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REVIEW

Outcome of primary root canal treatment: systematic review of the literature – Part 2. Influence of clinical factors

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Abstract

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Aims (i) To carry out meta-analyses to quantify the influence of the clinical factors on the efficacy of primary root canal treatment and (ii) to identify the best treatment protocol based on the current evidence.

Methodology The evidence for the effect of each clinical factor on the success rate (SR) of primary root canal treatment was gathered in three different ways: (i) intuitive synthesis of reported findings from individual studies; (ii) weighted pooled SR by each factor under investigation was estimated using random-effect meta-analysis; (iii) weighted effect of the factor under investigation on SR were estimated and expressed as odds ratio for the dichotomous outcomes (success or failure) using fixed- and random-effects meta-analysis. Statistical heterogeneity amongst the studies was assessed by Cochran's (Q) test. Potential sources of statistical heterogeneity were investigated by exploring clinical heterogeneity using meta-regression models which included study characteristics in the regression models.

Results Out of the clinical factors investigated, pre-operative pulpal and periapical status were most frequently investigated, whilst the intra-operative factors were poorly studied in the 63 studies. Four factors were found to have a significant effect on the primary root canal treatment outcome, although the data heterogeneity was substantial, some of which could be explained by some of the study characteristics.

Conclusions Four conditions (pre-operative absence of periapical radiolucency, root filling with no voids, root filling extending to 2 mm within the radiographic apex and satisfactory coronal restoration) were found to improve the outcome of primary root canal treatment significantly. Root canal treatment should therefore aim at achieving and maintaining access to apical anatomy during chemo-mechanical debridement, obturating the canal with densely compacted material to the apical terminus without extrusion into the apical tissues and preventing re-infection with a good quality coronal restoration.

Keywords: outcome, root canal treatment, success, systematic review.

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Introduction

Root canal treatment (RCT) may be defined as the combination of mechanical instrumentation of root canal system, its chemical debridement and filling with an inert material, designed to maintain or restore the

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health of the periradicular tissues. The manner of execution of treatment procedure(s) is so diverse even within prescribed protocols that it is difficult to define it any more precisely and it is accepted that this treatment intervention is not by its nature standardizable. In fact, the procedure is dominated by the tooth in question, in terms of its anatomical complexity and biological status, that is, its pre-operative status. The latter part of the definition alludes to the fact that essentially the same procedure is used to treat two distinct disease entities: (i) the vital but diseased pulp where the goal is to maintain existing periapical health and prevent periapical disease; or (ii) the nonvital or dying pulp associated with periapical disease where the goal is to restore the periradicular tissues back to health. The goal of root canal treatment is therefore to prevent or treat periapical disease; and this simple statement embraces a diverse range of pre-operative and treatment parameters that may or may not all be recorded.

Part 1 of this review has already explored the characteristics of the root canal treatment outcome studies and their effects on the SRs. It was found that there was a substantial variation between studies in their assessment of teeth during follow-up, including the method of radiographic assessment, the radiographic criteria for success (loose and strict), the unit of outcome measure (root and tooth) and the length of follow-up.

The aims of this, part 2 of the systematic review, were (i) to carry out meta-analyses to quantify the influence of the clinical factors on the efficacy of primary root canal treatment and (ii) to identify the best treatment protocol based on current evidence.

Material and methods

In total, 63 studies were included in this part of the systematic review, based on the protocol for literature search, study selection, quality assessment and data extraction described in part 1.

Statistical analyses were performed using the STATA version 9.2 statistical software (Statacorp, College Station, TX, USA). The effects of each clinical factor on the SR of primary root canal treatment were analysed through three different approaches:

1. Intuitive synthesis of reported findings from individual studies. Those studies excluded for the purpose of the statistical analyses were included for this synthesis.

2. Weighted pooled SR by each factor under investigation (all relevant data accumulated from available studies) was estimated using random-effects meta-analysis.

