel method for the treatment of dental caries. In particular, it is suggested that HealOzone may reverse, arrest, or slow the progression of dental caries. The complete HealOzone procedure involves the direct application of ozone gas to the caries lesion on the tooth surface by means of an HealOzone device, the use of a re-mineralising solution immediately after application of ozone, and the supply of a ‘patient kit’, which consists of  toothpaste, oral rinse, and oral spray all containing fluoride.

## Methods

Electronic searches were conducted to identify published and unpublished studies. The following databases were searched: MEDLINE (1966 - May 2004), EMBASE (1980 – May 2004), MEDLINE Extra (17th May 2004), Science Citation Index (1981

– May 2004), Biosis (1985 – May 2004), AMED (1985 – May2004), Cochrane Library, Issue 2 2004, National Research Register (Issue 2, 2004), Current Controlled Trials ($18^{th}$ May 2004), Clinical Trials ($18^{th}$ May 2004), SCI proceedings (1991 – May 2004), Conference Papers Index (1982-May 2002), ZETOC conferences (1993 – May2004), IADR meeting abstracts (2002-2004). Two reviewers independently assessed the methodological quality of included studies and extracted data. A systematic review of the effectiveness of HealOzone for the management of tooth decay was carried out.

A systematic review of existing economic evaluations of ozone for dental caries was also conducted. Only one study was identified in the literature, but as it did not meet the methodological criteria for classification as an economic evaluation it was not further reviewed. The economic evaluation included in the industry submission was critically appraised and summarised.

Markov modelling techniques were used to assess the cost-effectiveness of HealOzone in addition to current management for the management of dental caries. The Markov model was used to estimate costs for up to five years and it incorporated sensitivity analyses around the key assumptions of the model.

## Number and quality of studies, and direction of evidence

Five full-text reports and five studies published as abstracts met the inclusion criteria for studies of clinical effectiveness of ozone treatment. Of these only one was published in a refereed journal, but it lacked some study details. The remaining studies were PhD theses, unpublished reports, or conference proceedings. The five full-text reports consisted of two RCT's assessing the use of HealOzone for the management of primary root caries and two PhD theses of three unpublished randomised trials assessing the use of HealOzone for the management of occlusal caries. Of the five studies published as abstracts, four assessed the effects of HealOzone for the management of occlusal caries and one the effects of HealOzone for the management of root caries.

Criteria for assessment of study quality included method and unit of randomisation, concealment of allocation, comparability of groups at baseline, blinding procedures, number of withdrawals/dropouts, and completeness of assessment at follow-up.

Overall the quality of the studies was modest with many important methodological aspects not reported. In particular there were some concerns about the statistical analyses being conducted in all full-text studies at the level of the lesion without taking into account the clustering of the lesions within a patient.

A quantitative synthesis of results was not feasible.

## Summary of benefits

Two studies (one published and one unpublished) assessing the use of HealOzone for the management of primary non-cavitated root caries reported high success rates for ozone-treated lesions and no significant changes in the control lesions, despite application of topical fluoride. This is puzzling, since topical fluoride is known to be effective. Results of cavitated root lesions were poorly defined and reported in one of these two studies. Cavitated lesions did not seem to benefit from ozone application showing indeed a negative effect over time.

One unpublished study showed that fissure sealants preceded by the application of ozone for the preventive treatment of non-cavitated root lesions were more likely to remain intact (61% versus 42%, $p<0.05$).

One unpublished study did not show any significant benefits of HealOzone for the management of non-cavitated pit and fissure lesions in the permanent dentition. Similarly a small unpublished pilot study did not show any significant differences between cavitated occlusal lesions treated with or without ozone apart from an improvement in the hardness and visual clinical indices. In contrast findings from conference proceedings (methodologically less reliable) reported very high success rates (from 86.6% to 100% of reversal of caries).

The adjunct of ozone to a fissure sealant did not seem to produce better sealant retention in occlusal lesions extending 2-4 mm into dentine.

Data on the use of HealOzone for the treatment of occlusal lesion in the deciduous dentition were available from only one unpublished study. An overall reduction in clinical severity scores was reported for non-cavitated occlusal lesions in primary molars treated with ozone.

*On the whole, there is not enough evidence from published randomised controlled trials on which to judge the effectiveness of ozone for the management of both occlusal and root caries.*

## Costs

The perspective adopted for the study was that of the National Health Service (NHS) and Personal Social Services. The analysis carried over a five-year period indicated that treatment using current management plus HealOzone cost more than current management alone for non-cavitated pit and fissure caries (£40.49 versus £24.78) but cost less for non-cavitated root caries (£14.63 versus £21.45).

## Costs/QALY

It was not possible to measure health benefits in terms of quality adjusted life years (QALYs). This was mainly due to uncertainties around the evidence of clinical effectiveness, and to the fact that the adverse events avoided are transient (e.g. a few seconds pain from injection of local anaesthetic; the anxiety/fear of having a drill; numbness till local anaesthesia wears off).

## Sensitivity analyses

One-way sensitivity analysis was applied to the model to assess the robustness of the results to variations of the underlying data. The probability of caries being cured was varied for each comparator separately, while using the base cure rate for the alternative comparator. These results indicated that when higher probability cure rates were used the proportion of teeth filled was lower at 12 months.

One-way sensitivity analysis was also performed on using similar SDR codes to those that are used in the industry submission. This did not alter the results for non-cavitated pit fissure caries as the discounted NPV of current management remained lower than that of the HealOzone comparator (£22.65 versus £33.39).

## Limitations of the calculations

The economic analysis was severely constrained by the lack of evidence on effectiveness. The long-term effects of HealOzone are not known and the assumption that reversed caries remain reversed may not be reliable. A complete cost-effectiveness analysis was hampered by the fact that there were no comparative data on the benefits. It was therefore not possible to identify the utility gain required over the lifetime of a patient to achieve a defined cost-effectiveness acceptability threshold.

## Need for further research

There is a need for further research into the clinical effectiveness of ozone treatment. Independent randomised controlled trials of the effectiveness and cost-effectiveness of HealOzone for the management of occlusal caries and root caries need to be properly conducted with adequate design, outcome measures, and methods for statistical analyses.

# Contents Page

# Appendices

**List of Tables**

## List of Figures

## List of Abbreviations

| | |
|---|---|
| CDC | Centers for Disease Control and Prevention |
| DFS | Decayed and filled surfaces |
| DMFS | Decayed, missing, and filled surfaces |
| DMFT | Decayed, missing, and filled teeth |
| ECM | Electrical conductance measurement |
| FDA | Food and Drug Administration |
| GDS | General Dental Services |
| NCHS | National Centre for Health Statistics |
| NC-PFC | Non-cavitated pit and fissure caries |
| NC-RC | Non-cavitated root caries |
| NHANES III | USA National Health and Nutrition Examination Survey |
| NHS EED | NHS Economic Evaluation Database |
| NPV | Net present value |
| QALY's | Quality adjusted life years |
| QLF | Quantitative light-induced fluorescence |
| QOTI/ FOTI | Quantitative fiber-optic transillumination |
| RCT | Randomised controlled trial |
| SDR | NHS Statement of Dental Renumeration |
| TACT | Tuned aperture computed tomography |
| UCD | Ultrasound caries detector |
| USPHS | US Public Health Service criteria |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS).

## Aim of the Review

The review aims to assess the effectiveness and cost-effectiveness of ‘HealOzone’ for the management of both pit and fissure caries and root caries.

# 2. Background

## 2.1 Dental caries

### 2.1.1 Aetiology, pathology and prognosis

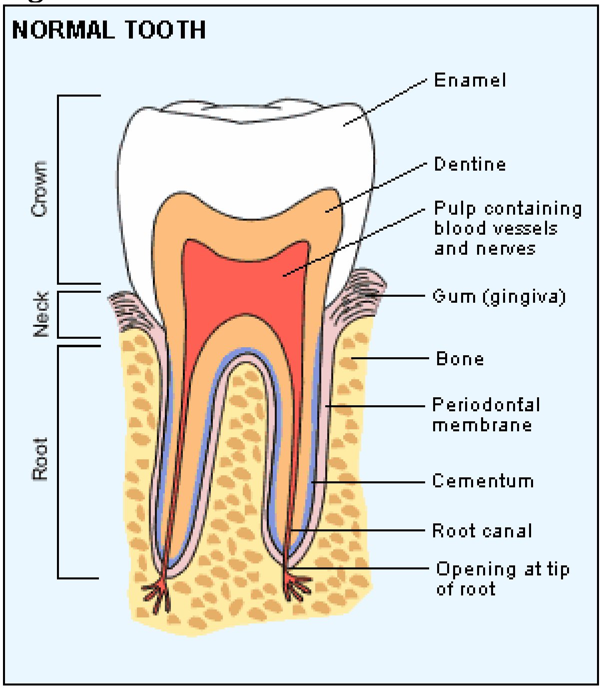
Dental caries (tooth decay) is a chronic disease caused by the localized and progressive demineralisation of the hard tissues of the coronal and root surfaces of the teeth. The demineralisation is caused by the interaction of acid-producing oral micro-organisms (in particular Streptococcus mutans, Lactobacillus, and Actinomyces species) with dietary carbohydrates (sugar).

Caries occurs when the natural dynamic balance between mineralisation and demineralisation of dental tissues is disrupted. The process begins on the surface of the enamel (outer surface of the tooth - see Figure 1). In enamel caries, the lesion may reverse or arrest by re-mineralization. If re-mineralisation does not occur, the lesion may penetrate the enamel and consequently result in the formation of a cavity, which may progress through the dentine and the pulp of the tooth. In the absence of treatment, dental caries may ultimately destroy the tooth. Caries location, development, and progression are influenced by a range of environmental, social, and genetic factors and vary greatly amongst individuals. In most individuals dental caries tend to progress slowly over time, with lesions often taking more than two years to cavitate, though in some it can take a shorter time. Conversely, some lesions never cavitate.

According to the anatomical location of carious lesions, it is possible to differentiate between 'coronal lesions', which may affect the pits and fissures or the smooth surfaces of a tooth, and 'root lesions', which affect the exposed root cementum and dentine. Root caries occurs in the same manner as coronal caries but demineralisation begins at a higher pH, and is more common in older people. The term 'primary caries' is used to indicate lesions on the unrestored surfaces of teeth whilst caries that develops adjacent to a filling is referred to as 'recurrent' or 'secondary caries'. 'Hidden caries' is a term used to identify carious lesions in the dentine that are not detected by visual examination but are large enough to be identified radiographically.

According to their 'activity' carious lesions may be classified as 'active' or 'inactive/arrested'. A lesion that is considered to be progressive is described as 'active' whilst a lesion that has stopped further progression is described as 'arrested'. This distinction is clinically important as arrested lesions do not require any further preventive interventions.

**Figure 1. Structure of a sound tooth**




The occlusal surfaces (pits and fissures) of teeth are particularly susceptible to dental caries due to their morphological structure (minute dimensions of pits and fissures) and because microbial plaque is more likely to grow in these areas (plaque stagnation). The teeth are more prone to plaque stagnation during eruption. Occlusal caries is more often seen in molar teeth rather than in premolar or anterior teeth.

Root caries incidence begins at about age 30-40 years and tends to increase thereafter. Root caries is most prevalent in the elderly due to the fact that, when people get older and retain their natural teeth, their gums tend to recede and expose the root surfaces. According to the published NHS Plan for Modernising NHS Dentistry "nearly 90% of people aged over 65 years show some signs of gum disease compared with 14% of 16-24 year olds".[1]

### 2.1.2 Significance in terms of ill-health

#### 2.1.2.1 Impact on patient's quality of life

Dental caries may have a significant impact on an individual's life. The most common consequences of untreated lesions are discomfort and pain. Restorative dental treatments can be now provided 'pain free', apart from the pain of the local anaesthetic injection. However, for some people they are associated with fear and anxiety which may become barriers to dental attendance. Treatment avoidance can subsequently lead to further progression of caries which in turn may cause more distress and long-term complications. Gross decay may lead to disturbances in eating and sleeping patterns because of pain. Psychological distress can arise from the embarrassment and self-consciousness of having missing or decayed teeth, especially in the anterior dentition. Communication problems may ultimately occur as a possible result of tooth loss.

In addition to human cost, dental caries can also be costly for the patients receiving treatment. For many patients NHS charges can be quite expensive, especially for those who earn just enough to disqualify them from exemption or remission of charges. Moreover, where provision of NHS dentistry is patchy, patients may have to depend on private dental care.

#### 2.1.2.2 Impact on the NHS

Treatments for dental care carry considerable costs for both the NHS and society. NHS General Dental Services data reveal that the total number of claims in England and Wales for dental interventions in the financial year 2002/2003 was 34 million. 48% of claims were for treatments requiring no dental intervention (i.e. examination, simple scaling, x-ray, fissure sealant, topical fluoride). The total number of teeth filled was about 19 million whilst the number of teeth with roots filled was just over one million. Overall, the total gross fees authorised was £1,634 million. The care and treatment for children accounted for 27% (£461 million) of all gross fees authorised.

### 2.1.3 Epidemiology

There has been a significant reduction in dental caries over the past 30 years in industrialised countries, due to environmental and educational factors such as the increased use of fluoride in public water supplies, dentifrices, and dental products; improved oral hygiene and prophylaxis; dietary counselling; and increased access to dental care. Nevertheless, dental caries is still a common disease experienced by almost 80% of children by the age of 18 and by almost 90% of adults.[2]

#### 2.1.3.1 Prevalence in children

After the significant decline in the 1970s and 1980s, it seems that over the past 20 years caries prevalence rates have become relatively stable.[2] The 2003 Children's Dental Health Survey commissioned by the UK Health Departments provides the most recent estimate of the prevalence of dentine decay in children in England and Wales.[3] The 2003 survey is the fourth in a series of dental health surveys carried out every 10 years since 1973. The criteria used in the survey to assess dental caries were the following:

- *Filled decay, otherwise sound* = teeth with amalgam, or other fillings that had no cavitated dentine caries present;
- *Obvious decay experience* = all teeth with cavitated dentine caries, restorations with cavitated dentine caries, teeth with filled decay (otherwise sound) and teeth extracted due to caries. The term relates to the DMFT (decayed, missing, and filled teeth) dental decay index.

The preliminary findings of this survey indicate that:

- there has not been a substantial change in the proportion of five and eight-year-olds who presented with obvious decay in the primary (milk) teeth between the 1993 and 2003 dental survey (Table 1);
- the proportion of filled primary teeth as well as the proportion of the total obvious decay experience represented by filled primary teeth in five and eight-year-olds has declined since 1983, indicating a decline in restorative interventions (Table 1);

- the mean number of primary teeth with obvious decay has decreased since 1983 in five and eight-year-olds (Table 2), but the mean number of primary teeth with obvious decay amongst children with decay has not changed considerably since 1993 apart from the decline in the number of filled teeth in the eight-year-olds (Table 3);
- the proportion of eight, 12 and 15-year-olds with obvious tooth decay and cavities into dentine in permanent teeth has decreased considerably since 1983 (Figures 2 and 3);
- the proportion of filled permanent teeth has declined considerably since 1983 in 12 and 15-year-olds but not in eight-year-olds (Figure 4);
- the proportion of the total obvious decay experience represented by the number of filled permanent teeth in eight, 12 and 15-year-olds has increased since 1993, indicating an increase in restorative interventions (Table 4).

**Table 1. Percentage of children with obvious tooth decay in primary teeth by age (Children Dental Health in the United Kingdom 2003)[3]**

| **Tooth condition** | **Year** | | |
|---|---|---|---|
| | **1983** | **1993** | **2003** |
| | Percentage of children: | | |
| Obvious decay experience | | | |
| 5 year olds | 50 | 45 | 43 |
| 8 year olds | 70 | 61 | 57 |
| Teeth with cavities into dentine | | | |
| 5 year olds | 41 | 40 | 40 |
| 8 year olds | 49 | 50 | 50 |
| Filled decay (otherwise sound) | | | |
| 5 year olds | 23 | 15 | 12 |
| 8 year olds | 47 | 33 | 26 |
| Filled teeth as a proportion of total obvious decay experience | | | |
| 5 year olds | 28 | 17 | 15 |
| 8 year olds | 50 | 35 | 28 |

**Table 2. Mean number of primary teeth with obvious tooth decay by age (Children Dental Health in the United Kingdom 2003)[3]**

| Tooth condition | | Year | | |
|---|---|---|---|---|
| | | **1983** | **1993** | **2003** |
| | | Mean numbers of teeth | | |
| Teeth with cavities into dentine | | | | |
| | 5 year olds | 1.3 | 1.4 | 1.4 |
| | 8 year olds | 1.2 | 1.3 | 1.3 |
| Filled decay (otherwise sound) | | | | |
| | 5 year olds | 0.5 | 0.3 | 0.2 |
| | 8 year olds | 1.2 | 0.7 | 0.5 |
| Obvious decay experience | | | | |
| | 5 year olds | 1.8 | 1.7 | 1.6 |
| | 8 year olds | 2.3 | 2.0 | 1.8 |

**Table 3. Mean number of primary teeth with obvious tooth decay in children with obvious decay experience by age (Children Dental Health in the United Kingdom 2003)[3]**

| Tooth condition | | Year | |
|---|---|---|---|
| | | 1993 | 2003 |
| | | Mean number of teeth | |
| Teeth with cavities into dentine | | | |
| | 5 year olds | 3.1 | 3.2 |
| | 8 year olds | 2.1 | 2.3 |
| Filled decay (otherwise sound) | | | |
| | 5 year olds | 0.6 | 0.6 |
| | 8 year olds | 1.1 | 0.9 |
| Obvious decay experience | | | |
| | 5 year olds | 3.7 | 3.8 |
| | 8 year olds | 3.2 | 3.2 |

**Table 4. Proportion of children with obvious tooth decay in permanent teeth by age (Children Dental Health in the United Kingdom 2003)[3]**

| Tooth condition | | Year | | |
|---|---|---|---|---|
| | | 1983 | 1993 | 2003 |
| | | Percentage in children: | | |
| Filled teeth as a proportion of total obvious decay experience | | | | |
| | 8 year olds | 58 | 37 | 52 |
| | 12 year olds | 70 | 58 | 70 |
| | 15 year olds | 74 | 68 | 77 |

**Figure 2. Proportion of children with obvious decay experience in permanent teeth by age (Children Dental Health in the United Kingdom 2003)[3]**

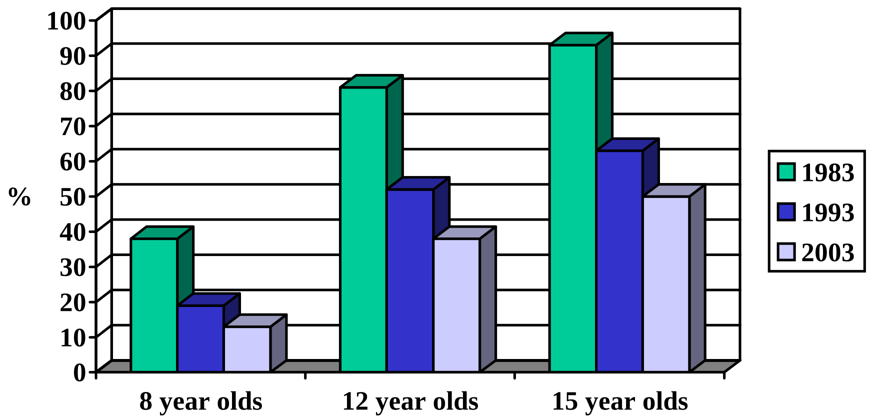



**Figure 3. Proportion of children with cavities into dentine in permanent teeth by age (Children Dental Health in the United Kingdom 2003)[3]**

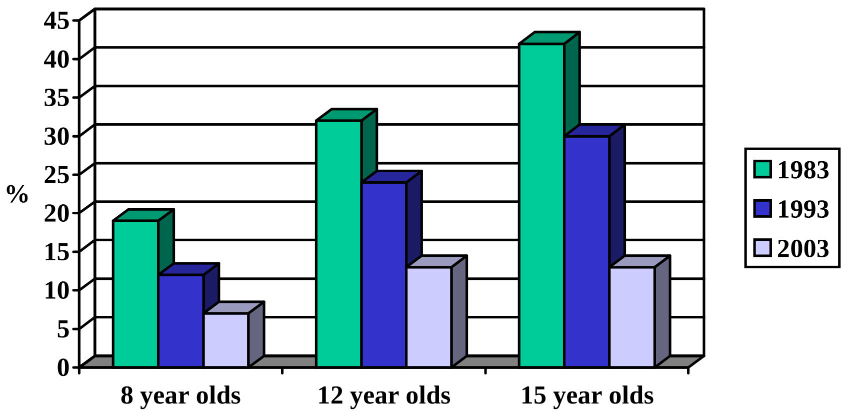



**Figure 4. Proportion of children with filled permanent teeth by age (Children Dental Health in the United Kingdom 2003)[3]**

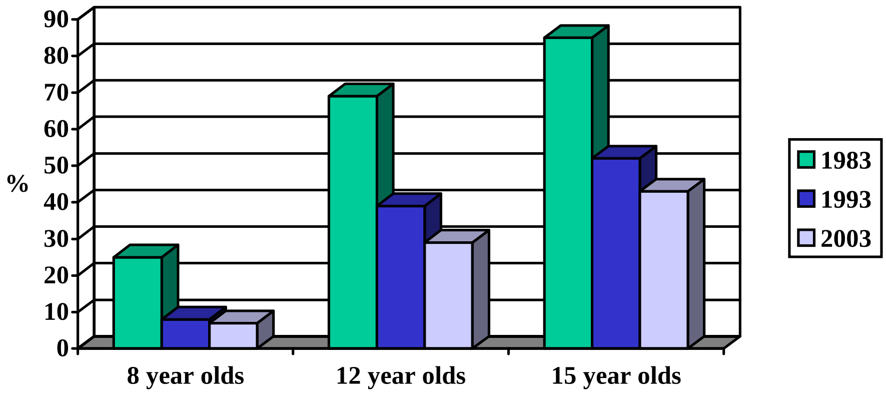


**Figure 5. Proportion of children with tooth decay and untreated caries by age (USA Third National Health and Nutrition Examination Survey)[4]**

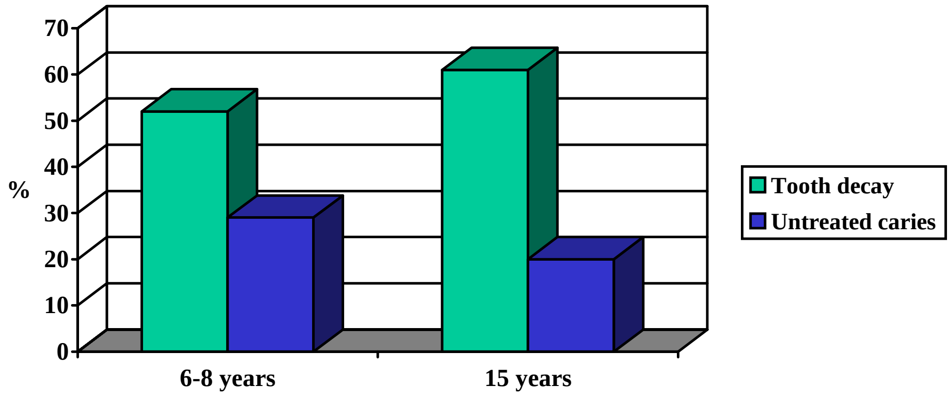
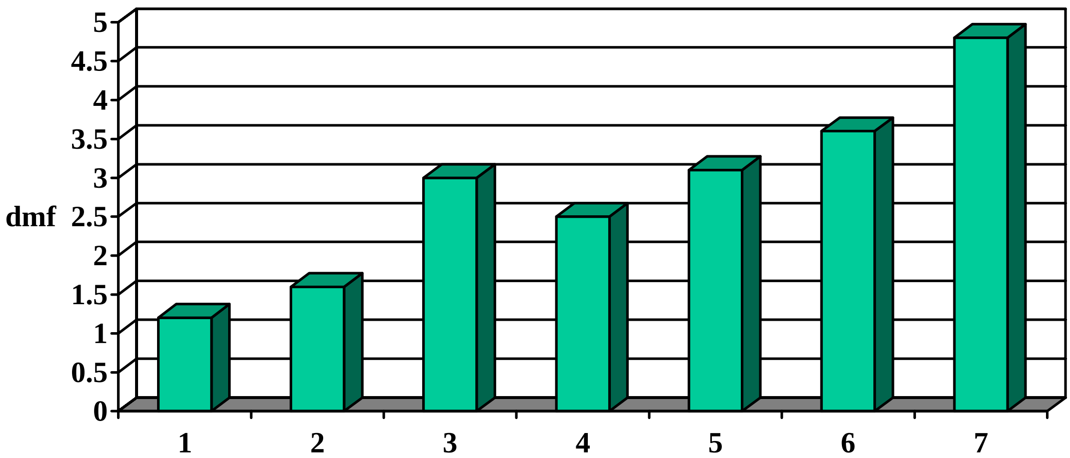


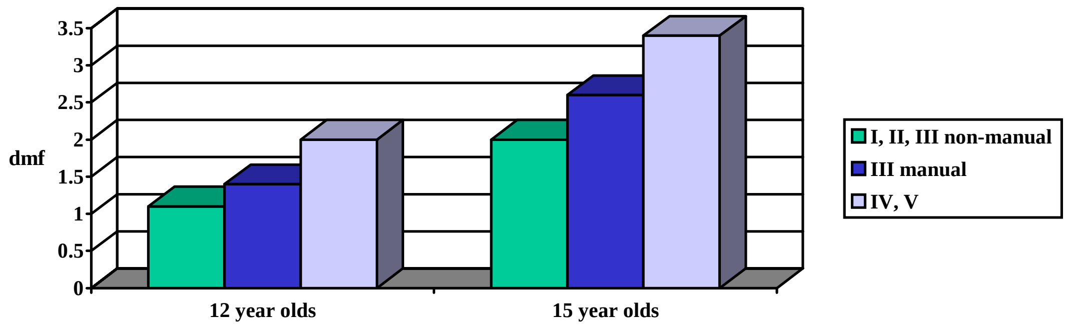

**Figure 6. Caries distribution by 'deprivation categories' in Scottish schoolchildren aged 5 years (Sweeney et al., 1999)[5]**




These findings are consistent with those found by the USA Third National Health and Nutrition Examination Survey II, CDC, NCHS[4] and the National Survey of Dental Caries in US School Children 1986-1987 where 52% of children aged 6-8 years and 61% of children aged 15 years presented with tooth decay in permanent or primary teeth. The proportion of children with untreated caries in permanent or primary teeth was 29% for the 6-8-year-olds and 20% for the 15-year-olds group (Figure 5).