3. Weighted effects of the factor under investigation on SR were estimated and expressed as odds ratio (OR) for the dichotomous outcomes (success or failure) using fixed- and random-effects meta-analysis. This analysis was restricted to studies providing partitioned data on SRs, enabling direct comparison of sub-categories of the factor investigated in the same study.

Statistical heterogeneity amongst the studies was assessed by Cochran's (Q) test. Potential sources of statistical heterogeneity were investigated by exploring clinical heterogeneity using meta-regression models which included study characteristics that were investigated in part 1, as the covariates. If either the estimated proportion of total variation because of the heterogeneity across studies (I^2) or the estimated between-study variance (*tau*2) from the meta-regression model without covariate in the model was reduced substantially (more than 10%), when a covariate was included into the model, the respective covariate was considered to be a potential source of heterogeneity.

Results

Amongst the 63 studies reviewed, none of the studies had evaluated all the clinical factors, consequently, different aspects of data were missing from different studies (Table 1). Pre-selection of individual factors for analysis therefore gave a unique subset of the overall pool of studies that could vary significantly with the combination of factors under scrutiny. For each factor under investigation, the outcomes from each of the three approaches in analysis are reported in their respective section. The estimated pooled SRs by each pre-, intra- and post-operative factor are presented in Tables 2–4. The estimated pooled effects of these factors on the success of treatment are presented in Table 5, whilst the results of meta-regression analyses to explore the source of statistical heterogeneity are presented in Tables 6–8.

Pre-operative factors

Gender

All except two of the previous studies reporting on the influence of this factor ([1]Ingle *et al.* 1965, Adenubi & Rule 1976, Jokinen *et al.* 1978, Oliet 1983, Swartz *et al.* 1983, Smith *et al.* 1993, [2]Friedman *et al.* 1995,

Table 1 Profile of outcome data by potential prognostic factors by the included studies. (Reproduced from part 1 of this review)

Author (year)	Gender	Age	Health	Tooth type	Pulpal status	Periapical status	Lesion size	Rubber dam	Obstruction	Apical size	Canal taper	Irrigant	Medicament	Culture test	RF material and technique	Sealer	RF extent	Quality of RF	Acute flare up	Apical disturbance	Visits of treatment	Restoration	Abutment
Blayney (1922)					✔	✔		✔				✔											
Auerbach (1938)					✔	✔						✔											
Buchbinder (1941)					✔	✔		✔				✔	✔	✔							✔		
Morse & Yates (1941)					✔	✔		✔				✔		✔							✔		
Castagnola & Orlay (1952)					✔	✔		✔													✔		
Grahnén & Hansen (1961)		✔			✔	✔						✔			✔		✔				✔		
Seltzer *et al.* (1963)					✔	✔								✔	✔		✔						
Zeldow & Ingle (1963)								✔				✔		✔	✔						✔		
Bender *et al.* (1964)					✔	✔								✔	✔		✔				✔		
Engström & Lundberg (1965)					✔								✔	✔							✔		
Harty *et al.* (1970)		✔						✔				✔					✔	✔		✔	✔		
Heling & Tamshe (1970, 1971))					✔	✔		✔				✔	✔			✔	✔						
Cvek (1972)					✔	✔		✔				✔		✔							✔		
Selden (1974)					✔	✔	✔																
Werts (1975)					✔	✔																	
Adenubi & Rule (1976)	✔	✔		✔	✔	✔						✔	✔		✔	✔	✔	✔		✔	✔		
Heling & Shapira (1978)					✔	✔		✔					✔	✔	✔	✔	✔				✔	✔	
Jokinen *et al.* (1978)	✔	✔		✔	✔	✔							✔		✔		✔				✔		✔
Kerekes (1978)				✔											✔		✔	✔					
Kerekes (1978)				✔				✔							✔		✔	✔					
Soltanoff (1978)												✔			✔		✔				✔		
Heling & Kischinovsky (1979)					✔	✔		✔				✔	✔		✔	✔	✔						
Barbakow *et al.* (1980a,b, 1981))		✔		✔	✔	✔		✔					✔		✔	✔	✔				✔		
Cvek *et al.* (1982)					✔	✔		✔	✔			✔			✔								
Nelson (1982)		✔			✔	✔										✔	✔	✔		✔			
Boggia (1983)					✔	✔										✔	✔			✔	✔		
Klevant & Eggink (1983)								✔				✔	✔			✔	✔						
Morse *et al.* (1983a,b,c))					✔	✔						✔	✔		✔		✔				✔		
Oliet (1983)	✔	✔			✔	✔						✔			✔	✔	✔				✔		
Swartz *et al.* (1983)	✔	✔		✔		✔									✔		✔					✔	
Pekruhn (1986)					✔	✔		✔				✔				✔					✔		
Byström *et al.* (1987)					✔	✔		✔						✔	✔		✔				✔		
Halse & Molven (1987)					✔	✔									✔		✔						