Dental caries is not evenly distributed across the child population with about 26% of children (worst cases) presenting with 75% of all carious lesions.[6] This can be interpreted in the light of the fact that dental caries is a disease of lifestyle with strong socio-economical and geographical differences.  The use of 'deprivation categories' in the assessment of Scottish school children aged 5 years is a good example of how measures of socio-economic status may correlate with dental caries experience (Figure 6).[5]  The link between social status and prevalence of caries is also supported by the data from the National Children's Dental Health Survey carried out in UK in 1993 (Figure 7).[7]

**Figure 7.  Average number of decayed, missing or filled teeth in adolescents in the United Kingdom by social class (1993 National Children's Dental Health Survey)[7]**




### 2.1.3.2 Prevalence in adults

Fewer prevalence data are available for adults.

According to the UK 1998 Adult Dental Health Survey[8] adults had an average of 1.5 decayed or unsound teeth (teeth with visual or cavitated caries or those with an unsound restoration) and 55% had at least one decayed or unsound tooth.  The numbers of adults with decayed or unsound teeth varied according to the regions surveyed.  The proportion of dentate adults with tooth decay in England, Wales, Scotland and Northern Ireland is shown in Figure 8.

The mean proportion of filled permanent teeth ranged from 9% for people aged 16-24 years to 39% for people aged 45-54 years (Figure 9).

Overall 66% of the adult population showed at least one tooth with a root surface that was exposed, worn, decayed or filled.  Overall, root surface fillings were found in 43% of people 65 and older.

**Figure 8. Proportion of adults with decaying or unsound teeth by country (United Kingdom Adult Dental Health Survey 1998)[8]**

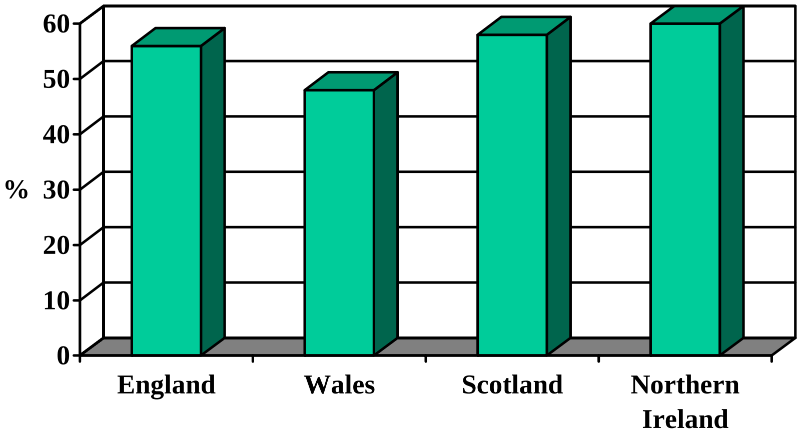
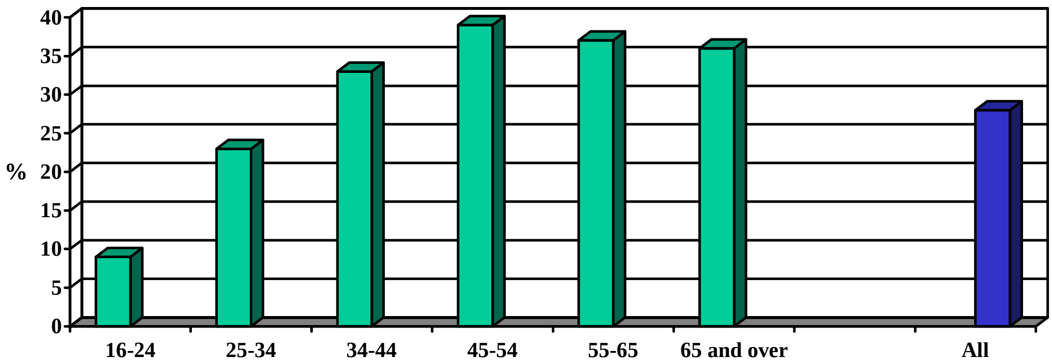



**Figure 9. Mean proportion of filled teeth by age (United Kingdom Adult Dental Health Survey, 1998)[8]**




Similarly, the USA National Health and Nutrition Examination Survey – Phase 1 (NHANES III) found evidence of coronal carious lesions in 94% of the studied population. The mean score for decayed and filled surfaces on permanent teeth in adults (DFS) was 22.2. Carious lesions were found in 23% of all dentate adults and in 47% of people aged 65 years and over (Third National Health and Nutrition Examination Survey 1998-1991).[4]

## 2.2 Current service provision

### 2.2.1 Current management of dental caries

Increasing emphasis has been recently dedicated to the provision of caries prevention and management strategies. In particular, attention to risk assessment and to preventive non-operative methods for assisting re-mineralization of early caries have been advocated. Despite the acknowledged importance for the prevention of caries, non-operative, preventive treatments are not fully funded by the NHS at present. Changes are likely to be introduced with the implementation of the new contract in 2005.

Efficient management of dental caries depends upon the knowledge of patient's dental and medical history and risk assessment; correct identification of carious lesions; and identification of the best treatment options for dental caries. A thorough dental and medical history provides information about patients' previous experience of dental caries, number of active lesions, and factors that might affect caries activity (e.g. general oral hygiene, diet and sugar intake, exposure to fluoride, salivary flow rate, certain medical conditions and medications). Caries risk assessment aims at identifying high-risk individuals who might benefit more from preventive treatments, and low-risk individuals for whom restorative treatments might be delayed. Carious lesions are firstly identified on the basis of the findings of the clinical examination (visual criteria). For visual detection of occlusal caries and for predicting their activity and severity, the ranked scoring system described by Ekstrand and colleagues[9] is recognised as a valid and reliable tool although mainly used in clinical research. For assessing the extent and severity of root caries the tactile criteria of 'soft, leathery, and hard' on probing are commonly used in dental practice and dental research. Radiographic investigations (X-rays) have been widely used for decades as an adjunct to clinical examination to estimate the depth of occlusal lesions into dentine or to identify lesions, which are hidden from clinical examination. More recently, other quantitative, more advanced methods have been proposed for the diagnosis of dental caries. These include methods based on:

- digital radiology (e.g. digital image enhancement, digital subtraction radiography, tuned aperture computed tomography – TACT);
- visible light (e.g. quantitative fiber-optic transillumination – QOTI/FOTI; quantitative light-induced fluorescence – QLF);
- laser fluorescence (e.g. DIAGNOdent);
- electrical current (e.g. electrical conductance measurement – ECM);
- ultrasound (e.g. ultrasound caries detector - UCD).

However, with the exception of digital radiology, these diagnostic procedures are not widely used in dental practice. Some procedures need further investigations (e.g. QOTI/FOTI, QLF) or further development (e.g. UCD) before their use could be recommended in dental practice. Others are prone to false-positive measurements (i.e. small amount of plaque identified as a carious lesion by DIAGNOdent) or unreliable findings (e.g. because of inadequate tooth isolation during ECM),[10] which require a careful interpretation and sometimes correction by the dentist. In particular, to our knowledge the validity of DIAGNOdent as an instrument for detecting occlusal caries has yet to be demonstrated in *in-vivo* studies.

#### 2.2.1.1 Treatment of early caries (non-cavitated pit and fissure caries and root caries)

For early caries treatment options include the following:

- provide information about oral hygiene;
- diet assessment and advice;
- fluoride-delivery methods;
- application of chlorhexidine;
- pit and fissure sealants; and
- recall at regular intervals.

*Oral hygiene*

Instructions on oral hygiene aim at improving personal removal of plaque by toothbrushing. Regular toothbrushing in children may help to reduce the incidence of caries[11] and children whose level of oral hygiene is good experience less decay.[12] Despite the lack of evidence on the effectiveness of oral hygiene instructions,[13] toothbrushing - together with the use of fluoride toothpaste and the advice of reducing sugar intake - is usually recommended in the dental practice for maintaining a good level of oral hygiene.

*Diet assessment and advice*

Evidence from epidemiological and experimental studies indicates that frequent consumption of fermentable carbohydrates is associated with prevalence of dental caries.  For some patients the frequency of intake of a certain type of food may primarily contribute to their caries risk and modification of this factor may be sufficient to change their risk.  The association 'diet-caries' is, however, complex and needs to be evaluated not only on the basis of the quantity and type of fermentable carbohydrates consumed, but also considering several other background factors such as age, total food intake, dietary habits, salivary flow rate, use and type of medications, and use of fluoride products. Dietary assessment is usually recommended in patients with multiple active lesions.  In contrast no diet modifications are suggested for patients with inactive caries.  The dentist, however, may still provide information on how unhealthy dietary habits may become a problem especially when associated with a poor level of oral hygiene.[14]

*Fluoride-delivery methods*

Use of fluoride-delivery products and water fluoridation are amongst the factors that contributed to the observed progressive improvement in oral health since the 1970s. Evidence indicates that fluoridation of the water supply is associated with an increased proportion of children without caries and a reduction in the number of teeth affected by caries.[1,15,16] Topical fluoride-delivery methods in the form of toothpastes, mouth rinses, gels, or varnishes are effective measures to prevent dental caries.  Their effectiveness has been established on evidence from randomised trials and more recently from a series of Cochrane systematic reviews of randomised trials.[17-22] Overall, fluoride toothpaste is the cheapest and the most widespread method to control dental caries.[23-25] The use of fluoride mouth rinses and gels, as an adjunct to fluoride toothpaste, is usually advised for individuals at high-risk of developing caries. Fluoride varnish is used to provide fluoride delivery to specific tooth sites and surfaces and is usually applied at intervals of 3 or 6 months.  A recent systematic review by Marinho and colleagues[17] examined the effectiveness of fluoride varnish in preventing dental caries in children and adults and commented on the ability of fluoride varnish to promote remineralisation of early caries. The included studies also considered “non-cavitated incipient enamel lesions” - clinically visible as white spots or discoloured fissures - which would be included amongst those lesions eligible for ozone application. The treatment effect was measured in terms of ‘prevented fraction’ (mean increment in caries in controls minus mean increment in fluoride group divided by the mean increment in the controls). For the seven studies that contributed to the main meta-analysis the DMFS prevented fraction pooled estimate was 0.46 (95% CI 0.30 to 0.63; p<0.0001), indicating a substantial benefit and demonstrating that fluoride varnish alone can result in reversal of early caries. Similarly, the meta-analysis of the three studies assessing the effect of fluoride varnish on deciduous teeth suggested a 0.33 % (95% CI, 0.19% to 0.48%, p<0.0001) reduction in decayed, missing and filled tooth surfaces. Another recent systematic review[26] of selected caries prevention methods has reached similar conclusions, demonstrating that there is a fair body of evidence of the effectiveness of fluoride varnish to arrest or reverse non-cavitated carious lesions in permanent teeth. Other fluoride products such as fluoride supplements (i.e. fluoride tablets or drops) are regarded as less effective methods of delivering fluoride because they rely entirely upon patient compliance. Their use is usually limited to high-risk categories of children, adults and, particularly, the elderly.[27]

*Application of chlorhexidine*

The effectiveness of chlorhexidine as an antimicrobial for preventing progression of non-cavitated caries has yet to be established. Current evidence is derived mainly from small studies evaluating the effects of different forms of chlorhexidine (varnish, gel or rinse) in combination with other concomitant preventive measures.[26,28]

*Pit and fissure sealants*

Pits and fissures are sealed to prevent caries development.[28] Evidence indicates that caries does not progress as long as the sealant remains in place.[29,30] Sealant applications may be suitable for both young children and older patients.[31] Materials that are currently used to seal a lesion include different types of composite resin and glass-ionomer cements. The resin-based sealants are divided into generations according to their mechanism for polymerisation and their content. The first generation sealants which were activated by ultraviolet light are no longer available and the fourth – most recently developed - generation sealants contain fluoride. The effectiveness of resin sealants for the prevention of caries in the permanent teeth of children and adolescents has been demonstrated by Ahovuo-Saloranta and colleagues[32] in a recent Cochrane systematic review. The review compared second, third, and four generation resin-based sealants or glass ionomer sealants with a control (no sealant) and compared one type of fissure sealant with another type. The focus of the review was on prevention and the children and adolescents included did not seem to present with obvious caries. The review concluded that resin-based sealants are effective in preventing caries of the occlusal surfaces of permanent molars. Reduction of caries ranged from 86% at 12 months to 57% at 48-54 months. Resin sealant retention was good across studies and sealants were retained completely in 79% and 92% of cases at 12 months. Sealant retention decreased with time and at 36 months ranged from 61% to 80%. Evidence on the effects of glass-ionomer-based sealants was less convincing.

*Treatment of cavitated pit and fissure caries and root caries*

For lesions that have progressed to the stage of cavity restorative interventions are often used to remove the decayed tissue and fill the cavity in order to aid plaque control. However, cavitated root lesions that are still accessible to cleaning need not always be filled because cleaning alone can arrest caries. There are a number of different materials that can be used to restore a tooth. These include composite resin, glass-ionomer cement, and amalgam. Amalgam is still the material of choice for large restoration of molar teeth. Root caries are usually restored with composite resin or glass-ionomer cement. According to the NHS Dental Review 2002-2003[33] in the quarter ending December 2002 the number of teeth filled was 4,896,951 and on average one tooth was filled for every two claims (55%). Overall, restorations showed a median survival interval to next restorative intervention of just over eight years. The main factors which were associated with different likelihoods of re-intervention were the age of the patient at the date of restoration, the tooth position, and the type/material of restoration.[33]

## 2.3 Description of new intervention

### 2.3.1 Rationale

The antimicrobial effects of ozone gas ($O_3$) have been known for many years. Direct application of ozone gas ($O_3$) to the coronal or root tooth surface is claimed to have a sterilizing effect. In particular ozone is claimed to stop the action of the acidogenic and aciduric micro-organisms responsible for the tooth decay. It is consequently alleged to be able to reverse, arrest, or slow down the progression of dental caries. It is also maintained that ozone is useful for reducing the microbial flora in cavitated lesions, before fillings are inserted.

### 2.3.2 HealOzone development

The ozone unit for dental use was initially developed by Curozone Inc. (Canada) and subsequently manufactured under licence and distributed by KaVo-Dental GmbH & Co. (Germany) under the name 'HealOzone'. Its use has been pioneered by Professor Edward Lynch and his team at Queen's University in Belfast, Northern Ireland and Barts and the London Queen Mary's School of Medicine and Dentistry in London, UK. HealOzone is a certified Medical Device (CE marked) for the management of occlusal pit and fissure caries, and root caries. According to the manufacturer, 294 HealOzone units (as at June 2004) are currently in use in dental practices in the UK and more than one million people have already received HealOzone treatment. The HealOzone technology has not yet received FDA approval in the USA.

The new version of HealOzone (Mark3) was launched in July 2004. According to the manufacturer previous models can be upgraded to the most recent technical functions.

### 2.3.3 HealOzone procedure

The 'HealOzone procedure' consists of a package, which includes the application of $O_3$, the use of re-mineralising agents, a 'patient kit', and information on oral hygiene. The HealOzone device comprises: an air filter, a vacuum pump, an ozone generator, a hand piece fitted with sealing silicone cup, and a flexible hose. The silicone cups are available in a range of 5 sizes from 3mm to 8mm in diameter. The HealOzone unit requires high voltage power to generate ozone from the air and to convert ozone back to oxygen when the process is completed. The air is exposed to high voltage current to generate ozone at concentration of 2,100 ppm ± 10% and passes through the instrument hose and hand piece. The flow of air into the system, the delivery ozone to the tooth, and the removal of ozone from the system after completion of treatment are achieved by a vacuum pump, which works at an adjustable flow rate of 615 $cm^3$/minute in order to maintain ozone concentration at 2,100 ppm.

The procedure usually takes between 20 and 120 seconds per tooth. Immediately after ozone application the tooth surface is treated with a re-mineralising solution (reductant) containing fluoride, calcium, zinc, phosphate, and xylitol dispensed from a 2 ml ampoule. The reductant is supplied in packs of 100 ampoules. Patients are also supplied with a 'patient kit', which consists of toothpaste, oral rinse and oral spray all containing fluoride, calcium, zinc, phosphate, and xylitol, and aims to enhance the re-mineralisation process. HealOzone application for the treatment of non-cavitated lesions is usually repeated at three and six months. There is no clear information on how delivery of ozone at the correct concentration can be ensured by the device.

## 2.4 Key questions

This review aims to answer the following questions:

1) For the management of pit and fissure caries, is the 'HealOzone procedure' more effective than the combination of oral hygiene, diet advice, chlorhexidine/fluoride varnish, and fissure sealant? If so, is it a cost-effective alternative?
2) For the management of non-cavitated root caries, is the 'HealOzone procedure' more clinically effective than the combination of oral hygiene, diet advice, and varnish? If so, is it cost-effective?
3) For the management of cavitated caries, how often, if at all, is 'HealOzone procedure' an alternative to fillings?
4) For the management of cavitated caries, does the application of ozone gas and of a re-mineralising solution to the cavity prior to restoration prolong the life of a filling? If so, is it cost-effective?

# 3. Effectiveness

## 3.1 Methods for reviewing effectiveness

### 3.1.1 Search strategy

Initial database searches were undertaken to identify relevant systematic reviews and other evidence-based reports. Several websites were also consulted to obtain background information. Full details of the main sources consulted are listed in Appendix 1.

**Table 5. Electronic databases searched**

| Database | Coverage |
|---|---|
| Medline/Embase/Medline Extra multifile search | Medline: 1966 - May Week 1 2004<br>Embase 1980 - Week 20 2004<br>Medline Extra 17th May 2004 |
| Science Citation Index | 1981 - 16th May 2004 |
| Biosis | 1985 - 12th May 2004 |
| Amed | 1985 - May 2004 |
| Cochrane Controlled Trials Register (CCTR) | Cochrane Library, Issue 2 2004 |
| National Research Register (NRR) | Issue 2, 2004 |
| Current Controlled Trials (CCT) | 18th May 2004 |
| Clinical Trials | 18th May 2004 |
| SCI Proceedings | 1991 - May 15th 2004 |
| Conference Papers Index | 1982 – May 2002 |
| ZETOC Conferences | 1993 - May 2004 |
| IADR Meetings abstracts | 2002 - 2004 |

Electronic searches were conducted to identify published and unpublished studies on the clinical and cost-effectiveness of ozone therapy for dental caries. The electronic databases searched are detailed in Table 5. Full details of the search strategies are documented in Appendix 1. It was anticipated that there was a small body of research available, therefore a sensitive search strategy for clinical effectiveness studies was undertaken to retrieve all information, which might be useful on ozone therapy for dental caries. Additional searches were carried out for economic data and these are detailed in Chapter 4. In addition, selected conferences proceedings that were not available electronically were handsearched. These were IADR conference proceedings for 1999-2001 and the annual ORCA Congresses 2000-2003. Research abstracts, published on industry and users websites (KaVo Dental Ltd., CurOzone USA Inc., HealOzone and DentalOzone see Appendix 1 for full details), were also identified. Reference lists of included studies were also checked for additional study reports.

### 3.1.2 Inclusion and exclusion criteria

All citations identified by the search strategy were assessed for relevance by two reviewers. Copies of the full-text, published papers of those considered to be relevant were then obtained. It was decided that studies reported in languages other than English would be identified but not included in the review.

For clinical effectiveness assessment, included studies were randomised controlled trials (RCT's) of ozone treatment (HealOzone) versus at least one comparator (nil, placebo, or active treatment). Data from studies other than randomised trials were collected but not included in the review. The outcome measures were required to be measures of clinical effectiveness (e.g. reversal/progression of caries). Only in-vivo studies involving human subjects were deemed to be suitable for inclusion whilst studies reporting in-vitro results were excluded. Studies were also excluded if their follow-up was less than six months or did not report clinically relevant outcome measures.

### 3.1.3 Data extraction strategy

A data abstraction form was designed (Appendix 2) to collect details from each individual study. This included the type of study design, number of participants and their characteristics, intervention characteristics, caries information including location and severity of lesion and patient outcomes such as reversal of caries, progression of caries, and any reported adverse events.

In particular, the outcomes sought for the included studies were as follows:

a) Non-cavitated caries

- Reversal of caries;
- Progression of caries;
- Utilisation of dental services (e.g. visits to dental care units; duration of dental treatment);
- Adverse events;
- Patient centred measures (e.g. patient satisfaction and preference, relief of pain/discomfort);
- Quality of life.

b) Cavitated caries

- Time to restorative interventions;
- Need for further restorative interventions and length of time between restorations;
- Symptoms of pulpal pathology.

Inclusion criteria were assessed independently by two reviewers. Any disagreements were resolved by consensus or referred to a third reviewer. Reviewers were not blinded to the names of study authors, institutions, or publications.

### 3.1.4 Quality assessment strategy

Two reviewers assessed the methodological quality of all included studies and any disagreements were resolved by discussion. The quality assessment of randomised controlled trials was formally assessed using a published checklist modified by the reviewers for the purpose of this review.[34] The checklist consists of 12 questions, which focus on the following methodological aspects: method of randomisation, unit of randomisation, concealment of allocation, comparability of groups at baseline, blinding procedures, number of withdrawals/dropouts, and completeness of assessment at follow-up.

For each question a ‘Yes’, ‘No’ or ‘Unclear’ answer is required. The quality assessment checklist is presented in Appendix 3.

## 3.2 Results

### 3.2.1 Quantity and quality of research available

After removing duplicates a total of 331 reports were identified (78% (257) were abstracts and 22% (74) were full-text reports). 85 reports (seven full-text papers and 78 abstracts) were selected for full assessment, of which 21 (three full-text papers and 18 abstracts) met the pre-defined criteria for inclusion in the review. In additional two reports, both PhD theses, were identified from reference lists. All 23 identified reports were written in English.

#### 3.2.1.1 Number of studies identified

In total five studies reported in five full-text papers and 13 abstracts, and five studies reported only as abstracts met the inclusion criteria for studies of clinical effectiveness. In case of multiple publications the report with the longest follow-up time and/or largest sample size was chosen as the main source of information.

**Table 6. Number of screened and selected reports according to database searched**

| Database Searched | Number screened | Number selected | Included studies |
|---|---|---|---|
| Medline/Embase/Medline Extra | 46 | 4 | 1 |
| SCI | 38 | 7 | 1 |
| Biosis | 38 | 1 | 0 |
| CENTRAL | 8 | 1 | 0 |
| IADR abstracts | 175 | 43 | 12 |
| Handsearch | | 14 | 2 |
| Websites | | 15 | 5 |
| Other databases | 26 | 0 | 0 |
| Total | 331 | 85 | 21 |

#### 3.2.1.2 Number and type of studies excluded

After identifying duplicates, a number of studies were excluded as they did not meet the inclusion criteria. The main reasons for exclusion together with the corresponding number of studies excluded are listed in Table 7.

**Table 7. Number of studies and reasons for exclusion**

| Reason for exclusion | Number of studies/abstracts |
|---|---|
| Follow-up less than six months | 17 |
| No HealOzone treatment - other experiments involving ozone | 14 |
| No measures of clinical effectiveness | 6 |
| HealOzone used on extracted teeth (*in-vitro* studies) | 4 |
| Evaluation of diagnostic tests for detection of dental caries – no clinical effectiveness measures | 5 |
| Time studies no clinical effectiveness measures | 3 |
| Discussion paper - no comparative information on clinical effectiveness | 1 |
| Costs no clinical effectiveness measures | 1 |
| No random allocation | 2 |
| Patients Attitudes not effectiveness | 7 |
| Studies not involving ozone | 4 |

#### 3.2.1.3 Number and type of studies included

The five full-text studies consisted of two RCTs assessing the use of HealOzone for the management of primary root caries - one published trial by Holmes[35] and one unpublished trial by Baysan and Lynch,[36] and two PhD theses assessing the use of HealOzone for the management of pit and fissure caries, one by Abu-Naba'a[37] reporting two unpublished trials and one by Abu-Salem[38] reporting one unpublished trial.

### *Root caries studies*

**Holmes** published randomised trial[35,39,40] of management of primary non-cavitated root caries consisted of two treatment groups: ozone plus reductant plus patient care kit versus air treatment plus reductant plus patient care kit. This study was set in a general dental practice.

**Baysan and Lynch** unpublished randomised trial on cavitated and non-cavitated root caries[36,41-44] consisted of four treatment groups: ozone plus reductant versus reductant only, and ozone plus sealant versus sealant only. It recruited patients who attended the School of Dentistry in Belfast.

### *Pit and fissure caries studies*

**Abu-Naba'a** PhD thesis[37] consists of two randomised studies: a main study (Abu-Naba'a 2003) and a pilot study (Abu-Naba'a pilot study 2003), which are considered separately as they do not include the same patient population. The main study assessed exclusively non-cavitated occlusal lesions, whilst the pilot study included cavitated occlusal lesions. Patients were recruited from the School of Dentistry in Belfast for both the main and pilot studies.

Abu-Naba'a main study[37,45-50] consisted of four treatment groups: ozone plus reductant versus air treatment plus reductant, and ozone plus reductant plus sealant versus reductant plus sealant only. It involved 90 patients with 254 lesions.

The Abu-Naba'a pilot study[37,51,52] consisted of two treatment groups: ozone plus reductant versus reductant only. It involved eight patients with 38 lesions.

The **Abu-Salem** study[38] consisted of two treatment groups: HealOzone plus reductant versus reductant only. It recruited 21 patients with 74 lesions, from Belfast primary schools.

Of the five studies published only as abstracts, four assessed the effects of HealOzone for the management of occlusal pit and fissure carious lesions (Holmes and Lynch, 2004,[53] Holmes 2003,[54] Hamid 2003,[55] Megighian and Bertolini[56]) and one assessed the effects of HealOzone on primary root carious lesions.[57]

### 3.2.1.4 Tabulation of quality of studies, characteristics of studies and evidence rating

The characteristics of the five full-text studies (type and number of participants and carious lesions, details of study design, inclusion criteria, characteristics of intervention, and main results) are shown in Appendix 4.

Method of randomisation was reported in three studies.[35,37,38] Concealment of allocation was not specified in any of the included studies. One study was described as double-blind[35] and another study stated that outcome assessment was undertaken by a blinded examiner.[38] In particular the double-blind study by Holmes was reported to involve three dentists: the first dentist performed the initial assessment of primary root carious lesions; the second randomised the lesions to treatment groups; the first then treated and assessed the result without knowing which were given ozone and which air, using a modified HealOzone machine; the third dentist independently assessed lesions in 15 patients. The practicality of the entire process is however doubtful. Holmes is the only author of the study whilst the other assessors are neither listed as authors nor acknowledged in the paper.

It was unclear whether blinding procedures were secured in the remaining three included studies. The total number of people in the studies was 287, with a total of 768 carious lesions. Across the studies, the ages of the participant groups ranged from 7 years to 82 years. Only three studies provided information on the gender of the participants.[36-38] The length of follow-up ranged from 6 months to 21 months.

Each study involved either two or four intervention groups. Ozone was always used in combination with other active interventions (i.e. ozone plus reductant, ozone plus reductant plus patient care kit, ozone plus sealant, ozone plus reductant plus sealant) and compared to the same intervention without ozone or to a sham procedure (air treatment). The dosage of ozone treatment varied between studies. In the Baysan and Lynch study,[36] the Abu-Salem study,[38] and the Abu-Naba'a main study[37] ozone was administered for 10 seconds, whilst in the Holmes study[35] and the Abu-Naba'a pilot study[37] ozone was administered for 40 seconds. In all studies ozone applications were repeated at some point before the final follow-up time point. None of the included studies provided information on the model/version of the HealOzone device.

The main outcome measure was reversal of caries. This included the proportion of carious lesions becoming hard and - for some of the included studies - the proportion of lesions reversing from 'leathery' to 'leathery approaching hard texture' but not necessarily hardening. The proportion of lesions that deteriorated from leathery to soft was also recorded although not consistently. Where appropriate the proportion of intact sealants was documented. Changes in the ECM and DIAGNOdent readings were also reported in the identified studies, but not considered in this review, due to the unreliability of their measurements (high false positive rates) and poor correlation with clinical outcomes.[58]

In the majority of the included studies, data analysis was conducted at the level of the lesion. Holmes used chi-squared statistics, but without specifying whether this was suitable for related samples, i.e. McNemar chi-squared test. In the Baysan and Lynch study no information was provided on the choice of the statistical test used. In both Abu-Naba'a studies the unit of analysis was tooth-pair, but it was unclear whether the occurrence of multiple pairs of lesions per mouth was taken into account. Abu-Salem used a mixed-effects analysis of variance (ANOVA) with random effects for patient and teeth within patient, and fixed effects for group and time of treatment.

The characteristics of the five studies published as abstracts are shown in Appendix 5.

#### 3.2.1.5 Tabulation of results and assessment of effectiveness

The clinical effectiveness results are presented according to type of carious lesions (root caries results are presented separately from occlusal caries results). Within this categorisation studies results are presented according to:

- type of outcome measures;
- type of publication (results of full-text studies are presented separately from results of studies published as conference proceedings);
- type of dentition (treatment results of primary teeth are presented separately from treatment results of permanent teeth).

It was planned to undertake further statistical analyses of the data reported in the full-text studies and when appropriate to combine them quantitatively. However, due to the limited raw data provided, this proved unfeasible. The p-values of statistical analyses in the results section are those originally quoted by the studies' authors. However, as the data were not analysed as 'paired data' on a patient basis, their validity and reliability are open to question.

#### 3.2.1.5.1 Primary Root Carious Lesions (PRCLs)

Two full-text studies by Holmes[35] and Baysan and Lynch[36] and one abstract by Lynch and colleagues[57] assessed the use of ozone for the management of primary non-cavitated root carious lesions. The Baysan and Lynch study also included the assessment of a non-specified number of cavitated root lesions. In the Holmes studies the clinical criteria of 'soft, leathery, and hard' were adopted for the assessment of carious lesions whilst in the Baysan and Lynch study lesions were classified according to a 5 points severity index as follows:

- 0 All 'hard' lesions
- 1 'Leathery' lesions considered to be small, easily cleansable and approaching a 'hard' texture
- 2 'Leathery' lesions judged to be shallow and where the surface of the exposed sound dentine could be easily maintained plaque-free
- 3 'Leathery' lesions judged to be in surfaces, which were difficult to maintain plaque-free and large, cavitated 'leathery' lesions where pulpal integrity was judged to be at risk
- 4 All 'soft' lesions

No information was provided on the validity and reproducibility of the above severity index as well as on how lesions were clinically identified as 'leathery' 'soft' or 'hard'. In particular the distinction between three degrees of 'leathery' seemed rather artificial.

*Change in clinical severity*

Table 8 shows for each of the included studies the proportions of carious lesions that according to the studies' authors reversed (became hard), improved (became less severe), or deteriorated in both the ozone-treated group and the control group. The Holmes study[35] reported that 100% of ozone treated PRCLs had reversed by 18 months, whilst 37% of PRCLs in the control group had worsened from leathery to soft and 1% had reversed. However, comparisons of results at different follow-up points show some inconsistencies in the way data were reported (Table 9). In particular the results at 21 months (published as an abstract) showed an increase in the number of control lesions that stabilised (from 54/87 at 18 months to 65/81 at 21 months) and a subsequent decrease in the number of control lesions that had become soft (from 32/87 at 18 months to 10/81 at 21 months) indicating an improvement over time in lesions receiving treatment other than ozone. No comments on these changes were provided by the authors.

In the Baysan and Lynch study,[36] 47% of the ozone-treated lesions had arrested by 12 months whilst none had become hard in the control group ($p<0.001$) and 52% had reversed from index 2 (leathery) to index 1 (leathery approaching hard texture) in the ozone group compared with 12% of lesions in the control group ($p<0.001$). So if we combine the "approaching hard" (from index 2 to 1) and "hard" lesions (from index 2 to 0), 99% of lesions improved, as in the Holmes study. This study included both cavitated and non-cavitated root lesions but results were not clearly presented according to the type of lesions and it is unclear how many cavitated and non-cavitated lesions were assessed in each intervention group. Only one figure in the paper presented results for both types of lesions in the ozone group: the percentage of cavitated lesions that had reversed (become hard) decreased from 9.1% at one month to 1.4% at nine months indicating an increase/progression in the severity of cavitated root lesions treated with ozone. No corresponding data were given for the control group and no comments on reversal/progression of cavitated lesions were provided in the text of the paper.

**Table 8. Results of root carious lesions**

| | Ozone final follow-up No. (%) | Control final follow-up No. (%) |
|---|---|---|
| **PRCLs becoming hard** | | |
| Baysan and Lynch 2004[36] (12 months)[a] | NR (47) | NR (0) |
| Holmes 2003[35] (18 months)[b] | 87/87 (100) | 1/87 (1) |
| **PRCLs becoming less severe (from index 2 to 1)** | | |
| Baysan and Lynch 2004 [36] (12 months)[a] | NR (52) | NR (12) |
| **PRCLs becoming soft** | | |
| Holmes 2003[35] (18 months)[b] | 0/87 (0) | 32/87 (37) |

NR: not reported (the denominator was not clearly reported in the study so the number of caries cannot be calculated, hence only percentages given)

[a]Baysan and Lynch: non-cavitated and cavitated primary root carious lesions

[b]Holmes : non-cavitated primary root carious lesions

In addition, the Lynch, Johnson, and Johnson abstract[57] indicated that 80% (48/60) of non-cavitated primary root carious lesions treated with ozone reversed from severity index 4 to 3 whilst none of the soft lesions in the control group significantly changed, and that 94% (189/200) of leathery lesions became hard and arrested in the ozone group whilst those in the control group did not significantly change.

**Table 9. Results of the Holmes study at each recall visit**

| | Ozone at follow-up No. (%) | Control at follow-up No. (%) |
|---|---|---|
| **PRCLs becoming hard** | | |
| 12 month | 85/87 (98) | 1/87 (1) |
| 18 month | 87/87 (100) | 1/87 (1) |
| 21 month | 81/81 (100) | 6/81 (8) |
| **PRCLs remaining leathery** | | |
| 12 month | 2/87 (2) | 65/87 (75) |
| 18 month | 0/87 (0) | 54/87 (62) |
| 21 month | 0/81 (0) | 65/81 (80) |
| **PRCLs becoming soft** | | |
| 12 month | 0/87 (0) | 21/87 (24) |
| 18 month | 0/87 (0) | 32/87 (37) |
| 21 month | 0/81 (0) | 10/81 (12) |

*Marginal adaptation of the root sealant*

The Baysan and Lynch study[36] also assessed the effects of ozone with or without a fissure sealant using the modified US Public Health Service (USPHS) criteria. In the ozone plus sealant group 61% of sealants were retained compared to 42% in the sealant only group ($p<0.05$) at 12 months.

It is worth noticing that both groups had the same other active interventions such as reductant, patient care kits, sealants. The very low improvement rates in the control groups are therefore surprising.

*Summary Root Carious Lesions*

The two full-text studies assessing the use of ozone for root carious lesions both report very high success rates with ozone, and very low improvement rates in the controls.

Fissure sealants after application of ozone for the preventive treatment of non-cavitated root lesions are more likely to remain intact (61% versus 42%, $p<0.05$).

### 3.2.1.5.2 Pit and Fissure Carious Lesions

The three remaining studies - Abu-Naba'a 2003 main study,[37] Abu-Naba'a 2003 pilot study,[37] and Abu-Salem, 2004 study[38] - assessed the effects of ozone for pit and fissure carious lesions. Both Abu-Naba'a studies involved patients aged over 12 years with primary lesions in the permanent posterior teeth, whilst the Abu-Salem study involved children seven to nine years old with carious lesions in the posterior primary teeth. The Abu-Naba'a main study and the Abu-Salem study assessed non-cavitated lesions, whilst the Abu-Naba'a pilot study included lesions with cavitation.

*Change in clinical severity – permanent dentition*

*Full-text studies' results*

Tables 10 and 11 illustrate the results of the Abu-Naba'a main study.[37] Clinical severity of non-cavitated pit and fissure lesions was assessed using the criteria described by Ekstrand and colleagues (0 - least severe, 1, 2, 3, 4 - most severe).[9] The change in severity score is calculated as the score at follow-up minus the score at baseline. Thus a negative change indicates an improvement whilst a positive change implies a worsening of lesion severity. The mean change from baseline in clinical severity score at 12 months was not significantly different (p = 0.112) between the two intervention groups - ozone (10 seconds) plus reductant group versus reductant only group (Table 10).

**Table 10. Mean change in clinical severity score of pit/fissure lesions from baseline (Abu-Naba'a main study)**

| Change in clinical severity score | Ozone group (n = 106) | Control group (n = 106) | P value |
|---|---|---|---|
| Mean change from baseline | 0.283 | 0.443 | P = 0.112 |
| Standard deviation | 0.64 | 0.74 | |
| Standard error | 0.06 | 0.07 | |

It was also reported that a greater proportion of ozone-treated lesions improved or stabilised compared to control lesions at all recalls (Table 11). However, statistical analyses of these data were not provided. The relationship between clinical severity score and the need for future fillings was not explained.

No significant difference in the clinical severity score was found between the ozone and control groups in the Abu-Naba'a main study. The reported proportions of lesions improved, stabilised, and deteriorated appeared similar between groups but no statistical analyses were undertaken and the clinical relevance of these findings is not explained in terms of fillings avoided.

**Table 11. Percentage of pit/fissure lesions that improved, remained stable, or increased in clinical severity at each recall visit (Abu-Naba'a main study)**

| Month(s) of follow-up | Treatment Group | Decreased severity (improvement) | Stable | Increased severity (worsening) |
|---|---|---|---|---|
| 1 | Ozone | 11.4% | 74.6% | 14.0% |
| | Control | 5.3% | 81.6% | 13.2% |
| 3 | Ozone | 17.7% | 63.9% | 18.5% |
| | Control | 8.4% | 73.1% | 17.6% |
| 6 | Ozone | 10.8% | 55.9% | 33.3% |
| | Control | 5.9% | 59.8% | 34.3% |
| 9 | Ozone | 7.8% | 57.8% | 34.5% |
| | Control | 6.9% | 56.0% | 37.1% |
| 12 | Ozone | 7.4% | 56.5% | 36.1% |
| | Control | 5.6% | 48.6% | 45.8% |

*Abu-Naba'a Pilot Study*

In the Abu-Naba'a pilot study,[37] 17 lesions (with cavitation) were treated with ozone plus reductant and 17 reserved as controls (reductant only) in eight patients. Outcomes were measured using the Ekstrand and colleagues' clinical index[9] as well as the following clinical indices: hardness index (hard, leathery, soft); visual index (sound, arrested, active); cavitation score (1 = no cavitation, 2 = micro cavitation, 3 = frank cavitation); colour index (normal, yellow, light brown, grey, dark brown, black); frosted enamel measure (mm); stained enamel measure (mm), perceived treatment need index (e.g. requiring no intervention, requiring preventive resin restoration, requiring drilling and filling). Thirteen lesions in the treatment group and 12 lesions in the control group were assessed at six months. Lesions treated with ozone showed a significant reduction in the hardness and visual indices (Table 12). No significant differences between groups were found for all other indices and for the Ekstrand clinical index (p>0.05).

**Table 12. Number of pit/fissure lesions showing a reduction in the clinical indices at six months (Abu-Naba'a pilot study)**

| | Hardness index[a] | Visual index[b] | Cavitation score[c] | Colour index Darker[d] | Colour index Lighter[e] | Perceived treatment need[f] |
|---|---|---|---|---|---|---|
| Treatment | 11/13 (84.6%) | 8/13 (61.5%) | 6/13 (46.2%) | 3/13 (23.1%) | 2/13 (15.4%) | 12/13 (92%) |
| Control | 4/12 (33.3%) | 1/12 (8.3%) | 5/12 (41.7%) | 2/12 (16.7%) | 2/13 (50%) | 9/12 (75%) |
| P value | p<0.05 | p<0.05 | NS | p=0.084 (NS) | | p=0.16 (NS) |

[a] The proportion of lesions becoming hard
[b] The proportion of lesions with increasing score
c The proportion of lesions with reduction in cavity score
[d] The proportion of darker lesions
[e] The proportion of lighter lesions
f The proportion of lesions with a reduced treatment need

This study was only a pilot study, which did not add much to the results of Abu-Naba'a main study.

*Abstracts' results*

Abstracts gave little detail of studies, their methodology could not be easily assessed, and therefore their findings must be interpreted with caution. We included them here for completeness and as a guide to emerging research.

Three abstracts compared pit and fissure lesions receiving ozone (at different concentrations) with pit and fissure lesions receiving no-ozone treatment.[54-56] Their results are presented in Table 13. The proportion of lesions reported as clinically reversed, the extent of which was not specified, ranged from 86.6% to 100% in the ozone-treated groups. All studies reported that no significant clinical changes were observed in the control groups but no numerical information was given.

**Table 13. Reversal of pit/fissure caries – findings from abstracts**

| | Ozone at follow-up<br>No. (%) | Control at follow-up<br>No. (%) |
|---|---|---|
| **Clinical reversal of pit and fissure caries** | | |
| **Holmes 2003**[54]<br>(12 months) | 1918/1937 (99) | 0/427 (0) |
| **Hamid 2003**[55]<br>(6 months) | 80/92 (86.6) | 0/92 (0) |
| **Megighian and Bertolini, 2004**[56]<br>(6 months) | 220/220 (100) | 0/80 (0) |

Another abstract[53] compared the use of ozone versus conventional treatment in 35 patients - each with two occlusal lesions extending radiographically 2-4mm into dentine. The authors defined the occlusal lesions as non-cavitated, but lesions 2-4mm into dentine on radiographs are likely to have small cavities that trap plaque and are likely to progress unless cleaned thoroughly. The ozone-treated lesions received ozone for 40 seconds and application of a glass-ionomer preventive sealing, which was subsequently replaced with a posterior composite at three months. The control lesions received conventional drilling and filling (posterior composite). All the ozone-treated lesions were reported to have reversed at three months. Six complaints (17.1%) of post-operative sensitivity were reported after conventional drilling and filling at six months compared to none after ozone treatment ($p<0.05$). Post-operative sensitivity is, however, a measure commonly used to assess large carious lesions and it is questionable whether should be used for early carious lesions. Moreover, complaints of post-operative sensitivity after occlusal restorations are rare.

*Clinical reversal of caries – primary dentition*

One full-text study assessed the use of ozone for the treatment of non-cavitated primary posterior teeth in children 7-9 years old.[38] Occlusal lesions were assigned to receive ozone for 10 seconds followed by a reductant or a reductant only. The proportion of lesions that improved, remained stable or deteriorated in each intervention group was not provided and the clinical severity findings were only presented graphically. The graph showed a steady increase in the mean change from baseline clinical severity scores for the control group, compared with an initial slight decrease and a subsequent levelling in the ozone group at 12 months. The overall change in the clinical severity scores [9] were analysed using a mixed-effects ANOVA. This analysis assumed that patients and teeth within patients had a random effect, while group and time of treatment had a fixed effect. There was overall little reduction in clinical severity scores in the ozone-treated group, whilst an overall increase was observed in the control group. There was a statistically significant effect of treatment upon clinical severity scores with time ($p<0.01$).

*Sealant Retention*

Abu-Naba'a main study[37] assessed also the use of ozone for 10 seconds with and without a fissure sealant. No sealants were reported to be lost in either the ozone plus sealant group or the sealant only group. The percentage of partial loss in the ozone plus sealant group at 12 months was 32.7%, and in the sealant only group was 29.8% with no significant differences between groups (this indicates similar rates of re-interventions between groups for repairing partial sealant loss).

## 3.3 Discussion of results and conclusions of the evidence for and against the intervention

Only a limited number of randomised controlled studies (five full-text reports and five studies reported as abstracts) were available for assessing the effects of ozone for the management of root carious lesions and pit and fissure carious lesions. Of these only one was published in a refereed journal, but lacked some study details, whilst the remaining studies were derived from PhD theses, unpublished reports, or conference proceedings. All full-text studies with the exception of the Holmes study were conducted by the same research team who developed the procedure, led by Professor Lynch of Queen's University, but Holmes was at one time part of the same group, having done his PhD in Belfast. The methodological quality varied across studies and information on method of randomisation, concealment of allocation, blinding procedures, and statistical methods was lacking in many of them. Therefore interpretation of studies results was not straightforward. A quantitative synthesis of results was not feasible due to the differences amongst studies of intervention, dosage of ozone, and outcome measures.

There were some concerns over the appropriateness of the methods of analysis adopted by study investigators. All studies in this review were of a hierarchical structure, although not necessarily treated so for analysis. Specific types of analysis are required when data have a hierarchical structure. The hierarchy occurs as smaller units, such as lesions or teeth, are clustered together within a larger unit, the patient. In most studies included in this review, the statistical analysis has been carried out at the lesion level. However, two lesions within one patient are not strictly independent, so analysis at the lesion level is inappropriate. A more suitable statistical analysis takes into account the hierarchical clustering of lesions within a subject.[59]

In the simple case of two lesions per person, one receiving control and one receiving the ozone treatment, paired data are produced. In this case, the appropriate paired analysis would be a McNemar chi-squared test for dichotomous data, Wilcoxon signed rank test for ordinal data and a paired t-test for continuous data. The choice of statistical test that ignores the pairing of the data is more conservative and may fail to detect important difference found by paired analysis.[59] In the case of more than two lesions per subject, multilevel modelling procedures would need to be employed.

Baysan and Lynch[36] stated that statistical tests were used, but they did not specify which particular tests. Holmes used chi-square tests, but does not specify whether they were McNemar chi-squared tests. Abu-Naba[37] (main and pilot studies) recognised the fact that there were pairs of teeth. However, in some cases there were multiple pairs of teeth per person and it is not clear whether this was taken into account. Abu-Salem[38] used analysis of variance for a mixed effect model. This type of analysis is hierarchical in nature, with one component for the patients and one for the tooth within patient. However, as not enough information was provided by the author it was not possible to determine whether the statistical analysis was conducted appropriately.

For primary non-cavitated root caries both the Holmes study[35] and the Baysan and Lynch study[36] reported high success rates for ozone-treated lesions compared to control lesions. However, the lack of reversal of caries amongst controls receiving conventional treatment (reductant) known to be efficacious is puzzling.

Cavitated root lesions did not seem to benefit from ozone application showing indeed a negative effect over time.

Treatment results of pit and fissure caries of permanent teeth were not consistent across studies. The Abu-Naba' main did not show any significant differences between non-cavitated lesions treated with or without ozone. Similarly Abu-Naba' pilot study[37] - which included lesions with cavitation - did not demonstrate any significant effect of ozone apart from an improvement in the hardness and visual clinical indices. On the contrary, results from conference proceedings (methodologically less reliable) provided very high success rates (from 86.6% to 100% of reversal of caries).

Data on the use of ozone for the treatment of primary teeth were available from only one study which suggested an overall reduction in clinical severity scores for non-cavitated occlusal lesions in primary molars treated with ozone ($p<0.01$).[38]

The adjunct of ozone to a fissure sealant produced a better sealant retention in root carious lesions (61% of sealant retention versus 42%, $p<0.05$)[36] but not in pit and fissure carious lesions (32.7% versus 29.8%).[37]

On the whole, and despite the differences reported in some studies (for example Holmes), there are as yet insufficient published full-text studies (only one refereed journal article) to provide convincing evidence on the effectiveness of ozone for the management of caries.

This review was done independently of the Cochrane systematic review on ozone therapy for the treatment of dental caries,[60] which concluded that at present there is not reliable evidence on the effectiveness of ozone applications to arrest or reverse the decay process. The present version of the Cochrane review does not include the Holmes (2003) and Abu-Salem (2004) studies.

### 3.3.1 Important sub-group differences

There are not enough data on which to assess the effects of ozone on cavitated caries in the permanent dentition (both occlusal caries and root caries), or on non-cavitated occlusal caries in the deciduous dentition (only one study involved children with primary teeth[38]). No data are available on cavitated occlusal caries in deciduous teeth, secondary caries, or high-risk patient categories.

### 3.3.2 Adverse effects of intervention

None of the studies reported any adverse events in the intervention group.

# 4. Systematic Review of Economic Evaluations

## 4.1 Methods

### 4.1.1 Search Strategies

In addition to the electronic and hand searches detailed in Chapter 3, a search of the NHS Economic Evaluation Database (NHS EED) and the Health Management Information Consortium was undertaken for economic evaluations of ozone for dental caries. Details of the searches are provided in Appendix 1.

Studies that reported both costs and outcomes of HealOzone compared with any of the comparators were sought. The manufacturer's submission to NICE was also scanned for relevant economic evidence.

### 4.1.2 Inclusion and exclusion criteria

To be included, studies needed to compare HealOzone to any of the existing comparators in terms of their costs and effectiveness. Studies reported in languages other than English were identified from their abstracts but would not be included in the review unless a structured abstract were available from the NHS EED. A single economist assessed all abstracts for relevance. Full papers were then obtained for all studies that appeared potentially relevant and were formally assessed for relevance.

### 4.1.3 Data abstraction

The following data were extracted for each included study.

1. Study characteristics

- Research question;
- Study design;
- Comparison;
- Setting;
- Basis of costing.

2. Characteristics of the study population or of the populations that formed the basis of data used in a modelling exercise

- Numbers receiving or randomised to each intervention;
- Dates to which data on effectiveness and costs related.

3. Duration of follow-up for both effectiveness and costs

4. Results

- Summary of effectiveness and costs (point estimate and, if reported, range or standard deviation (sd));
- Summary of cost-effectiveness/utility (point estimate and, if reported, range or standard deviation (sd));
- Sensitivity analysis.

5. Conclusions as reported by the authors of the study

### 4.1.4 Quality assessment

A single economist assessed the quality of included studies using a published checklist.[61] The questions were set out on a standard form generated before the review.

### 4.1.5 Data synthesis

Data from included studies were assessed and summarised by a single economist, and interpreted alongside the results of the systematic review of effectiveness so that conclusions could be drawn on the relative efficiency of HealOzone compared with the comparator treatment.

## 4.2 Results

The search revealed no published economic evaluations of HealOzone. One published trial was found which compared the costs and effectiveness of the management of primary root caries with HealOzone.[35] However, the study did not meet all of the methodological criteria to be classified as an economic evaluation and was therefore not reviewed further. Two abstracts concerning studies of the costs and benefits of HealOzone for dental caries were found, but did not provide sufficient details of study design or data for the purpose of this review.[62,63] However, the industry submission from KaVo Dental Ltd. (KaVo Dental Ltd., August 2004) provided an economic evaluation. The remainder of this section provides a summary and critique of that submission.

The unpublished industry submission from KaVo Dental Ltd., UK (KaVo) included an economic model of HealOzone compared with current treatment for non-cavitated pit and fissure caries, cavitated pit and fissure caries, and root caries. Both a base case and a probabilistic analysis were included. The submission comprised both a text document and supporting Excel spreadsheets.

Table 14 provides a summarised assessment of the KaVo industry submission based on the 10 critical appraisal components.[61]

**Table 14. Quality assessment of the economic evaluation presented in the industry submission by KaVo**

| Quality component | Assessment and comments |
|---|---|
| 1. Was a well-defined question posed in an answerable form? | Yes |
| 2. Was a comprehensive description of the competing alternatives given (i.e., can you tell who did what, to whom, where, and how often)? | Yes. Current treatments were defined as:<br>NC-PFC: sealants<br>C-PFC: glass ionomer, composite resin and amalgam restoration<br>RC: glass ionomer and composite resin restoration |
| 3. Was there evidence that the programmes' effectiveness had been established? | Limited due to short follow-up of included studies and inability to compare/combine results from more than one study due to differences in study characteristics. None of the studies used specifically considered cavitated PFC, although the model does include such effectiveness data based on assumptions outlined in the following critique |
| 4. Were all the important and relevant costs and consequences for each alternative identified? | Yes |
| 5. Were costs and consequences measured accurately in appropriate physical units? | Yes |
| 6. Were costs and consequences valued credibly | Not always – see critique of QALY estimation |
| 7. Were costs and consequences adjusted for differential timing? | Yes – a discount rate of 3.5% was used |
| 8. Was an incremental analysis of costs and consequences of alternatives performed? | Yes – see critique |
| 9. Was allowance made for uncertainty in the estimates of costs and consequences? | Yes |
| 10. Did the presentation and discussion of study results include all issues of concern to users? | Yes |

## 4.3 Review of industry submission

The first part of this section provides a summary of the methods and results from the economic evaluation of HealOzone reported in the industry submission. This is followed by a critical review of the evaluation.

*Summary of the industry submission*

The submission by KaVo included a cost-effectiveness analysis over a five-year time horizon of HealOzone treatment versus current management for non-cavitated pit and fissure caries, cavitated pit and fissure caries, and cavitated root caries. The current management treatments were defined as follows:

- Non-cavitated pit and fissure caries: sealants;
- Cavitated pit and fissure caries: glass ionomer, composite resin, and amalgam fillings;
- Root caries: glass ionomer and composite resin restorations.

These comparators were identified from the expert opinion of four dentists. *The submission does not consider preventive treatments such as oral hygiene/advice on diet along with surface applications of fluoride and sealants as a comparator*. The intervention with HealOzone is defined as an initial treatment with HealOzone followed by 12 weeks of treatment with mineralising toothpaste, oral rinse and spray, with the possible addition of restorative treatments. An opinion survey of 243 dentists practising HealOzone treatment was used to estimate the proportion of teeth, which would require additional restorative treatment at the same time as the HealOzone application or at any time subsequently but only 48 provided usable responses.

Effectiveness data were obtained from a review of published evidence for HealOzone and the current management of dental caries. Clinical outcomes included caries progression and reversal.

Costs included that of comparators plus costs of re-restorations avoided. The costs of each current treatment comparator were estimated from published data for the treatments defined above. All cost data was estimated from the perspective of the NHS and was presented in UK pounds sterling (£) at 2003 prices. Their method was to translate the treatments into relevant treatment codes listed in the Statement of Dental Remuneration (SDR codes)[64] and then to use General Dental Services (GDS)[65] data to identify the total annual numbers of such treatments. These data are presented separately for patients aged less than 18 years and those aged 18 years and over. The same source (GDS) gives annual total treatment costs which, when combined with annual treatment numbers gave a unit cost per treatment item. These figures were adjusted to take account of SDR codes relating to more than one tooth and more than one type of caries. The unit cost estimates do not appear to differentiate between primary restorations on virgin tooth surfaces and secondary restorations, the latter being outwith the scope of the study since these would be unsuitable for treatment with HealOzone. Finally these unit cost estimates were adjusted to reflect the fact that patients under 18 years receive free NHS dental care and those aged 18 years and over pay 80% of their NHS dental fees, unless they are eligible for free treatment. It was assumed that the dental practice and not the NHS would fund the capital cost and running cost of the actual HealOzone device.

Using these unit cost estimates the industry model assesses the annual cost to the NHS for each comparator. To estimate the annual cost to the NHS of the HealOzone comparator the industry submission carried out a survey of dentists to estimate the proportion of teeth currently treated for either non-cavitated pit and fissure caries, cavitated pit and fissure caries or root caries, which would be suitable for treatment with HealOzone. This survey also asked dentists to estimate the proportion of HealOzone treated teeth which would require some restorative treatment either at the time of HealOzone treatment or sometime afterwards. These restorative treatments were defined similarly to current management treatments for each caries type.

The unit cost of HealOzone treatment was based on the cost of patient consumables and dentists' time (in practice a dentist is remunerated by a fee per item of service as listed in the SDR and these fees are intended to reflect the costs incurred by dental practices). Using the results of a questionnaire survey of dentists who use HealOzone in their own practice the estimated unit cost for a course of HealOzone treatment was then adjusted to reflect the estimated percentages of HealOzone treated teeth, which would require additional restorative treatment. On the basis of responses to this questionnaire an additional cost of restoration (using current management in addition to HealOzone) was applied to 44% of non-cavitated pit and fissure caries, 84% of cavitated pit and fissure caries and 47% of root caries.

The cost to the NHS of HealOzone also took into account the proportion of treatment fees paid by the NHS rather than patients as described above for current treatment costs. The unit cost for a course of HealOzone procedure was based on an assumption of more than one HealOzone application per course of treatment. The model used a mean of 2.5 HealOzone applications per course of treatment (range 1 to 4). This was based on data from KaVo Dental Ltd.

An additional cost was added to reflect the weighted average cost per tooth year of re-restorations avoided. This was based on data from a study that reported the average cost per tooth year of restoration in teeth previously filled with amalgam or composite resin for each type of caries over five and 10 years. When calculating the cost of re-restorations avoided the costs of the original restoration are removed to avoid double counting.[66]

The model uses rates of caries progression and regression taken from a variety of unpublished and published clinical studies. The mean values for annual rates of caries progression for the current treatments assumed in the industry submission, along with the study reference from which these values were obtained, are as follows. non-cavitated pit and fissure caries: 0%;[67] cavitated pit and fissure caries: 4.9%;[68-70] and for root caries: 3.9%.[68,69]

The progression rates cited for HealOzone were all 0%, taken from studies with follow-up of three to 21 months.[35,40,42,44,53,71,72]

*Caries reversal rates for non-HealOzone treatments were assumed to be zero.* The industry submission does cite a 15% reversal rate found in a study reporting the use of varnish (chlorhexidine) but this value was excluded from the industry submission on the grounds that such varnish is not cited in the SDR codes. Rates of caries reversal in teeth treated with HealOzone were derived from eleven studies with follow-up times ranging from three to 21 months. The annualised mean used for base case analysis were as follows: non-cavitated pit and fissure caries: 93.3%;[53,55] cavitated pit and fissure caries: 79.0% ;[72-77] root caries 84.5%.[35,40,42,44,57,71]

Although no evidence was available to estimate underlying QALY scores, the industry submission model estimated alternative cost/QALY thresholds of between £10,000 and £40,000 assuming quality of life benefits from one day up to one month. The assumptions for QALY estimates were utility gains of 0.01, 0.02, 0.05 and 0.1 for restorations avoided.

The model was run to provide results using base case data. The deterministic base case analysis used mean values from the minimum and maximum values inputted for each parameter. Both one-way and multivariate sensitivity analysis was also conducted. Stochastic analysis was conducted using Monte Carlo simulation over 10,000 cycles. Random numbers were used to select data inputs from those provided.

*Results*

The average baseline figure estimated in the industry model, across all caries types, for the incremental cost to the NHS per tooth treated with HealOzone was £6.24. Allowing for the cost of re-restorations avoided, (see earlier description) the net incremental cost per tooth treated with HealOzone was 'minus' £9.70. The industry model also resulted in an estimated NHS cost of £61 per case of caries progression avoided (for all caries types) using a five year model time horizon, and assuming up to 35 cases per 1,000 avoided per year (152 over five years). An estimated 846 cases of caries reversal per 100 cases treated with HealOzone was reported, with an estimated NHS cost case of per caries reversal of £7.38, again for all caries types.

The estimated minimum utility gain (at 0.095) to achieve a cost per QALY of £30,000 was found to be for the use of HealOzone for root caries treatment. This was estimated using alternative cost-effectiveness acceptability thresholds based on varying the length of time over which a utility gain was accrued (see Table 22 in the industry submission).

Sensitivity analysis indicated that the main drivers of cost and cost-effectiveness were numbers of teeth treated per treatment session and the numbers of treatments per course of therapy. Multivariate analysis revealed that despite uncertainty around the cost of HealOzone, HealOzone would be likely to be cost effective over a 10 year follow-up period.

The report also discusses the wider implications to the NHS, impact on patient health and equity issues. The results of the economic evaluation are used to estimate the budget impact to the NHS from the use of HealOzone technology for all caries treatment of all eligible teeth. The figures include both initial treatment costs and the estimated costs of re-restorations avoided. On this basis, an annual net incremental cost of £48.1 million in year one, reducing to £11.8 million by year five was estimated for HealOzone. These results assume that the capital and running costs of the HealOzone device is funded by dental practices themselves with no contribution from the NHS apart from the fee for service. If the exchequer provided additional funds for the device this would cost the NHS an additional £110.4 million, assuming one device per dental practice in England and Wales. Additional annual servicing costs are estimated at £10.8 million.

While the evaluation does not include patient health as an outcome in the model, the results include a brief description of possible effects on patient health, based on studies of patient attitudes to dental treatment.

Equity issues are also briefly discussed in the results. The report cites evidence suggesting a link between caries incidence and deprivation and that this would be one group less likely to benefit from HealOzone technology as long as it is only available through private dental treatment.

*Critique of industry submission*

On the whole, the economic evaluation submitted by KaVo Ltd. is based on reasonable economic evaluation methodology. Nevertheless, there are a number of concerns that can be raised relating to the choice of comparators and the quality of data used to parameterise the economic model.

The comparators used in the industry submission for non-cavitated caries were based on restorative treatment of caries. The evaluation did not consider preventive measures for early caries.  Although management of non-cavitated caries does often involve fillings, it is now well established that preventive treatments for early lesions can be effective in reversing and arresting further progression of caries.  Furthermore, HealOzone has been cited as being “most effective in the role of prevention and early management of lesions.”[78] It would therefore have been appropriate for the industry model to include reversal of early caries as an additional comparator for non-cavitated caries.

The HealOzone comparator includes an assumption about the proportions of teeth, which would require additional treatment to HealOzone treatment alone. These assumptions are taken from a survey of 243 dentists who currently use HealOzone of whom only 48 provided usable responses.  Given the absence of robust, objective clinical data, options to obtain relevant model parameter values are limited. Nonetheless, such data are potentially biased and unreliable and the considerable uncertainty would be reduced if actual clinical evidence were to exist.  This was a non-randomised survey of opinion and cannot therefore be interpreted as having a strong evidence source.  It does not appear that any random selection process was used to the recruit dentists for the survey, and therefore it is unclear whether any attempt made to get a balanced opinion.

The industry evaluation of implications to the NHS includes an assumption about the numbers of teeth suitable for treatment with HealOzone.  These figures were again estimated from information taken from a survey of dentists who are users of HealOzone.

The assumption concerning the funding of the capital cost of providing a HealOzone device in dental surgeries was that this would not affect the fee for service.  In reality, however, it would be expected that any additional contribution by the NHS towards capital costs incurred by dental practices would be offset by lowering susbsequent fees paid to dentists for the associated therapy.

Estimates of caries progression and reversal rates were extracted from a range of studies of varying degrees of quality, including published and unpublished RCTs, conference abstracts and PhD theses.  Some of the limitations of these data sources are discussed in Chapter 3. Caries progression rates for current management were extracted from studies that did not include HealOzone as a comparator and the patient mix may be different. Caries progression rates for HealOzone were estimated from studies with follow-up periods from as little as three months, all of which claimed a 0% caries progression rate. Other studies show higher caries progression rates. Selecting the most favourable studies biases the results.

Rates of caries reversal with current management were assumed to be zero despite a 15% reversal rate being reported in one study. This rate was excluded from the analysis on the grounds that it was associated with the application of chlorhexidine varnish and this was assumed by the authors of the industry report not to be a standard NHS dental treatment. However, dentists commonly rank application of varnish among ‘treatments for sensitive cementum or dentine’ - code 3631 in the SDR.

Source data for caries reversal associated with the use of HealOzone came from a fourteen studies, three of which had follow-up of less than three months. The latter were only included in sensitivity analysis. The remaining 11 studies differed in design and quality. For non-cavitated pit and fissure caries effectiveness data were extracted from studies with three to six month follow-up.[53,55] For cavitated pit and fissure caries, despite finding no available evidence (see industry submission section 2.2.4) data from five studies are used in the model. The assumption used to justify this is cited in section 2.2.4.as follows:

“None of the available studies specifically describes the treatment of cavitated pit and fissure caries. In the absence of such detail, the studies presented in this section refer to carious lesions, which are deemed to require drilling and filling. While non-cavitated caries may be treated in this way, drilling and filling is the conventional treatment for cavitated caries and it is therefore assumed that these studies included a proportion of cavitated caries.”[79]

A further concern is that, although the industry submission report does acknowledge the limitation of combining data from more than one study, given the disparity in inclusion/exclusion criteria and other study characteristics, the reversal rates and progression rates used as the mean rates for base case analysis were calculated using the results from more than one study.

Estimates of the cost of re-restorations avoided are based on a number of assumptions and the report does acknowledge the absence of published data for rates of future re-restorations. Instead the model uses published data for the average cost per tooth year of re-restoration in teeth previously filled with amalgam or composite resin over five and 10 years.[79] It is unclear in the report exactly how estimates of the numbers of future re-restorations would be avoided as a result of HealOzone treatment, although the report does provide estimates for the cost of such re-restorations avoided. Given the considerable uncertainty surrounding the rate of re-restorations the figures used should be interpreted with care. Realistically, such data could only be obtained from the outcomes of a long-term study of the effectiveness of the relevant comparators. QALY estimates are included in the economic evaluation, but are not based on quality of life data. Instead, assumptions concerning the amount of utility gain and duration of gain were used to derive QALY thresholds. Given the short duration of any potential intermittent change in quality of life, along with the high degree uncertainty around any estimates of QALY scores, the additional information value of such QALY thresholds is dubious.

Although the economic evaluation in the industry submission is well presented the choice of comparator is questionable and considerable uncertainty surrounds many of the parameter values used in the model. Therefore their results over-estimate the benefits of HealOzone.

# 5. Economic Analysis

Given the current state of the clinical effectiveness evidence, with little published in full in peer-reviewed journals, it could be argued that economic analysis is premature. However NICE always requests some attempt at economic appraisal, if only to clarify the data deficits. We have therefore produced the following analysis more as illustrative modelling than as hard evidence.

## 5.1 Methods for economic analysis

The economic evaluation aimed to assess the cost-effectiveness of HealOzone relative to the alternative interventions for the treatment of both occlusal pit and fissure caries and root caries. As identified in the previous section, economic evaluations of HealOzone versus conventional treatments of dental caries were virtually non-existent at the time of this review. This section provides an economic evaluation using cost-effectiveness analysis and presents economic models of the treatment of non-cavitated pit and fissure (NC-PFC) and root caries (NC-RC). They compare current management versus current management plus HealOzone. The results over the extended time period must be qualified by the fact that follow-up data on HealOzone are limited to two years from the one RCT identified. The results reported in this section should be interpreted on the understanding that they entirely dependent on the model parameters and assumptions made. We recommend that the model be re-run in the future if evidence on clinical effectiveness is published.

### 5.1.1 Markov model framework

This section presents a description of the Markov model developed for the assessment and parameters that were common across all models are described. Key parameters specific to each model and results are then presented separately for each comparator. The section concludes with a summary of the results for all comparators and of the factors deemed to be most critical in affecting the results.

Markov modelling techniques were used to assess the cost-effectiveness of HealOzone plus current management relative to the standard current management of dental caries. A Markov model is composed of a set of defined health states between which a patient can move over successive time periods and is run using a hypothetical cohort of patients. The model incorporates both the logical and temporal sequences of treatment including the events that follow from the initial treatment procedure and the outcomes for the patient that are associated with each possible scenario or clinical pathway. Transition probabilities are used to allow patients to move within and between these states of health. A patient can only be in one state of health at any time and can only make one transition per cycle. A relevant time period is chosen for the length of a cycle and the cycles then link together to form a “Markov chain”. The length of cycle used in this study was one year. When the model is run over the defined number of cycles, a discounted net present value (NPV) for the cost of an intervention is calculated, determined by the occurrence of different states, and the length of time in various states.

The models were designed to estimate a typical patient’s costs and outcomes for the alternative treatments over a five year period. A five-year time horizon was chosen to facilitate comparison with the results from the industry model. Figure 10 summarises the basic structure of the model. Similar models were developed to carry out the analysis for non-cavitated pit and fissure caries and non cavitated root caries

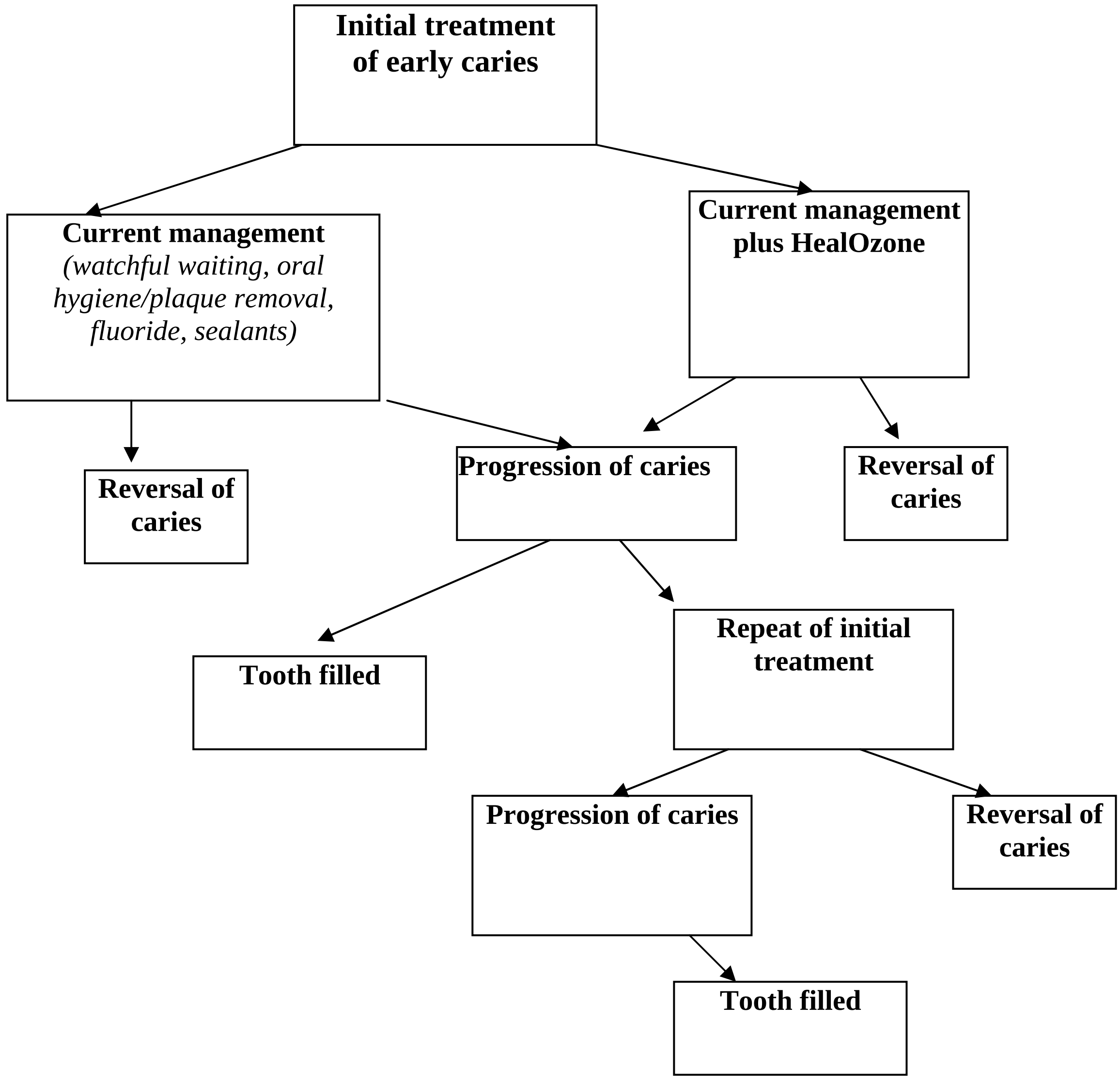
#### 5.1.1.1 Non-cavitated pit and fissure caries

The model for non-cavitated pit and fissure caries compares current management strategies (i.e. watchful waiting, oral hygiene/removal of plaque, fluoride applications and sealants) versus the same strategy plus HealOzone.

#### 5.1.1.2 Non-cavitated root caries

The model for non-cavitated root caries compares current management strategies, (i.e. root debridement, in conjuction with the application of remineralising fluorides, chlorhexidine and a sealant) versus the same strategy plus HealOzone.

**Figure 10. Model for primary non-cavitated pit and fissure caries**




### 5.1.1.3 Model pathways

The pathways for each model were developed in accordance with the protocol for the assessment along with expert opinion from members of a local dental school. All models have simplified clinical event pathways but are designed to reflect those clinical events of importance to the evaluation (Figures 15-18 in Appendix 6).

### 5.1.1.4 Non-cavitated pit and fissure caries and root caries

Following initial treatment the lesion enters one of the following states: it is either reversed (cured) or not reversed. For carious lesions that are not cured with the initial intervention, additional treatment is provided. This is a further application of the initial preventive/non–restorative treatment, or a restorative treatment (i.e. drilling and filling). In those receiving further preventive/non-restorative treatments, caries can again be reversed or treated with filling (Figure 10). The event pathway is split into two mutually exclusive events the reversal (cure) of caries and no reversal of caries. The arrows between these states represent the possible transitions between them. Movement between the different states is governed by the transition probabilities such as the chance of the caries reversing. The absorbing state in this model is tooth with a filling. While this is not an absorbing state in reality, given the 5 years time scale of the model, and that a typical filling would last longer than 5 years, no states beyond filling were included. It was assumed that once a tooth was cured it remained in a cured state for the rest of the 5 years. TREEAGE DATA 4.0 software[80] was used to construct the model.

### 5.1.2 Estimation of parameters

#### 5.1.2.1 Probabilities

The time horizon considered in the Markov model was a maximum of five years. The outcome considered in the economic evaluation was the numbers of carious lesions cured. The main probabilities used in the model were the rates of reversal (cure) of caries. These rates were derived from the effectiveness study (Chapter 3) and consultation with dental practitioners. The probability of cure rates (Table 15) obtained from the effectiveness studies and used in the first run of the economic model were: HealOzone 0.074 (7.4%) for the non-cavitated pit and fissure caries[37]and 0.98 (98%)[35] for the non-cavitated root caries. Those rates used for current management were 0.056 (5.6%)[37] for non-cavitated pit and fissure caries and 0.01(1%) for non-cavitated root caries.[35] These values were different from those used in the industry model which aggregated data from a number of studies, some of which did not meet the inclusion criteria specified in this review. In the absence of any alternative information, it was assumed for the purposes of the model that, following initial treatment, there was a 0.50 (50%) chance of subsequent treatment being the same treatment as the initial one received or a filling.

**Table 15. Probabilities used in Economic model**

| Intervention | Probability | Source |
|---|---|---|
| HealOzone cure rate (non cavitated pit fissures) | 0.074 | Table 9 chapter 3 |
| Current management cure rate (non cavitated pit fissures) | 0.056 | Table 9 chapter 3 |
| HealOzone cure rate (non cavitated root caries) | 0.98 | Table 11 chapter 3 |
| Current management cure rate (non cavitated root caries) | 0.01 | Table 11 chapter 3 |
| Percentage being retreated with initial treatment | 0.50 | Discussions with expert |
| Percentage being retreated with filling | 0.50 | Discussions with expert |

Please note that the root caries cure rates are taken from the Holmes study, whose results we find puzzling; they reflect a best possible case for Healozone.

#### 5.1.2.2 Costs

The perspective adopted for the study is that of the National Health Service (NHS) and Personal Social Services. The unit costs of dental treatments were taken directly from cost data published by the NHS.[65] Table 16 provides details of the different treatments with corresponding codes from the Statement of Dental Remuneration (SDR codes) for each treatment item. Unit costs are listed for each treatment item and represent the fee paid by the NHS to the dentist for each item of service.

**Table 16. Unit cost per item[1]**

| Type | Current Treatment (SDR code) | Cost |
|---|---|---|
| Non-cavitated pit and fissure caries | | |
| | Hygiene/diet advice (0601) | £7.70 |
| | Chlorhexidine gel/varnish or Fluoride varnish (3631) | £4.60 |
| | Fissure sealant (0701) | £6.95 |
| | Total (sum of above) | £19.25 |
| Non-cavitated root caries | | |
| | Hygiene/diet advice (0601) | £7.70 |
| | Chlorhexidine gel/varnish or Fluoride varnish (3631) | £4.60 |
| | Total (sum of above) | £12.30 |
| Cavitated pit and fissure caries | | |
| | Sealant only (1441) | £6.95 |
| | Composite resin (1442) | £9.80 |
| | Glass-ionomer (1443) | £10.55 |
| | Amalgam (1401 or 1421) | £7.15 (posterior) £14.15 (anterior) |
| | Total (average of above) | £16.98 |
| HealOzone | (No SDR Code) | £20 (estimate) |

Resource use data were identified from existing literature, reports from manufacturers and advice from the experts in this field. Based on existing evidence and clinical opinion, patients were assumed to visit the dentist every six months. Cost data were measured in Pounds Sterling (£) for the year 2004. As specified by the guidelines for conducting health technology assessment, cost-effectiveness results should reflect the present value of the stream of costs and benefit accruing over the time horizon of the analysis. To make the analysis consistent with the model used in the industry submission the analysis was carried out over period of five years. An annual discount

[1] Costs are costs which would be incurred by the NHS and exclude patient contributions to dental fees

rate of 3.5% was applied to both costs and benefits accrued, the rate currently specified in the HTA guidelines.[81]

The per-item fee for service paid by the NHS was used as a proxy for costs to the NHS of current management. Under the current NHS dental system patients pay 80% of the dentist's fee with the remaining 20% being paid by the exchequer (except that there is a maximum charge for a course of dental treatment of £366). Some patients, including all those under 18 years old, are entitled to free treatment and the exchequer pays the full cost of treatment. Recent figures report that 25% of all claims for patients aged 18 years and over were exempt from patient charges.[65] The other 75% of claims for patients aged 18 and over therefore include a patient contribution at 80% of the amount of the claim, and an NHS contribution of 20%. Taking these data into account the average net NHS contribution equates to 40% [25% + (20% of 75%)] of any one NHS dental claim for patients aged 18 and over. As children (persons under 18 years of age) are exempt from paying NHS dental treatment fees, the full cost of all claims for those less than 18 years old was used as the cost to the NHS. The data used in the industry model indicated that the NHS contribution to those aged 18 and over was 52%.

In the absence of separate effectiveness data for adults and children it was decided to combine all age groups for the base case analysis. A two-stage process was required to weight the unit costs to represent a mixed population of adults and children. Published statistics[65] indicate that adults and children do not receive similar proportions of each treatment item among the different treatment items listed in Table 16. The first stage was therefore to calculate the percentage mix of children and adults for each identified SDR component of the treatment. These proportions were then weighted by the amount that the NHS contributed using the figures described earlier, at 100% of the amount of a claim per child and 40% per adult. Following this two stage weighting process, the adjusted costs to the NHS used in the model were £9.02 for the non-cavitated pit and fissure caries, £6.09 for non-cavitated root caries and a filling was estimated at £12.75. Details of the costs are included in Table 17 below.

The costs of HealOzone were calculated using the existing NHS methods and information from the manufacturer. Most of the studies have indicated that HealOzone treatment is given at the start, and repeated at three months and six months. The cost of HealOzone therefore took into account that patients could receive between one and three applications. The cost of HealOzone treatment also included that of current management as HealOzone was considered as an additional treatment and not as a stand-alone treatment. The weighted average costs of ‘current management plus HealOzone treatment’ used in the model were £20.03 for non-cavitated pit and fissure caries and £17.10 for non-cavitated root caries. These values were not similar to those used in the industry model as they focused in costs and benefits to the NHS in England and Wales as a whole rather than the costs and benefits faced by the average patient.

**Table 17. Weighted average costs used in the model[1]**

| Intervention | Cost | | |
|---|---|---|---|
| | **Under 18** | **Over 18** | **Weighted** |
| *Current management* | | | |
| Non-cavitated pit and fissure caries | £19.25 | £7.70 | £9.02 |
| Non-cavitated root caries | £12.30 | £4.92 | £6.09 |
| *Current management plus HealOzone* | | | |
| Non-cavitated pit and fissure caries | £39.25 | £15.70 | £20.03 |
| Non-cavitated root caries | £32.30 | £12.92 | £17.10 |
| *Restorative interventions* | | | |
| Filling | £19.67 | £7.87 | £12.75 |

#### 5.1.2.3 Quality of life

It was not possible to measure health benefits in terms of quality adjusted life years (QALYs). This was mainly because the adverse events avoided are transient – a few seconds pain from injection of local anaesthetic; the anxiety/fear of having the drill; numbness until local anaesthesia wears off.

[1] Costs are costs which would be incurred by the NHS and exclude patient contributions to dental fees

#### 5.1.2.4 Sensitivity analysis

As every economic analysis contains some degree of uncertainty, imprecision or methodological controversy, and this one more than most, a sensitivity analysis was performed. Given the limited effectiveness data for estimating rates of caries reversal the models were re-run using different probability values of reversal of caries. Assumptions were also made about what items to include in each of the interventions and sensitivity analysis was performed using different codes to determine the costs, namely the SDR codes used in the industry submission.

### 5.1.3 Results

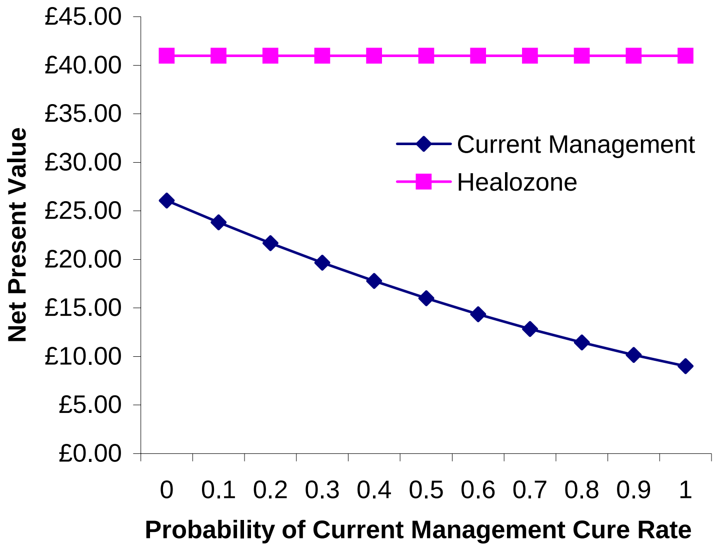
The analysis carried over a five-year period using the data reported in the trials indicated that treatment using current management plus HealOzone cost more than current management alone for non-cavitated pit and fissure caries (£40.49 versus £24.78), but cost less for non-cavitated root caries (£14.63 versus £21.45). For non-cavitated pit and fissure caries 91.8% of the teeth treated using current management received a filling while 8.2% teeth got cured. For teeth treated with current management plus HealOzone 89.2% received fillings whilst 10.8% were cured. This was different from the results of the Cochrane review[32] that reported the reduction of caries ranged from 86% at 12 months to 57% at 48-54 months. However, the focus of the review was on prevention and the children and adolescents included did not seem to present with obvious caries. Based on the Holmes study, 1.5% of the teeth were cured in the non-cavitated root caries treated with current management at five years and 98.5% teeth were filled, whereas, 99.90% teeth were cured by current management plus HealOzone and 0.01% were filled. We remain sceptical about these results.

### 5.1.4 Sensitivity analysis

There was very little suitable evidence on the effectiveness of the HealOzone comparator. One-way sensitivity analysis was applied to the model to assess the robustness of the results to variations of the underlying data. The probability of caries being cured was varied for each comparator separately, while using the base cure rate for the alternative comparator. These results indicated that when higher probability cure rates were used the proportion of teeth filled was lower at 12 months. Although these results were similar to those of the Cochrane review[32] they should be interpreted with caution as the review only focused on prevention among children and adolescents. The generalisability of these results is also questionable as there is considerable debate as to whether these results can be extrapolated to adults.

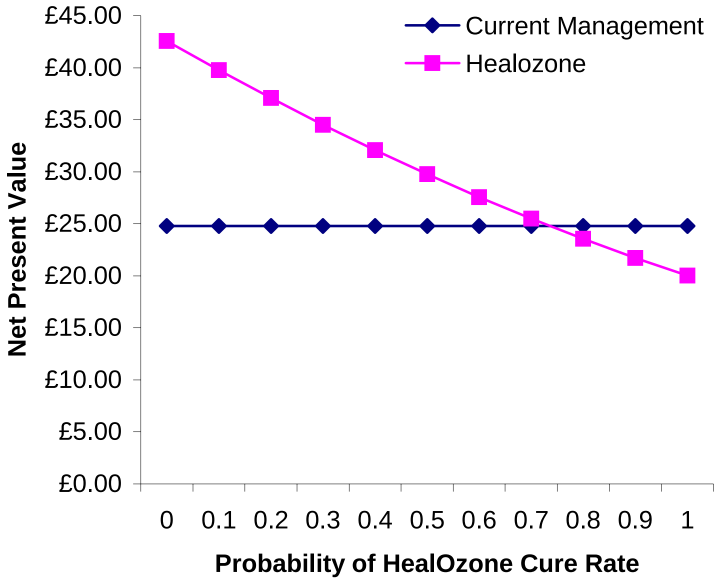
The results of the one-way sensitivity analyses are illustrated in following figures below.

**Figure 11 One-way sensitivity analysis for non-cavitated pit and fissure caries: Discounted net present value of each comparator at alternative cure rates for 'current management' holding the base-line cure rate for 'HealOzone plus current management' constant.**




The costs refer to those of current management when the baseline cure rates of HealOzone are used (0.074). The discounted net present value (NPV) for the cost of HealOzone was £40.99. The above results indicate that the discounted NPV of the cost of the HealOzone comparator, using baseline parameter values for HealOzone, was higher than that of current management at *any* probability of cure with current management. This is mainly attributable to the fact that the baseline cure rate used in the model is less than 10%. The results also indicate that as the probability of cure rate increases the cost reduces and the number of teeth filled also reduces.

**Figure 12 One-way sensitivity analysis for non-cavitated pit and fissure caries: Discounted net present value of each comparator at alternative cure rates for 'HealOzone plus current management' holding the base-line cure rate for 'current management' constant.**




Costs refer to those of HealOzone plus current management when the when the baseline cure rate of current management is used (0.056). The discounted NPV for the cost of current management was £24.78. Varying the probability of the cure rates of HealOzone plus current management, and using the base rate cure probability for current management, indicated that the HealOzone option was always more expensive than current management when the probability of cure using the HealOzone option was 70% or lower.

**Figure 13. One-way sensitivity analysis for non-cavitated root caries: Discounted net present value of each comparator at alternative cure rates for 'HealOzone plus current management' holding the base-line cure rate for 'current management'
constant.**

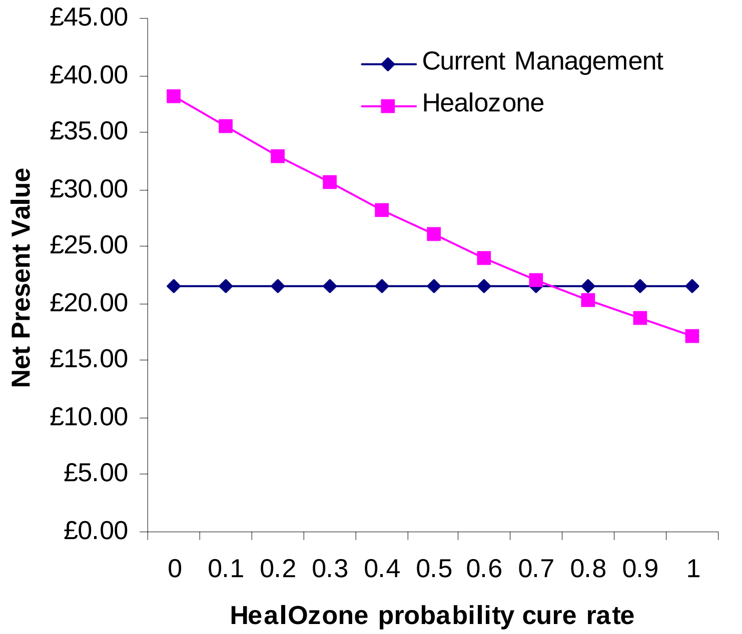
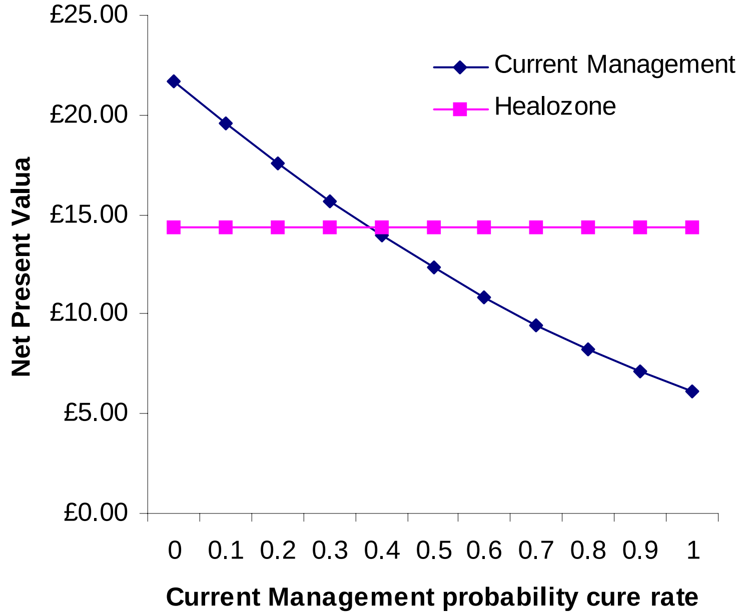



**Figure 14. One-way sensitivity analysis for non-cavitated root caries: Discounted net present value of each comparator at alternative cure rates for 'current management' holding the base-line cure rate for 'HealOzone plus current management'
constant.**



The costs of HealOzone reflect the costs when the baseline probability of cure of current management (0.01) was used and the probability of cure of HealOzone management was varied accordingly. The one way sensitivity analysis results show that discounted NPV for the costs of current management plus HealOzone were lower than those of current management only where cure rates from current management plus HealOzone were at least 80% and above.

The costs of current management reflect the costs when the baseline probability of cure of HealOzone (0.98) was used and the probability of cure of current management was varied accordingly. The discounted NPV for the costs of current management were higher than those of current management plus HealOzone when the cure rate for current management was 40% or lower.

**Table 18. Industry submission model inputs for annual treatment items and cost for patients under 18 years of age***

| Procedure | SDR Code | Unit cost |
|---|---|---|
| **Non-cavitated pit and fissure caries** | | |
| Fissure sealant - sealant only | 1441 | £6.50 |
| Fissure sealant - composite resin | 1442 | £9.15 |
| Fissure seal – Composite resin & glass ionomer | 1444 | £13.71 |
| **Root Caries** | | |
| Composite/synth-1 filling | 1421 | £13.22 |
| Composite/synth-2 or more fillings | 1421 | £10.32 |
| Glass ionomer-1 filling | 1426 | £12.08 |
| Glass ionomer-2 or more fillings | 1426 | £8.22 |

* The current costs of treatment were estimated using the General Dental Service (GDS) treatment items reported for the year ending March 2003 (Industry submission page 62).[79]

One-way sensitivity analysis was also carried out using similar SDR codes to those that are used in the industry submission. Table 18 illustrates the SDR codes used by the industry for patients under 18 years of age and the figures for those over 18 years were quite similar. This did not alter the results for non-cavitated pit fissure caries as the discounted NPV of current management remained lower than that of the HealOzone comparator (£22.65 versus £33.39). These results could be attributed to the fact that there was the assumption that patients received the same treatment as the initial one and the cost of current management plus HealOzone is much higher than that of current management alone given that HealOzone is an additional treatment rather than an alternative treatment. Results using the SDR codes used for non-cavitated root caries in the industry model gave similar results to those in the baseline analysis. HealOzone cost less than current management (£17.66 versus £30.41).

### 5.1.5 Discussion

The economic analysis was greatly constrained by the lack of reliable effectiveness data therefore the results should be interpreted cautiously as they reflect the parameter values and assumptions used in the model. A further constraint was the lack of long-term data on the effectiveness of HealOzone (it is not known whether caries that are reversed will always stay in the reversal state or whether they will need future treatment). This lack of long-term data necessitated the extrapolation of relatively short term (12 months) to five years. It is not known at this stage whether this assumption is valid. Another possible area of uncertainty was related to the whether the response to HealOzone treatment would increase with increasing dose levels.

A complete cost-effectiveness analysis was hampered by the fact that there were no comparative data on the benefits. It was therefore not possible to identify the utility gain required over the lifetime of a patient to achieve a defined cost-effectiveness acceptability threshold. It was not possible to model the treatment of cavitated caries since no effectiveness data on direct comparisons were available. The analysis was carried out on a hypothetical cohort of teeth with carious lesions and did into take into account the proportion of teeth that are unsuitable for HealOzone treatment.

# 6. Implications for the NHS

## 6.1 National service framework

The majority of general dental practitioners in the UK are contracted to the NHS through General Dental Services, although, as independent contractors, dentists who offer NHS treatment may also offer certain treatments on a private basis. Dentists receive fixed fees per item of treatment for adults, while for children they receive a combination of fixed fees per item and capitation fees. Under this NHS system patients can pay up to 80% of the cost of their treatment up to a maximum cost of around £366. Some patients are entitled to free NHS dental treatment, including children, young people in full time education, pregnant women and those with a child under one year old, and people on low incomes. The costs of running a dental practice, including capital costs of equipment, are met by the dental practice itself rather than the NHS and recovered from the fee for service charges paid by the patients and the NHS. In addition to dentists contracted to provide NHS treatment, some of which also offer private treatment, there are many dentists in the UK who *only* provide treatment on a private basis. Currently, HealOzone treatment is only available as a private treatment from a limited number of dentists.

## 6.2 Health targets

There are no specific health targets although in England the Department of Health did set a target to reduce tooth decay in five year olds to low levels by 2003, whilst in Wales the official target was to achieve no more than 48% of five year olds having tooth decay by 2002. (Audit commission report 2002).

The new Base Dental Contract (based on the personal dental services model) will be introduced for all practices on 1 October 2005. The new contract will be more likely to have a greater preventive and capitation element (http://www.dh.gov.uk/assetRoot/04/08/68/59/04086859.pdf).

## 6.3 Fair access

At the time of writing HealOzone treatment is only available through private dental care and it is estimated that there are 294 HealOzone units in the UK (at June 2004). Were ozone therapy to be made available, provision of HealOzone units would have to be increased much beyond this to allow all suitable patients fair access to the treatment.

## 6.4 Equity issues

The availability of HealOzone treament is currently limited to those people who are able and willing to pay for the treatment privately. However in the present state of knowledge, it cannot be said that people suffer by being unable to afford it.

## 6.5 Budget implications to the NHS

Currently HealOzone is only available to patients through private dental care. The aim of this section is to estimate what the implications would be to the NHS if HealOzone was made available as an NHS dental service.

The models used in the economic evaluation described in Chapter 5 considered the costs and effectiveness of current treatment with and without the addition of HealOzone for arresting the progression of dental caries. The evaluation does not consider those teeth with carious lesions, which would be unsuitable for HealOzone therapy. These could be considered in the estimated implications to the NHS for the total population of teeth with carious lesions if estimated numbers of such teeth were available. To achieve this it is necessary to make assumptions about the proportion of teeth currently treated for caries that would be suitable for alternative HealOzone treatment. This proportion would be used to calculate the total annual number of treated teeth.

Data from GDS provides statistics for the numbers of teeth treated by SDR code in a year for adults and children in England and Wales. At the time of writing the latest available GDS data was that pertaining to the year ending March 2003.

The following results were calculated by combining GDS data with our assumptions about the SDR codes relevant to each caries type in order to estimate annual numbers of teeth treated for non-cavitated pit and fissure caries and non-cavitated root caries. Again, teeth with cavitated caries were not considered given the absence of evidence on the effectiveness of HealOzone as a comparator treatment for cavitated caries.

*Non-cavitated pit and fissure caries*

The discounted net present value for the cost over 5 years of teeth treated initially with current management or HealOzone plus current management was reported in Chapter 5. These figures were combined with the numbers of teeth treated initially using annual GDS data for the SDR codes in our treatment definitions. The results were as follows, although all figures should be interpreted with extreme caution given that they are based on the limited effectiveness data available for the economic analysis, as reported earlier in Chapter 3 and Chapter 5 of this report.

The total discounted net present values over 5 years for treating non-cavitated primary fissure caries was estimated at £8,565,765 for current management and £13,996,280 for HealOzone therapy. The base case results showed that by 5 years fillings were present in 91.8% of teeth treated with current management compared to 89.2% of teeth treated with HealOzone plus current management. Using these figures the incremental cost per tooth treated is £15.71, at an initial total cost to the NHS of £5,430,515. The incremental cost over 5 years for the HealOzone comparator compared to current management (£13,996,280 - £8,565,765 ) was divided by the difference in numbers of teeth filled at five years for the HealOzone comparator and current management (308,340 –317,327). The incremental cost per filling avoided was estimated at only £0.001748.

The industry submission estimates for the percentage of teeth currently treated that would be suitable for HealOzone, obtained from the opinion of current users of HealOzone, were 92% for non-cavitated pit and fissure caries, 76% for cavitated pit and fissure caries and 76% for root caries. These figures were derived from Table 15 in the industry submission.

**Table 19. NHS annual cost for treatment of non-cavitated pit and fissure caries**

| | Net present value of treatment cost over 5 years |
|---|---|
| **Current management** | £8,565,765 |
| **HealOzone plus current management** | £13,996,280 |
| **Net difference in cost** | £5,430,515 |
| **Net difference in cost per tooth treated initially** | £15.71 |

*Non-cavitated root caries*

The total discounted net present values over 5 years for treating non-cavitated root caries was estimated at £7,371,882 for current management and £5,876,885 for HealOzone therapy. The net difference in these two costs show that HealOzone therapy saves the NHS £4.35 per tooth treated initially with HealOzone in addition to current management for root caries, a total cost saving over 5 years of £1,494,997. (Table 20)

**Table 20. NHS annual cost for treatment of non-cavitated root caries**

| | Net present value of treatment cost over 5 years |
|---|---|
| **Current management** | £7,371,882 |
| **HealOzone plus current management** | £5,876,885 |
| **Net difference in cost** | -£1,494,997 |
| **Net difference in cost per tooth treated initially** | -£4.35 |

These figures are estimated using base case values for caries reversal rates. Limited suitable effectiveness data were available for reversal rates of root caries, apart from a single study reporting reversal rates of 1% for current management and 98% for HealOzone treatment. Given the extreme values for reversal rates for the comparators, based on the limited effectiveness data available at the time of analysis, these results need to be interpreted cautiously. Given the available data, it was only possible to carry out limited one-way sensitivity analysis, varying cure rates separately for both the HealOzone and current management comparators. The results from this are reported in Chapter 5. From these results it can be seen that the net difference in cost per tooth treated initially was higher for current management unless the probability of cure for the HealOzone comparator was lower than approximately 80%.

It is advised that the reader interprets all such results as tentative values. Furthermore, in the light of limited evidence on effectiveness, a more detailed analysis of budget implications was not considered likely to add any additional useful information to the evaluation.

The cost implications over time are difficult to ascertain since there are many uncertain factors to take into account. Further research is required to model the cost implications over time taking into account the cost of re-restorations beyond the lifetime of first fillings, and also taking into account the effects over time on the tooth population. For example, it is unknown how long a reversed carious lesion remains cured. Any prospective trial should have sufficient follow up to allow for this.

Importantly, the above results are based on our assumptions for the treatment of the different types of caries.

Also, it is difficult to estimate the actual cost of HealOzone to the NHS. Assuming patients who pay some of their dental treatment fees are willing to pay no more than current treatment for the same condition initially what would the CE ratio be? Would patients opt for this treatment if it were more expensive?

Finally, would patients be given a choice for caries management or would dentists have to follow some sort of guidelines about the best treatment? This has implications on numbers of teeth treated.

# 7. Discussion

## 7.1 Main results

**Clinical effectiveness**

The literature on ozone treatment is still at a relatively early stage, in the sense that only one paper has been published in full in a refereed journal. Most of the reports are still in abstract form, as conference proceedings, and inevitably give little details. Many are still very short-term.

The evidence is conflicting with the root caries treatment showing much better results than pit and fissure caries. However, the results are surprising, partly because the ozone group did so well, with 99% cure or improvement, but mainly because the control group did very badly, despite getting the same care package (oral hygiene, topical fluoride, etc) but without application of ozone. The published Cochrane reviews show benefit from topical fluorides, so one would have expected many of the controls to have shown improvement.

**Cost effectiveness**

If HealOzone led to a reduction in future fillings, then the extra cost might be justified. We do not believe the evidence base yet supports that.

## 7.2 Need for further research

Nearly all the research to date comes from the same group who developed and pioneered the procedure, and have the greatest experience in its use. There is a need for large, well-conducted randomised controlled trials to assess the effectiveness and cost-effectiveness of HealOzone for the management of both occlusal and root caries. In particular future trials:

- should be conducted by independent research teams;
- should be proper randomised so that an equal number of lesions - or paired lesions - per mouth are allocated to intervention groups;
- should apply appropriate statistical methods for the analysis of ‘paired-data’ on a patient basis;

- should use validated and reproducible criteria for the assessment of caries;
- should measure relevant outcomes such as reduction in caries incidence over a reasonable period of time (at least 2 years);
- should mask participants and outcome assessors;
- should provide both a statistical and a clinical interpretation of their findings;
- should conform to the CONSORT guidelines for reporting of randomised controlled trials.

There also appears to be a need for evaluation of the different methods of assessing caries severity.  The base case might be clinical examination, with the marginal benefits and costs of more sophisticated techniques assessed.

## 8. Conclusion

Any treatment that preserves teeth and avoids fillings is welcome. However, the current evidence base for HealOzone is insufficient to conclude that it is a cost-effective addition to the treatment of occlusal and root caries.

# 9. References


1 Modernising NHS Dentistry - Implementing the NHS plan. London: Department of Health; 2000.

2 Marthaler TM, O'Mullane DM, Vrbic V. The prevalence of dental caries in Europe 1990-1995. ORCA Saturday afternoon symposium 1995. Caries Res 1996;30(4):237-55.

3 Children's dental health in the United Kingdom 2003. Obvious decay experience in children's teeth: preliminary findings. London: Department of Health; 2004.

4 Third national health and nutrition examination survey (NHANES III). National Center for Health Statistics, Department of Health & Human Services [accessed July 2004}. Available from:http://www.cdc.gov/nchs/about/major/nhanes/datalink.htm#NHANESIII

5 Sweeney PC, Nugent Z, Pitts NB. Deprivation and dental caries status of 5-year-old children in Scotland. Community Dent Oral Epidemiol 1999;27(2):152-9.

6 Murray JJ, Pitts NB. Trends in oral health. In: Pine CM, editor. Community oral health. Oxford: Butterworth Heinemann; 1996. p. 126-146.

7 Office for Population Censuses and Surveys. Children's dental health in the United Kingdom 1993. London: HMSO; 1994.

8 Kelly M, Walker A. Adult Dental Health Survey: Oral health in the United Kingdom 1998. London: Department of Health; 2000.

9 Ekstrand KR, Riketts DNJ, Kidd EAM, Qvist V, Schou S. Detection, diagnosing, monitoring and logical treatment of occlusal caries in relation to lesion activity and severity: an in vivo examination with histological validation. Caries Res 1998;32(4):247-54.

10 Ricketts DN, Kidd EA, Liepins PJ, Wilson RF. Histological validation of electrical resistance measurements in the diagnosis of occlusal caries. Caries Res 1996;30(2):148-55.

11 Chestnutt IG, Schafer F, Jacobson AP, Stephen KW. The influence of toothbrushing frequency and post-brushing rinsing on caries experience in a caries clinical trial. Community Dent Oral Epidemiol 1998;26(6):406-11.

12 Beal JF, James PM, Bradnock G, Anderson RJ. The relationship between dental cleanliness, dental caries incidence and gingival health. A longitudinal study. Br Dent J 1979;146(4):111-4.

13 Lewis DW, Ismail AI. Periodic health examination, 1995 update: 2. Prevention of dental caries. The Canadian Task Force on the Periodic Health Examination. CMAJ 1995;152(6):836-46.

14 Kidd.E, Nyvad B. Caries control for the individual patient. In: Fejerskov O, Kidd E, editors. Dental caries: the disease and its clinical management. Oxford: Blackwell Munksgaard; 2003.

15 Kleijnen J, McDonagh M, Misso K, Whiting P, Wilson P, Chestnutt I et al. Fluoridation of drinking water: a systematic review of its efficacy and safety. CRD Report 18. York: NHS Centre for Reviews and Dissemination; 2000.

16 McDonagh MS, Whiting PF, Wilson PM, Sutton AJ, Chestnutt I, Cooper J et al. Systemtic review of water fluoridation. BMJ 2000;321:855-9.

17 Marinho VC, Higgins JP, Logan S, Sheiham A. Fluoride varnishes for preventing dental caries in children and adolescents. The Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD002279. DOI: 10.1002/14651858.CD002279.

18 Marinho VC, Higgins JP, Logan S, Sheiham A. Fluoride gels for preventing dental caries in children and adolescents. The Cochrane Database of Systematic Reviews 2002, Issue 1. Art. No.: CD002280. DOI: 10.1002/14651858.CD002280.

19 Marinho VC, Higgins JP, Logan S, Sheiham A. Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents. The Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD002782. DOI: 10.1002/14651858.CD002782.

20 Marinho VC, Higgins JP, Logan S, Sheiham A. Fluoride toothpastes for preventing dental caries in children and adolescents. The Cochrane Database of Systematic Reviews 2003, Issue 1. Art. No.: CD002278. DOI: 10.1002/14651858.CD002278.

21 Marinho VC, Higgins JP, Logan S, Sheiham A. Fluoride mouth rinses for preventing dental caries in children and adolescents. The Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD002284. DOI: 10.1002/14651858.CD002284.

22 Marinho VC, Higgins JP, Logan S, Sheiham A. One topical fluoride (toothpastes, or mouth rinses, or gels, or varnishes) versus another for preventing dental caries in children and adolescents. The Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD002780. DOI: 10.1002/14651858.CD002780.pub2.

23 Clarkson JE, Ellwood RP, Chandler RE. A comprehensive summary of fluoride dentifrice caries clinical trials. Am J Dent 1993;6 Spec No:S59-106.

24 Davies RM, Holloway PJ, Ellwood RP. The role of fluoride dentifrices in a national strategy for the oral health of children. Br Dent J 1995;179(3):84-7.

25 Ripa LW. A critique of topical fluoride methods (dentifrices, mouthrinses, operator-applied, and self-applied gels) in an era of decreased caries and increased fluorosis prevalence. J Public Health Dent 1991;1:23-41.

26 Bader JD, Shugars DA, Bonito AJ. A systematic review of selected caries prevention and management methods. Community Dent Oral Epidemiol 2001;29:399-411.

27 Ellwood R, Fejerskov O. Clinical use of fluoride. In: Fejerskov O, Kidd E, editors. Dental caries: the disease and its clinical management. Oxford: Blackwell Munksgaard; 2003. p. 189-222.

28 Diagnosis and management of dental caries throughout life. NIH Consensus Statement March 26-28 2001;18(1):1-30.

29 Handelman SL. Effect of sealant placement on occlusal caries progression. Clin Prevent Dent 1982;4(5):11-6.

30 Mertz-Fairhurst EJ, Curtis JW, Jr., Ergle JW, Rueggeberg FA, Adair SM. Ultraconservative and cariostatic sealed restorations: results at year 10. J Am Dent Assoc 1998;129(1):55-66.

31 Ripa LW. Sealants revisted: an update of the effectiveness of pit-and-fissure sealants. Caries Res 1993;27 Suppl 1:77-82.

32 Ahovuo-Saloranta A, Hiiri A, Nordblad A, Worthington HV, Makela M. Pit and fissure sealants for preventing dental decay in the permanent teeth of children and adolescents. The Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD001830. DOI: 10.1002/14651858.CD001830.pub2.

33 Dental review of the general and personal dental services of the NHS. 2002-2003 [monograph on the Internet]. Dental Practice Board [accessed July 2004]. Available from: http://www.dpb.nhs.uk/

34 Verhagen AP. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by the Delphi consensus. J Clin Epiemiol 1998;51(12):1235-41.

35 Holmes J. Clinical reversal of root caries using ozone, double-blind, randomised, controlled 18-month trial. Gerodontology 2003;20(2):106-14.

36 Baysan A and Lynch E. Management of root caries using ozone. KaVo Dental Ltd website [accessed April 2004]. Available from: http://www.kavo.com/forum/upfiles/4/Db84539.pdf

37 Abu-Naba'a L.A. Management of primary occlusal pit and fissure caries using ozone. PhD Thesis: Queen's University Belfast; 2003.

38 Abu-Salem O. Reversal of occlusal caries in primary teeth. MPhil Thesis: Queen's University Belfast; 2004.

39 Holmes J. Ozone treatment of root caries after 18-months. IADR/AADR/CADR 82nd Annual Conference, Honolulu, Hawaii, March 2004 [Conference Proceedings on the Internet]. Available from: http://iadr.confex.com/iadr/2004Hawaii/techprogram/abstract_47251.htm

40 Holmes J. Ozone treatment of root caries after 21-months. BSDR Annual Scientific Meeting, Birmingham, UK, April 2004 [Conference Proceedings on the Internet]. Avaliable from: http://iadr.confex.com/iadr/bsdr04/techprogram/abstract_49444.htm

41 Baysan A and Lynch E. Clinical reversal of root caries using ozone. IADR/AADR/CADR 80th Annual Conference, San Diego, California, March 2002 [Conference Proceedings on the Internet]. Available from: http://iadr.confex.com/iadr/2002SanDiego/techprogram/abstract_20439.htm

42 Baysan A. Management of primary root caries using ozone therapies. PhD Thesis: University of London; 2002.

43 Baysan A and Lynch E. 12-month assessment of ozone on root caries. 81st Annual Conference of IADR, Goteberg, Sweden, June 2003 [Conference Proceedings on the Internet]. Available from: http://iadr.confex.com/iadr/2003Goteborg/techprogram/abstract_36145.htm

44 Baysan A and Lynch E. Clinical assessment of ozone on root caries. IADR/AADR/CADR 82nd Annual Conference, Honolulu, Hawaii, March 2004 [Conference Proceedings on the Internet]. Available from: http://iadr.confex.com/iadr/2004Hawaii/techprogram/abstract_47326.htm

45 Abu-Naba'a L.A., Al Shorman H.M., Stevenson M, Lynch E. Ozone treatment of pit and fissure caries: 6-month results. 32nd Annual Meeting of AADR, San Antonio, Texas, March 2003 [Conference Proceedings on the Internet]. Available from: http://iadr.confex.com/iadr/2003SanAnton/techprogram/abstract_27269.htm

46 Abu-Naba'a L.A., Al Shorman H.M., Lynch E. Ozone treatment of primary occlusal pit and fissure caries: 12 month clinical severity changes. Caries Res 2003;37(4):272.

47 Abu-Naba'a L.A., Al Shorman H.M., Lynch E. Ozone treatment of primary occlusal pit and fissure caries: 12 month electrical impedance results and clinical implications. Caries Res 2003;37(4):272.

48 Abu-Naba'a L.A. and Al Shorman H.M. 6-months fissure sealant retention over ozone-treated occlusal caries. IADR/AADR/CADR 82nd Annual Conference, Honolulu, Hawaii, March 2004 [Conference Proceedings on the Internet]. Available from: http://iadr.confex.com/iadr/2004Hawaii/techprogram/abstract_45125.htm

49 Abu-Naba'a L.A., Al Shorman H.M., Lynch E. Ozone management of occlusal pit & fissue caries(PFC): 12 month review. DentalOzone website.London:

Dental Clinique [accessed Aug 2004]. Available from: http://www.dentalozone.co.uk/research4.html

50 Abu-Naba'a L.A., Al Shorman H.M., Lynch E. Ozone efficacy in the treatment of pit and fissure caries. J Dent Res 2003;82(Spec Iss C):C-535.

51 Abu-Naba'a L.A., Al Shorman H.M., Lynch E. Clinical indices changes in ozone treatment of pit and fissure caries. 32nd Annual Meeting of AADR, San Antonio, Texas, March 2003 [Conference Proceedings on the Internet]. Available from: http://iadr.confex.com/iadr/2003SanAnton/techprogram/abstract_27273.htm

52 Abu-Naba'a L.A., Al Shorman H.M., Lynch E. 6-month clinical indices changes after ozone treatment of pit and fissure caries (PFC). 81st Annual Conference of IADR, Goteberg, Sweden, June 2003 [Conference Proceedings on the Internet]. Available from: http://iadr.confex.com/iadr/2003Goteborg/techprogram/abstract_35236.htm

53 Holmes J and Lynch E. Reversal of occlusal caries using air abrasion, ozone and sealing. IADR/AADR/CADR 82nd Annual Conference, Honolulu, Hawaii, March 2004 [Conference Proceedings on the Internet]. Available from: http://iadr.confex.com/iadr/2004Hawaii/techprogram/abstract_47218.htm

54 Holmes J. Clinical reversal of occlusal pit and fissure caries using ozone. 81st Annual Conference of the International Association for Dental Research, Goteberg, Sweden, June 2003.

55 Hamid A. Clinical reversal of occlusal pit and fissure caries using ozone. IADR/AADR/CADR 82nd Annual Conference, Honolulu, Hawaii, March 2004 [Conference Proceedings on the Internet]. Available from: http://iadr.confex.com/iadr/2004Hawaii/techprogram/abstract_47414.htm

56 Megighian G.D. and Bertolini L. In-vivo reversal of occlusal caries with ozone after six months. DentalOzone website.London: Dental Clinique [accessed Aug 2004]. Available from: http://www.dentalozone.co.uk/research8.html

57 Lynch E, Johnson J, Johnson J. Clinical reversal of root caries using ozone. DentalOzone website.London: Dental Clinique [accessed Aug 2004]. Available from: http://www.dentalozone.co.uk/research7.html

58 Kuhnisch J, Ziehe A, Brandstadt A, Heinrich-Weltzien R. An in vitro study of the reliability of DIAGNOdent measurements. Journal of Oral Rehabilitation 2004;31(9):895-9.

59 Macfarlane TV, Worthington HV. Some aspects of data analysis in dentistry. Community Dent Health 1999;16(4):216-9.

60 Rickard GD, Richardson R, Johnson T, McColl D, Hooper L. Ozone therapy for the treatment of dental caries. The Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004153. DOI: 10.1002/14651858.CD004153.pub2.

61 Drummond M, O'Brien B, Stoddard G, Torrance G. Critical assessment of economic evaluation. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 1997. p. 27-51.

62 Johnson N, Johnson J, Lynch E. Cost benefit assessment of a novel ozone delivery system vs conventional treatment. 32nd Annual Meeting of AADR, San Antonio, Texas, March 2003 [Conference Proceedings on the Internet]. Available from: http://iadr.confex.com/iadr/2003SanAnton/techprogram/abstract_27588.htm

63 Domingo H, Holmes J, Abu-Naba'a L.A., Al Shorman H.M., Baysan A, Freeman R. Economic savings treating root caries with ozone [accessed August 2004]. www.dentalozone.co.uk/reserach6.html.

64 Amendment 92 to the Statement of Dental Remuneration [document on the Internet]. UK Department of Health [accessed July 2004]. Available from: http://www.dh.gov.uk/assetRoot/04/08/11/28/04081128.pdf

65 General Dental Services Statistics. Dental Practice Board website.[accessed July 2004]. Available from: http://www.dpb.nhs.uk/gds/index.shtml

66 NHS Centre for Reviews and Dissemination. Dental restorations: what type of filling? Effective Health Care 1999;5(2):1-12.

67 Florio FM, Pereira AC, Meneghim MC, Ramacciato JC. Evaluation of non-invasive treatment applied to occlusal surfaces. J Dent Child 2001;68(5-6):326-31.

68 Qvist V, Laurberg L, Poulsen A, Teglers PT. Eight-year study on conventional glass ionomer and amalgam restorations in primary teeth. Acta Odontol Scand 2004;62(1):37-45.

69 Vilkinis V, Horsted-Bindslev P, Baelum V. Two-year evaluation of class II resin-modified glass ionomer cement/composite open sandwich and composite restorations. Clin Oral Investig 2000;4(3):133-9.

70 Qvist V, Laurberg L, Poulsen A, Teglers PT. Longevity and cariostatic effects of everyday conventional glass-ionomer and amalgam restorations in primary teeth: three-year results. J Dent Res 1997;76(7):1387-96.

71 Baysan A, Lynch E. Effect of ozone on the oral microbiota and clinical severity of primary root caries. Am J Dent 2004;17(1):56-60.

72 Morrison R and Lynch E. Remineralization of occlusal pit and fissure caries after using ozone. 32nd Annual Meeting of AADR, San Antonio, Texas, March 2003 [Conference Proceedings on the Internet]. Available from:http://iadr.confex.com/iadr/2003SanAnton/techprogram/abstract_27482.htm

73 Stinson P, Al Shorman H.M., Abu-Naba'a L.A., Lynch E. Clinical reversal of occlusal pit and fissure caries after using ozone. 32nd Annual Meeting of AADR, San Antonio, Texas, March 2003 [Conference Proceedings on the

Internet]. Available from:
http://iadr.confex.com/iadr/2003SanAnton/techprogram/abstract_27499.htm

74 Cronshaw M.A. Treatment of primary occlusal pit and fissure caries with ozone: six-month results. 81st Annual Conference of the International Association for Dental Research, Goteberg, Sweden, June 2003 [Conference Proceedings on the Internet]. Available from:
http://iadr.confex.com/iadr/2003Goteborg/techprogram/abstract_34889.htm

75 Domingo H, Abu-Naba'a L.A., Al Shorman H.M., Holmes J, Marashdeh M, Abu-Salem O et al. Reducing barriers to care in patients managed with ozone. 32nd Annual Meeting of AADR, San Antonio, Texas, March 2003 [Conference Proceedings on the Internet]. Available from:
http://iadr.confex.com/iadr/2003SanAnton/techprogram/abstract_27392.htm

76 Holmes J and Lynch E. Clinical reversal of occlusal fissure caries using ozone. 81st Annual Conference of the International Association for Dental Research, Goteberg, Sweden, June 2003 [Conference Proceedings on the Internet]. Available from:
http://iadr.confex.com/iadr/2003Goteborg/techprogram/abstract_36308.htm

77 Megighian G.D., Bertolini L, De Pieri A., Lynch E. In-vivo treatment of occlusal caries with ozone: one and two months effect with light induced fluoresence (QLF) as diagnostic methods. 81st Annual Conference of the International Association for Dental Research, Goteberg, Sweden, June 2003 [Conference Proceedings on the Internet]. Available from:
http://iadr.confex.com/iadr/2003Goteborg/techprogram/abstract_36918.htm

78 Healozone Users Congresses. July 2003 [Document on the Internet]. Healozone website [accessed April 2004]. Available from: http://www.the-o-zone.cc/O3cong.doc

79 Clinical and cost effectiveness of HealOzone for the treatment and management of dental caries. Kavo Dental Ltd; 2004.

80 Data 4.0 Professional. TREEAGE Software Inc; 2001.

81 Guide to the methods of technology appraisal (reference N0515). London: National Institute for Clinical Excellence; 2004.

# Appendix 1

## 1. Sources searched for systematic reviews, other evidence-based reports and background information.

**Databases**

Cochrane Database of Systematic Reviews (CDSR). The Cochrane Library (Issue 2, 2004).

Database of Abstracts of Reviews of Effects (NHS Centre for Reviews & Dissemination) April 2004

HTA Database (NHS Centre for Reviews & Dissemination) April 2004

Trip database. Available from: http://www.tripdatabase.com/ [accessed May 2004]

**Websites**

The Dental, Oral and Craniofacial Data Resource Center (DRC). Available from: http://drc.nidcr.nih.gov/default.htm [accessed July 2004]

National Center for Health Statistics. Available from: http://www.cdc.gov/nchs/nhanes.htm [accessed July 2004]

British Association for the Study of Community Dentistry. Available from: http://www.bascd.org/ [accessed July 2004]

KaVo Dental Ltd. Available from: http://www.kavo.com/En/default.asp [accessed April 2004]

CurOzone USA Inc. Available from: http://www.curozone.com/ [accessed April 2004]

DentalOzone. London: Dental Clinique. Available from: http://www.dentalozone.co.uk/ [accessed April 2004]

HealOzone. Dr Julian Holmes. Available from: http://www.the-o-zone.cc/ [accessed April 2004]

NHS Dental Practice Board. Available from: http://www.dpb.nhs.uk/gds/index.shtml [accessed July 2004]

Department of Health. Available from: http://www.dh.gov.uk/Home/fs/en [accessed April 20004]

## 2. Search strategies used to identify reports assessing ozone therapy for dental caries

### 2.A MEDLINE (1966 - Week 1 2004) EMBASE (1980 – Week 20 2004) (Medline Extra 17th May 2004)

**Ovid Multifile Search URL: http://gateway.ovid.com/athens**

1 (healozone or curazone).tw.
2 ozone/ (14334)
3 (ozone or o3).tw.
4 (oxidat$ or oxidis$).tw.
5 or/2-4
6 exp tooth demineralization/ use mesz
7 dental caries/ use emez
8 demineralization/ use emez
9 Dental Caries Susceptibility/ use mesz
10 Dental Enamel Solubility/
11 (caries or carious).tw.
12 ((tooth or teeth or dental or dentine or enamel or root? or occlusal) adj5 decay$).tw.
13 ((tooth or teeth or dental or dentine or enamel or root? or occlusal) adj5 cavit$).tw.
14 ((tooth or teeth or dental or root? or dentine or occlusal or enamel or cavitated) adj5 lesion?).tw.
15 ((tooth or teeth or dental or dentine or enamel) adj5 (minerali$ or demineralі$ or reminerali$)).tw.
16 or/6-15
17 1 or (5 and 16)
18 human/
19 animal/ use mesz
20 nonhuman/ use emez
21 (19 or 20) not 18
22 17 not 21
23 remove duplicates from 22

### 2.B Science Citation Index 1981 – 16th May 2004
### Web of Science Proceedings 1990 – 15th May 2004

**Web of Knowledge URL**: http://wok.mimas.ac.uk/

#1 TS= (Healozone or curazone)
#2 TS= (ozone or o3)
#3 TS=(oxidat* or oxidis*)
#4 #2 or #3
#5 TS=(caries or carious)
#6 TS=((tooth or teeth or dental or dentine or enamel or root* or occlusal) SAME decay*)
#7 TS=((tooth or teeth or dental or root* or dentine or occlusal or enamel or cavitated) SAME lesion*)
#8 TS=((tooth or teeth or dental or dentine or enamel or root* or occlusal) SAME cavit*)
#9 TS=(( tooth or teeth or dental or dentine or enamel) SAME (minerali* OR demineralі* OR reminerali*))

#10 #5 OR #6 OR #7 OR #8 OR #9
#11 #4 AND #10
#12 #1 OR #11

**2.C BIOSIS (1985 - 12th May 2004)**
**Edina URL: http://edina.ac.uk/biosis/**
(tn: (humans)) and (((al: (healozone)) or al: (curazone)) or ((((al: (oxidat*)) or al: (oxidis*)) or ((al: (ozone)) or al: (o3))) and ((((((al: (caries)) or al: (carious)) or ((((al: (root n5 decay*)) or al: (roots n5 decay*)) or (((al: (dentine n5 decay*)) or al: (enamel n5 decay*)) or al: (occlusal n5 decay*))) or (((al: (tooth n5 decay*)) or al: (teeth n5 decay*)) or al: (dental n5 decay*)))) or ((((al: (root n5 cavit*)) or al: (roots n5 cavit*)) or (((al: (dentine n5 cavit*)) or al: (occlusal n5 cavit*)) or al: (enamel n5 cavit*))) or (((al: (tooth n5 cavi*)) or al: (teeth n5 cavit*)) or al: (dental n5 cavit*)))) or (((((al: (root n5 lesion*)) or al: (roots n5 lesion*)) or (((al: (dentine n5 lesion*)) or al: (enamel n5 lesion*)) or al: (occlusal n5 lesion*))) or (((al: (tooth n5 lesion*)) or al: (teeth n5 lesion*)) or al: (dental n5 lesion*))) or (al: (cavitated n5 lesion*)))) or ((((((al: (tooth n5 minerali*)) or al: (tooth n5 reminerali*)) or al: (tooth n5 deminerali*)) or (((al: (teeth n5 mineral*)) or al: (teeth n5 reminerali*)) or al: (teeth n5 deminerali*))) or (((al: (dent* n5 minerali*)) or al: (dent* n5 reminerali*)) or al: (dent* n5 deminerali*))) or (((al: (enamel n5 minerali*)) or al: (enamel n5 reminerali*)) or al: (enamel n5 deminerali*))))))

**2.D AMED (1985 – May 2004)**
**Ovid URL: http://gateway.ovid.com/athens**
1 (healozone or curazone).tw
2 (ozone or o3).tw.
3 (oxidat$ or oxidis$).tw.
4 or/2-3
5 (caries or carious).tw
6 ((tooth or teeth or dental or dentine or enamel or root? or occlusal) adj5 decay$).tw
7 ((tooth or teeth or dental or dentine or enamel or root? or occlusal) adj5 cavit$).tw
8 ((tooth or teeth or dental or root? or dentine or occlusal or enamel or cavitated) adj5 lesion?).tw
9 ((tooth or teeth or dental or dentine or enamel) adj5 (minerali$ or deminerali$ or reminerali$)).tw
10 or/5-9
11 1 or (4 and 10)
12

**2.E Cochrane Library Issue 2, 2004**
**URL**: **http://www.update-software.com/clibng/cliblogon.htm**
**2.F National Research Register (Issue 2, 2004)**
**URL: http://www.update-software.com/National/**
#1. (healozone or curazone)
#2. OZONE single term (MeSH)
#3. (ozone or o3)
#4. (oxidat* or oxidis*)
#5. (#2 or #3 or #4)

#6. TOOTH DEMINERALIZATION explode tree 1 (MeSH)
#7. DENTAL CARIES SUSCEPTIBILITY single term (MeSH)
#8. DENTAL ENAMEL SOLUBILITY single term (MeSH)
#9. (caries or carious)
#10. ((tooth or teeth or dental or dentine or enamel or root* or occlusal) and decay*)
#11. ((tooth or teeth or dental or dentine or enamel or root* or occlusal) and cavit*)
#12. ((tooth or teeth or dental or dentine or enamel or root* or occlusal or cavitated) and lesion*)
#13. ((tooth or teeth or dental or dentine or enamel) and (mineralis* or demineralis* or remineralis*))
#14. ((tooth or teeth or dental or dentine or enamel) and (mineraliz* or demineraliz* or remineraliz*))
#15. (#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14)
#16. (#5 and #15)
#17. (#1 or #16)

**2.G DARE, NHS Economic Evaluation Database and HTA Databases(April 2004)**
**NHS Centre for Reviews & Dissemination**
**URL:http://nhscrd.york.ac.uk/welcome.htm**
Ozone or healozone or oxid* - all fields
Dental or caries or carious – all fields

**2.H Clinical Trials (18th May 2004)**
**URL: http://clinicaltrials.gov/ct/gui/c/r**

**2.I Current Controlled Trials (18th May 2004)**
**URL: http://www.controlled-trials.com/**
Ozone or healozone or oxid* - all fields

**2.J Health Management Information Consortium (May 2004)**
1 (healozone or curazone).tw.
2 dental caries/
3 (caries or carious).tw.
4 ((tooth or teeth or dental or dentine or enamel or root? or occlusal) adj1 decay$).tw.
5 ((tooth or teeth or dental or dentine or enamel or root? or occlusal) adj1 cavit$).tw.
6 ((tooth or teeth or dental or dentine or enamel or cavitated) adj1 lesion?).tw.
7 ((tooth or teeth or dental or dentine or enamel) adj1 (minerali$ or demineraIi$ or reminerali$)).tw.
8 or/1-7
9 limit 8 to yr=1995 - 2004

**2.K Conference Papers Index (1982-May 2002)**
**Cambridge Scientific Abstracts URL:http://www.csa1.co.uk/**
KW=(healozone or curazone) or (KW=(ozone or oxidat* or oxidis*) and KW=(caries or carious or dental)) or (KW=(ozone or oxidat* or oxidis*) and KW=(teeth or tooth or cavit*)) or (KW=(ozone or oxidat* or oxidis*) and KW=(occlusal or decay* or lesion*))

**2.L Zetoc Conference Search (1993 –May 2004)**
**MIMAS URL:http://zetoc.mimas.ac.uk/**
Ozone or healoaone or oxid* and (conference: dental or dentist or caries)

**2.M IADR Meeting abstracts**
**URL: http://www.iadr.com/Meetings/index.html**
IARD/AADR/CADR 80th General Session, San Diego, March 2002
IARD/AADR/CADR 82nd General Session, Honolulu, March2004
AADR 32nd Annual Meeting & Exhibition, San Antonio, March 2003
IADR 81st General Session, Goteberg 2003
IADR, Irish Division Annual Meeting, Belfast, 2004
BSDR Ann Scientific Meeting, Birmingham, April 2004

ozone or healozone or oxid*

## 3. Handsearching

*3.A Journal of Dental Research :*
Vol 79 Special issue 2000: 78th General Session of IADR, Washington, April 2000
Vol 79(5) 2000: British Section: Annual Scientific Session, Lancaster, April 2000; Irish Section: Annual Scientific Meeting, Newcastle, Ireland, Jan 1999.
Vol 80 Special Issue (AADR Abstracts) Jan 2001: 30th Annual Meeting AADR/25th Annual Meeting CADR Chicago, March 2001
Vol 80 (4) April 2001:British Society for Dental Research & Irish Division Continental European (1999 and 2000)

*3.B Caries Research:*
Vol 37(4):50th Annual ORCA Congress, Konstanz Germany, July 2003
Vol 36(3): 49th Annual ORCA Congress, Naantali Finland, July 2002
Vol 35(4): 48th Annual ORCA Congress, Graz, July 2001
Vol 34(4): 47th Annual ORCA Congress, Alghero, Sardinia , July 2000

## 4. Websites

KaVo Dental Ltd. Available from: http://www.kavo.com/En/default.asp [accessed April 2004]

CurOzone USA Inc. Available from: http://www.curozone.com/ [accessed April 2004]

DentalOzone. London: Dental Clinique. Available from: http://www.dentalozone.co.uk/ [accessed April 2004]

HealOzone. Dr Julian Holmes. Available from: http://www.the-o-zone.cc/ [accessed April 20

# Appendix 2

## 'HEALOZONE' TECHNOLOGY ASSESSMENT REVIEW

## DATA EXTRACTION FORM

**Reviewer ID:** **Date information extracted:**

***Study Details***

**Study ID**: ______________________________________

**Study identifier:** ______________________________
(Surname of first author + year of publication)

**Study origin**: __________________________________

**Language**: _____________________________________

**Published** ☐ **Unpublished** ☐

**Full text** ☐ **Abstract only** ☐

***Study Design***

RCT ☐ Other ________________________________________

Quasi - RCT ☐

Observational Study ☐

For RCTs only: What is the unit of randomisation?

Patient ☐

Tooth/lesion ☐

Tooth/lesion pair ☐

| ***Participants*** | |
|---|---|
| Number of eligible patients: | Number of patients randomised: |
| Inclusion criteria: | Exclusion criteria: |

| ***Interventions*** | | |
|---|---|---|
| | **Type of intervention** | **Number of participants** |
| Group 1: | | |
| Group 2: | | |
| Group 3: | | |

| ***Patient Characteristics*** | | | | |
|---|---|---|---|---|
| | Intervention 1 | Intervention 2 | Intervention 3 | Total |
| Age (mean, range) | | | | |
| Sex (M/F) | | | | |
| Permanent /Deciduous teeth | | | | |
| Primary or Secondary caries | | | | |
| Comparability at baseline | | | | |

| ***Characteristics of the intervention*** |
|---|
| Location of trial centre(s): |
| Source of participants: |
| Method of recruitment: |

| |
|---|
| Method of randomisation: |
| Dosage of HealOzone application: |
| Repeated applications: |
| Was a reductant applied? If yes, what was its formulation? |
| Did patient receive the aftercare kit (e.g. toothpaste, mouth rinse and spray)? |
| Length of follow-up: |
| Compliance with the treatment: |
| Number lost to follow-up: |

| ***Caries Information*** |
|---|
| Method of caries examination: |
| Tooth location, lesion location, and type of lesion: |
| Severity of caries: |
| ***Outcomes*** |

| | Intervention 1 | Intervention 2 | Intervention 3 |
|---|---|---|---|
| Non-cavitated caries | | | |
| Reversal of caries | | | |
| Progression of caries | | | |
| Utilisation of dental resources | | | |

| | |
|---|---|
| Adverse reactions | |
| Patient–centred measures (e.g. patient satisfaction and preference, relief of pain/discomfort) | |
| Quality of life | |
| *Cavitated caries*<br><br>Time to restorative interventions | |
| Need for further restorative interventions | |
| Symptoms of pulpal pathology | |

| ***Other comments*** |
|---|
| |

# Appendix 3

## Checklist for the quality assessment of randomised controlled trials

*(adapted from Verhagen et al, 1998[34])*

| Criteria | Yes | No | Unclear | Comments |
|---|---|---|---|---|
| **1. Was the assignment to the treatment groups really random?**<br>Adequate approaches to sequence generation<br>• computer-generated random tables<br>• random number tables<br>Inadequate approaches to sequence generation<br>• use of alternation, case record numbers, birth dates or week days | | | | |
| **2. Was the unit of randomisation clear?** | | | | |
| **3. Was the treatment allocation concealed?**<br>Adequate approaches to concealment of randomisation<br>• centralised or pharmacy-controlled randomisation<br>• serially-numbered identical containers<br>• on-site computer based system with a randomisation sequence that is not readable until allocation<br>• other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients<br>Inadequate approaches to concealment of randomisation<br>• use of alternation, case record numbers, birth dates or week days<br>• open random numbers lists<br>• serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation) | | | | |
| **4. Were the groups similar at baseline in terms of prognostic factors?** | | | | |
| **5. Were the eligibility criteria specified?** | | | | |
| **6. Were the groups treated in the same way apart from the intervention received?** | | | | |
| **7. Was the outcome assessor blinded to the treatment allocation?** | | | | |
| **8. Was the care provider blinded?** | | | | |
| **9. Were the patients blinded?** | | | | |
| **10. Were the point estimates and measures of variability presented for the primary outcome measures?** | | | | |
| **11. Was the withdrawal/drop-out rate likely to cause bias?** | | | | |
| **12. Did the analyses include an intention-to-treat analysis?** | | | | |

# Appendix 4

## Characteristics of included studies – full-text reports

| Author(s) | Characteristics of participants and carious lesions | Design | Inclusion criteria | Interventions | Results | Notes and caveats |
|---|---|---|---|---|---|---|
| ***Root caries studies – permanent dentition*** | | | | | | |
| ***Baysan and Lynch, 2004***[36,41-44]***.*** Belfast, UK. | 79 (220 primary cavitated and non-cavitated root carious lesions).<br><br>**Mean age:** 65 SD 14.76.<br><br>**Age range:** 30-72<br><br>**Gender (M/F):** 49/30<br><br>**Tooth and lesion location:** root surface lesions.<br><br>**Caries risk assessment:** not stated. | **Design:** RCT (unpublished).<br><br>**Unit of randomisation:** lesion<br><br>**Method of randomisation:** not stated.<br><br>**Concealment of allocation:** not stated.<br><br>**Blinding:** unclear.<br><br>**Intention-to-treat:** no.<br><br>**Length of follow-up:** 12 months. | Two or four primary non-cavitated and cavitated root carious lesions with severity index II (leathery lesions). | **Group 1:** cleaning of the tooth surface, application of $O_{3}$ + reductant.<br><br>The procedure was repeated after 1 month without ozone and at 3 months with ozone.<br><br>**Group 2:** reductant only. The procedure was repeated after 1 month and at the 3 months follow-up.<br><br>**Group 3:** $O_3$ + sealant (Seal & Protect, Dentsply, Germany).<br><br>The procedure was repeated at 3 months. Sealants were re-applied only if a partial or | **Reversal of caries -groups 1& 2:** at 12 months 47% of PRCLs reversed from severity index 1 to 0 (hard) in the ozone group, whilst none became hard in the control group ($p<0.001$). 52% of lesions reversed from 2 to 1 in the ozone group compared to 11.6% in the control group ($p<0.001$).<br><br>Cavitated lesions in the ozone group did not show the same trend of improvement of non-cavitated lesions. Percentage of lesions that became hard decreased from 9.1 at 1 month to 1.4 at 9 months suggesting worsening of cavitated carious lesions. Data for the control group were not given.<br><br>**Marginal adaptation of the root sealant (modified USPHS** | The number of lesions in each intervention group not clearly reported.<br><br>All subjects enrolled in the study received preventive advice, including oral hygiene and dietary advice, and were given a toothbrush and toothpaste (Natural White, Natural White Inc., USA, 1,100 ppm F).<br><br>Unclear whether cleaning of the root surface was performed before |

| | | | |
|---|---|---|---|
| **Lost at follow-up:** 5 subjects.<br><br>**Comparability of groups at baseline:** unclear<br><br>**Setting:** general dental practices. | complete loss of the sealant was suspected.<br><br>**Group 4:** sealant only (Seal & Protect, Dentsply, Germany).<br><br>Sealants were re-applied after 1 and 3 months only if a partial or complete loss of the sealant was suspected.<br><br>**Reductant formulation:** Sodium Fluoride(1,100ppm F), Xylitol, Sodium Benzoate amongst other active ingredients.<br><br>**Ozone dosage:** 10 seconds<br><br>**Caries assessment:** ECM III (Lode Diagnostics BV, The Netherlands), DIAGNOdent (KaVo, Germany), and clinical criteria. The severity of lesions was assessed on a 4 points scale (0 = hard lesions; 4 = soft lesions). In addition, modified USPHS criteria were used for assessing groups 3 and | **criteria):** 61% intact sealants in the ozone +sealant group compared to 26.1% in the sealant only group ($p<0.001$).<br><br>Significant differences in the changes in both the **ECM** readings and **DIAGNOdent** readings in the ozone and control groups ($p<0.001$).<br><br>**Adverse events:** none observed. | treatment in Groups 2, 3, and 4.<br><br>It was reported that subjects who "presented with any form of discomfort were immediately treated with conventional drilling and filling procedures" but not further information was provided.<br><br>Methods for statistical analyses not clearly reported. Unclear whether the results were adjusted for covariates/risk factors.<br><br>Emphasis on non-cavitated lesions. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | 4.<br><br>**Assessors/operators:** single operator (A. Baysan).<br><br>**Ozone device output:** not reported. | | |
| ***Holmes, 2003*[35,39,40]***}*<br>Berkshire, UK. | 89<br>(178 primary non-cavitated root carious lesions, 89 lesions in each group).<br><br>**Mean age:** 70.8 (6). Age range: 60-82.<br><br>**Tooth and lesion location:** Leathery roof surface lesions (severity index II).<br><br>**Caries risk assessment:** not stated. | **Design:** RCT.<br><br>**Unit of randomisation:** Lesion.<br><br>**Method of randomisation:** computer generated random tables.<br><br>**Concealment of allocation:** not stated.<br><br>**Blinding:** double blind.<br><br>**Intention-to-treat:** no.<br><br>**Length of follow-up:** 3, 6, 12, 18, 21 months.<br><br>**Lost at follow-up:** | Adults with two leathery non-cavitated primary root carious lesions. | **Group 1:** application of $O_{3\,+}$ reductant + patient care kit<br><br>**Group 2:** air treatment + reductant only + patient care kit<br><br>Repeated applications of $O_3$ + reductant at 3, 6, 12 and 18 months.<br><br>**Reductant formulation:** Xylitol, Fluoride, Calcium, Phosphate, and Zinc. (No concentrations provided).<br><br>**Ozone dosage:** 40 seconds<br><br>**Caries assessment:** ECM (Lode Diagnostics BV, The Netherlands), DIAGNodent (KaVo, Germany), and visual/tactile examination | **18 months follow-up.**<br><br>**Reversal of caries:** 87/87 lesions in the ozone group reversed (became hard) compared to 1/87 in the control group ($p<0.01$).<br><br>**Progression of caries:** 32/87 lesions in the control group worsened from leathery to soft and 54/87 did not change.<br><br>**Adverse events:** none observed. | All subjects enrolled in the study received information on oral hygiene, brushing techniques, and diet. In particular all subjects received instructions on how to use the re-mineralising toothpaste twice a day, the mineral mouth wash twice a day, and the re-mineralising spray four times per day.<br><br>All subject were offered a pharmacological treatment, which they all accepted as an alternative to the traditional drilling and filling. No |

| | | | |
|---|---|---|---|
| 2 at 18 months.<br><br>**Comparability of groups at baseline:** unclear.<br><br>**Setting:** general dental practice. | method.<br><br>**Assessors/operators:** the ozone treatment was applied by a different operator than the one recording the severity of lesions. Unclear whether the operator who did assess outcomes was the same one who did allocate subjects to intervention groups.<br>A sample of 15 subjects (30 lesions) were examined by a third dentist to test reproducibility of results.<br><br>**Ozone device output:** it was reported that the HealOzone unit was fitted with a modified control integrated electronic chip. Unclear whether this modified chip could allow better calibration and monitoring of ozone doses. | | details of the pharmacological treatment were, however, provided.<br><br>The two dentists who allocated subjects to intervention groups and assessed severity of lesions, and the third dentist who assessed reproducibility of data were not acknowledged in the paper.<br><br>The 21 months findings published in an abstract format (Holmes, 2004 [40,62]seem to contradict those reported in the full-text. |

***Pit and fissure caries studies – permanent dentition***

| | | | | | | |
|---|---|---|---|---|---|---|
| ***Abu-Naba'a 2003-Main study***[37,45-50] Belfast, Queens University, UK. | 90 (258 primary occlusal pit and fissure carious lesions).<br><br>**Age:** 79 subjects between 12-31 years; 8 subjects between 32-41 years, and 3 subjects >41 years.<br><br>**Gender (M/F):** 35/55<br><br>**Tooth and lesion location:** all posterior teeth in the upper and lower jaws. Central grooves and pits were the most common observed lesions.<br><br>**Caries risk assessment:** not stated. | **Design:** RCT (unpublished).<br><br>**Unit of randomisation:** lesion.<br><br>**Method of randomisation:** random sampling digit tables.<br><br>**Concealment of allocation:** not stated.<br><br>**Blinding:** unclear.<br><br>**Intention-to-treat:** no.<br><br>**Length of follow-up:** 1, 3, 6, 9 and 12 months.<br><br>**Lost at follow-up:** 32 subjects.<br><br>**Comparability of groups at baseline:** more severe lesions | Males and females over 12 years with primary occlusal pit and fissure carious lesions in at least two teeth of the permanent posterior dentition, which were accessible for the diagnostic procedures. | Before treatment all lesions were disclosed and cleaned with an air-abrasive system (PROPHYflex 2, KaVo, Germany).<br><br>**Group 1:** application of $O_3$ + reductant.<br><br>**Group 2:** reductant only/control.<br><br>**Group 3:** $O_3$ + reductant + fissure sealant (Guardian, Kerr).<br><br>**Group 4:** reductant + sealant.<br><br>**Reductant formulation:** Sodium fluoride (1,100ppm F), Xylitol, and Zinc Chloride amongst other active ingredients.<br><br>**Ozone dosage:** 10 seconds.<br><br>**Caries assessment:** ECM (Lode Diagnostics BV, | **<u>Groups 1 and 2</u>**<br><br>**Reversal of caries:**<br>No significant differences between groups in the mean change from baseline:<br>**Group 1:** 0.283 (0.64)<br>**Group 2:** 0.443 (0.74); p=0.112<br><br>**ECM values:** no significant differences in the mean change from baseline values between groups.<br>**Group 1 (109 lesions):** mean $\log_e$ change 0.020(1.4)<br>**Group 2 (109 lesions):** 0.073(1.61); p=0.75<br><br>*Excluding teeth with baseline ECM score 0:*<br>**Group 1 (77 lesions):** 0.327(1.32)<br>**Group 2 (69 lesions):** 0.073(1.37); p=0.54<br><br>**DIAGNOdent values:** no significant differences between groups (p>0.05) at all follow-up visits. | All subjects enrolled in the study received preventive advice and were given a toothbrush and toothpaste (Natural White, Natural White Inc., UK, 1,100 ppm F).<br><br>Sealant was re-applied if necessary and $O_3$ application repeated.<br><br>Subjects attendance to follow-up visits varied. The number of subjects assessed by ECM differed from the number of subjects assessed by DIAGNOdent at follow-up visits. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | (index scores of 2 and 3) in the treatment group (p=0.055). More molars in the treatment group than in the control group.<br><br>**Setting:** general dental practice. | | The Netherlands), DIAGNodent (KaVo, Germany), and clinical severity (Ekstrand, 1998). In addition, modified USPHS criteria + radiographic assessments were used for assessing groups 3 and 4.<br><br>**Assessors/operators:** three operators were reported to assess radiographs. A single operator assessed the lesions and interpreted ECM and DIAGNOdent findings (L. Abu-Naba'a).<br><br>**Ozone device output:** not reported. | **Groups 3 and 4**<br><br>**Secondary caries:** no significant differences between groups (2 secondary caries in the ozone group and 2 secondary caries in the control group).<br><br>**Sealant retention:** partial loss in the margins of the sealants in 32.7% in the ozone +sealant group compared to 29.8% in the sealant only group (p>0.05).<br><br>No significant differences in terms of fissure sealant colour and radiographic depth of radiolucency between groups. | |
| ***Abu-Naba'a 2003-Pilot study***[37,51,52] Belfast, Queens University, UK. | 8<br>(38 occlusal pit and fissure lesions, 19 in each group) | **Design:** RCT (unpublished).<br><br>**Unit of randomisation:** lesion<br><br>**Method of randomisation:** random sampling digit tables. | Males and females over 12 years with primary occlusal pit and fissure carious lesions in at least two teeth of the permanent posterior dentition, which | Before treatment all lesions were disclosed and cleaned with an air-abrasive system (PROPHYflex 2, KaVo, Germany).<br><br>**Group 1:** application of $O_3$ + reductant.<br><br>**Group 2:** reductant only. | **Clinical severity scores:** not significant differences between groups at any follow-up visits (p>0.05).<br><br>**ECM and DIAGNOdent readings:** not significant differences between groups (p>0.05).<br><br>Clinical Indices | All subjects enrolled in the study received preventive advice and were given a toothbrush and toothpaste (1,100 ppm F). |

| | | | |
|---|---|---|---|
| **Concealment of allocation:** not stated.<br><br>**Blinding:** unclear.<br><br>**Intention-to-treat:** no.<br><br>**Length of follow-up:** 1, 3, 6 months.<br><br>**Lost at follow-up:** unclear.<br><br>**Comparability of groups at baseline:** more severe lesions (index score of 3) in the control group.<br><br>**Setting:** general dental practice. | were accessible for the diagnostic procedures. | At 3 months Group 1 received another application of $O_3$.<br><br>**Reductant formulation:** Sodium fluoride (1,100 ppm F), Xylitol, and Zinc Chloride amongst other active ingredients.<br><br>**Ozone dosage:** 40 seconds<br><br>**Caries assessment:** ECM (Lode Diagnostics BV, The Netherlands), DIAGNOdent (KaVo, Germany), and clinical criteria (Ekstrand, 1998).<br><br>**Assessors/operators:** Unclear. It would seem that a single operator assessed the lesions and interpreted ECM and DIAGNOdent findings (L. Abu-Naba'a).<br><br>**Ozone device output:** 33% of the outcome expected. | **Hardness index score:** 11 lesions in the ozone group became harder compared to 4 in the control group ($p<0.05$).<br>2 lesions in the control group became softer.<br><br>**Change in the visual index score:** 8 teeth in the treatment group changed positively at the 6-month follow-up compared to 1 tooth in the control group ($p<0.05$).<br><br>**Change in the cavitation score:** 6 teeth had a decreased cavity score in the ozone group compared to 5 teeth in the control group. The difference between intervention groups was not significant ($p>0.05$).<br><br>**Change in colour:** not significant differences between groups ($p>0.05$).<br><br>**Change in frosted enamel and undermined enamel**: not significant differences between groups ($p>0.05$). |

*Pit and fissure caries studies – primary dentition*

| | | | | | | |
|---|---|---|---|---|---|---|
| ***Abu-Salem, 2004***[38] Belfast, Queens University, UK. | 21 patients (74 non-cavitated occlusal carious lesions in primary molars).<br><br>**Age range:** 7-9<br>7 years: 28%<br>8 years: 48%<br>9 years: 24%<br><br>**Gender (M/F):** 9/21<br><br>**Caries risk assessment:** not stated. | **Design:** RCT (unpublished).<br><br>**Unit of randomisation:** lesion<br><br>**Method of randomisation:** computer generated random tables.<br><br>**Concealment of allocation:** not stated.<br><br>**Blinding:** examiner blinded to results of previous tests and outcomes of previous records.<br><br>**Intention-to-treat:** no.<br><br>**Length of follow-up:** 3, 6, 9 and 12 months.<br><br>**Lost at follow-up:** 4 subjects (16 lesions). | Children 7-9 years old with at least two carious lesions in the posterior primary teeth and absence of occlusal restoration, fissure sealants, hypoplastic pits, and fractures extending into dentine or cavitations resulting from carious attack on the occlusal surface. | Before treatment, teeth were cleaned using the PROPHYflex-2 system for 5 seconds.<br><br>**Group 1:** Ozone plus reductant<br><br>**Group 2:** reductant only<br><br>**Reductant formulation:** Sodium Benzoate (1,100 ppm F), Xylitol, Zinc Chloride, and Sodium Citrate amongst other active ingredients.<br><br>**Ozone dosage:** 10 seconds.<br><br>**Caries assessment:** ECM (Lode Diagnostics BV, The Netherlands), DIAGNOdent (KaVo, Germany), and clinical criteria (Ekstrand, 1998). | **12 month follow-up**<br><br>**Clinical severity scores:** Overall there was a little reduction in clinical severity scores in the ozone group and an increase in scores in the control group. There was a significant effect of treatment upon clinical severity scores over time (mixed models ANOVA $p<0.01$).<br><br>**Log ECM and DIAGNOdent readings:** There was a significant effect of time and treatment upon the mean $Log_e$ ECM readings ($p<0.001$) and the mean DIAGNOdent readings ($p<0.001$). There was also an overall significant effect of time and treatment upon ECM scores ($p<0.001$) and an overall increase in the DIAGNOdent scores in the control group compared with the ozone group ($p>0.05$). | All subjects received preventative advice and were given a toothbrush (Brilliant, soft tooth brush, distributed by Brilliant Products, UK) and toothpaste (Natural White, Natural White Inc., (UK) Ltd: 1,100ppm F) at each recall to be used throughout the study.<br><br>The mean $Log_e$ ECM readings, the mean DIAGNOdent readings, ECM scores, DIAGNOdent scores and clinical severity index were analysed using ANOVA (mixed effect model).<br><br>Results reported in a format that did not allow any further |

analysis.

**Comparability of groups at baseline:** there was a significant difference in mean DIAGNOdent scores at baseline (p<0.01). Lesions in ozone group appeared to be more severe than those in the control group.

**Setting:** general dental practice.

# Appendix 5

## Characteristics of included studies – abstracts

| Author(s) | No. participants (no. and type of lesions) | Design | Inclusion criteria | Interventions | Results | Notes |
|---|---|---|---|---|---|---|
| ***Root Caries*** | | | | | | |
| ***Lynch, Johnson and Johnson,[2004]***[57] Belfast, UK**.** | 260 (two primary root carious lesions – 60 subjects with 2 soft PRCLs and 200 with 2 leathery non-cavitated PRCLs, least severe category) | **Design:** RCT.<br><br>**Unit of randomisation:** lesion.<br><br>**Concealment of allocation:** not stated.<br><br>**Blinding:** blinded outcome assessor<br><br>**Intention-to-treat:** no.<br><br>**Length of follow-up:** 6 months.<br><br>**Lost at follow-up:** not stated.<br><br>**Setting:** not stated | Two primary root carious lesions | **Group 1:** Ozone (260 lesions)<br><br>**Group 2:** No treatment (260 lesions)<br><br>**Ozone dosage:** not stated<br><br>**Caries assessment:** Clinical assessment | **Reversal of caries:**<br>*Soft lesions* - at 6 months, 48/60 of ozone treated soft PRCLs had reversed (from index 4 to 3), no significant changes in control soft lesions ($p<0.01$).<br>*Leathery lesions* – 189/200 of ozone treated PRCLs had reversed from index 1 to 0 (hard to arrested), no | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | significant changes for control lesions (p<0.01).<br><br>**Adverse events:** none observed. | |
| ***Pit and Fissure Caries*** | | | | | | |
| ***Holmes and Lynch, 2004*** [53]<br>Belfast, UK. | 38 subjects (76 non-cavitated occlusal caries lesions) | **Design:** RCT.<br><br>**Unit of randomisation:** lesion.<br><br>**Concealment of allocation:** not stated.<br><br>**Blinding:** not stated.<br><br>**Intention-to-treat:** no.<br><br>**Length of follow-up:** 6 months.<br><br>**Lost at follow-up:** 3 subjects. | Two non-cavitated early occlusal carious lesions with radiographic radiolucencies extending 2-4mm into dentine. | **Group 1:** air abrasion + ozone + mineral wash + glass ionomer sealant. After 3 months the glass ionomer sealant was dissecated and replaced with a posterior composite.<br><br>**Group 2:** conventional drilling and filling using posterior composite.<br><br>**Ozone dosage:** 40 seconds<br><br>**Caries assessment:** | No **post-operative sensitivity** was associated with ozone treatment whilst 6/35 subjects in the conventional treatment group complained of some post-operative sensitivity.<br><br>**Reversal of caries:** at 3 months all ozone dentine caries was hard and | Progression of caries in the conventional treatment group not reported.<br><br>“Sensitivity” is a measure used to assess large necrotic lesions and it is considered inappropriate for assessing early carious lesions. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | **Setting:** general dental practice. | | Radiographic and clinical assessment. | required no additional removal.<br><br>**Adverse events:** none observed. | |
| ***Holmes, 2003*[54]*.*** Berkshire, UK. | 376 (2364 primary non-cavitated occlusal fissure lesions). | **Design:** RCT.<br><br>**Unit of randomisation**: lesion<br><br>**Concealment of allocation:** not stated.<br><br>**Blinding:** not stated.<br><br>**Intention-to-treat:** no.<br><br>**Length of follow-up:** 12 months.<br><br>**Lost at follow-up:** 61.<br><br>**Setting:** general dental practice. | Primary occlusal fissure lesions with caries judged to extend 2 mms into dentine (1170 teeth). | **Group 1:** ozone treatment.<br><br>**Group 2:** no treatment.<br>**Ozone dosage:** 10, 20, 30, 40 seconds depending on the clinical severity. Applications were repeated every three months if reversal had not occurred.<br><br>**Caries assessment:** DIAGNOdent (KaVo, Germany) and clinical assessment. | **Reversal of caries:** 99% in the ozone group (1918 lesions); the control lesions did no significant change.<br><br>The DIAGNOdent values correlated with the clinical findings ($p<0.01$).<br><br>**Adverse events:** none observed. | A total of 1937/2364 received ozone application. Unclear how many lesions were randomly allocated to each group (unbalance randomisation ?). |

| | | | | | | |
|---|---|---|---|---|---|---|
| ***Hamid, 2003*[55]. London, UK | 184 (184 non-cavitated pit and fissure carious lesions) | **Design:** RCT.<br><br>**Unit of randomisation:** patient.<br><br>**Concealment of allocation:** not stated<br><br>**Blinding:** not stated<br><br>**Intention-to-treat:** unclear.<br><br>**Length of follow-up:** 6 months.<br><br>**Lost at follow-up:** unclear.<br><br>**Setting:** not stated. | Primary early occlusal pit/fissure lesions with caries extending up to 1 mm into dentine. | **Group 1:** ozone treatment (92 lesions).<br><br>**Group 2:** no treatment (92 lesions).<br><br>**Ozone dosage:** 40 seconds at baseline and at 3 months.<br><br>**Caries assessment:** clinical assessment and DIAGNOdent (KaVo, Germany). | **Reversal of caries:** 86.6% in the ozone group; the control lesions did no significant change (p<0.05).<br><br>The DIAGNOdent values correlated with the clinical findings.<br><br>**Adverse events:** none observed. | |
| ***Megighian and Bertoli I 2004*** [56] Verona, Italy | 80 (300 pit and fissure carious lesions) | **Design:** Randomised clinical trial.<br><br>**Unit of randomisation:** lesion<br>**Concealment of allocation:** not stated. | Pit and fissure carious lesions. | **Group 1:** Ozone (220 lesions).<br><br>**Group 2:** no treatment (80 lesions).<br><br>**Ozone dosage:** 20, 30, 40 seconds according to clinical severity. | **Reversal of caries:** Ozone-treated lesions clinically reversed (p<0.05) while control lesions did not.<br><br>**DIAGNOdent** | Unclear whether the proportion of lesions that clinically reversed or showed a reduction in DIAGNOdent readings were all ozone-treated lesions or included some control lesions. |

| | | | |
|---|---|---|---|
| **Blinding:** double blind.<br><br>**Intention-to-treat:** No.<br><br>**Length of follow-up:** 6 months.<br><br>**Lost at follow-up:** not stated.<br><br>**Setting:** private practice, Italy. | | **Caries assessment:** Clinical assessment and DIAGNOdent (KaVo, Germany). | **:** significant overall reduction in readings for ozone-treated lesions whilst control lesions showed an increase in DIAGNOdent readings.<br><br>The percentage of teeth, which clinically reversed and showed a DIAGNOdent reduction, was 85%. |

# Appendix 6
## Structure of the economic model

Decision Models to assess costs and benefits of HealOzone

The four models depicted in the appendix have a similar structure therefore, only current management plus HealOzone is described here. Markov models can be used to estimate costs and consequences that occur over a series of years (in this study up to 5 years). At the beginning of the first year each patient receives current management plus HealOzone and hence a probability of 1 is attached. At the end of the first year there is a chance that the patients are cured (caries are reversed) or they have progressed. If they have progressed there is a chance that they get the same treatment or get a new treatment (filling). The chance of a patient getting cured is 'pbcure1' and not getting cured is '1-pbcure1'. The chance a patient will receive the same treatment is 'probretreat'. In the model it is assumed that the patient has a fifty percent chance of getting the same treatment or getting a filling. If the first treatment fails the patient moves to the third branch or the fifth branch. The probability of cure does not change in the third branch and those go into the third branch are either cured or are filled. The filled tooth state is a terminal state and patients do not leave it. The model also assumes that when a patient is cured they remain cured for as long as the model runs.

**Figure 15. Decision model to assess the cost and benefits of current management plus HealOzone of non-cavitated root caries (Markov model)**

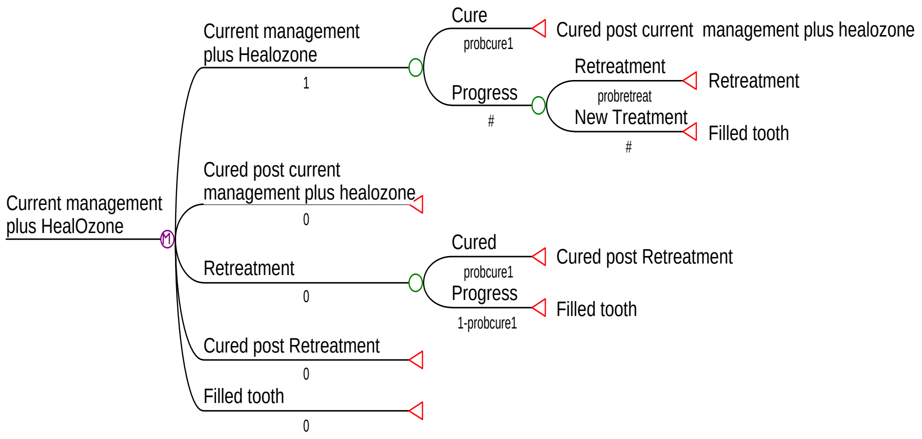



**Figure 16. Decision model to assess costs and benefits of current management of non-cavitated root caries**

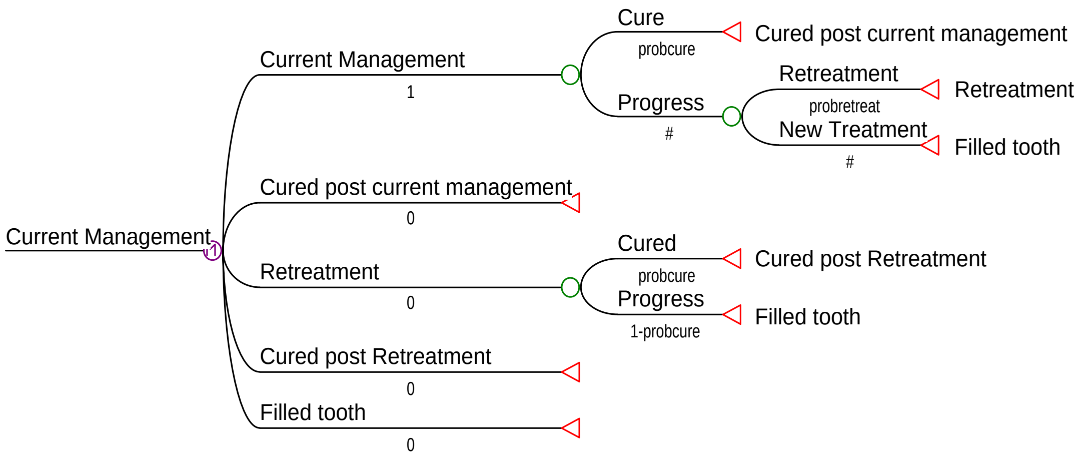


**Figure 17. Decision model to assess costs and benefits of current management of non-cavitated pit and fissure caries**

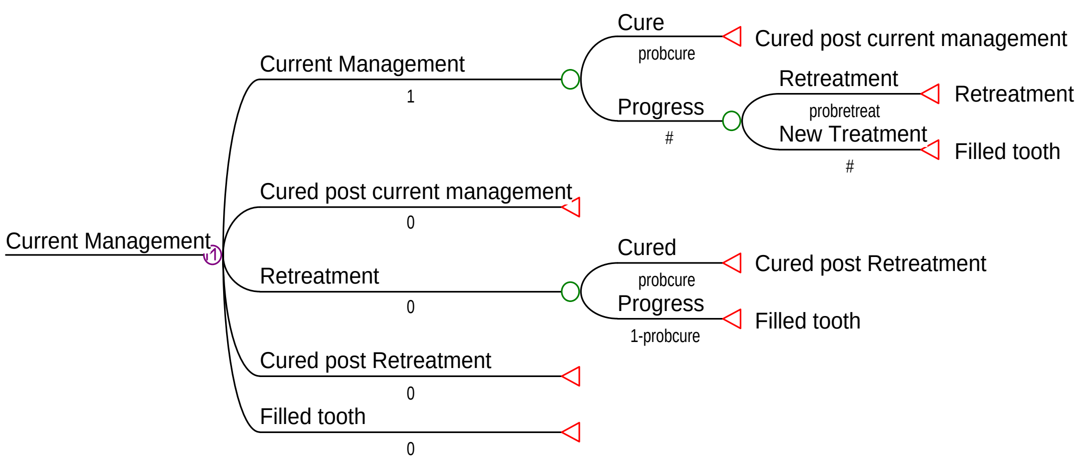



**Figure 18. Decision model to assess costs and benefits of current management plus HealOzone of non-cavitated pit and fissure caries**