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Matsumoto *et al.* (1987)					✔	✔	✔	✔					✔	✔			✔				✔		✔
Ørstavik *et al.* (1987) & Eriksen *et al.* (1988)					✔	✔						✔											
Safavi *et al.* (1987)					✔	✔						✔		✔	✔	✔					✔	✔	
Akerblom & Hasselgren (1988)					✔	✔	✔	✔	✔			✔	✔		✔						✔		
Shah (1988)					✔	✔		✔							✔	✔					✔		
Sjögren *et al.* (1990)				✔	✔	✔	✔	✔				✔		✔	✔		✔	✔			✔		
Murphy *et al.* (1991)					✔	✔																	
Cvek (1992)					✔	✔									✔		✔				✔		
Reid *et al.* (1992)								✔					✔		✔	✔					✔		
Jurcak *et al.* (1993)				✔											✔						✔		
Smith *et al.* (1993)	✔	✔			✔	✔		✔			✔				✔	✔	✔				✔		
Peak (1994)				✔	✔	✔									✔		✔						
Friedman *et al.* (1995)					✔	✔						✔	✔		✔	✔							
Çalişken & Şen (1996)			✔		✔	✔	✔	✔				✔	✔		✔	✔				✔	✔		
Ørstavik (1996)					✔	✔		✔				✔											
Peretz *et al.* (1997)		✔			✔	✔																	
Sjögren *et al.* (1997)					✔	✔		✔				✔		✔	✔						✔		
Lilly *et al.* (1998)			✔		✔	✔									✔	✔						✔	
Trope *et al.* (1999)			✔					✔				✔	✔		✔	✔					✔		
Ricucci *et al.* (2000)								✔				✔			✔							✔	
Weiger *et al.* (2000)					✔	✔		✔				✔	✔		✔	✔					✔		
Chugal *et al.* (2001)					✔																		
Deutsch *et al.* (2001)					✔			✔				✔			✔	✔					✔		
Heling *et al.* (2001)					✔	✔						✔				✔	✔	✔				✔	
Peak *et al.* (2001)				✔	✔	✔									✔		✔						
Pettiette *et al.* (2001)					✔	✔																	
Benenati & Khajotia (2002)	✔	✔		✔												✔							
Cheung (2002)	✔	✔		✔	✔	✔		✔					✔		✔	✔					✔		
Hoskinson *et al.* (2002)	✔	✔		✔	✔	✔	✔	✔		✔	✔	✔	✔			✔	✔					✔	
Peters & Wesselink (2002)			✔		✔	✔		✔				✔	✔	✔	✔	✔					✔	✔	
Total	8	13	4	13	51	49	6	33	2	1	2	32	20	14	38	25	29	7	0	5	35	8	2

RF, root filling.

Hoskinson *et al.* 2002, Cheung 2002, Benenati & Khajotia 2002) did not find any significant association between gender and SR. Swartz *et al.* (1983) & Smith *et al.* (1993) had independently reported root canal treatment in male patients to have a significantly higher SR than in female patients.

Only eight studies (Table 1) provided outcome data by gender. The pooled SRs for male patients were similar to those for female patients regardless of whether loose or strict criteria were used (Table 2). This is consistent with the pooled estimate of effects of gender (OR = 1.01; 95% CI: 0.83, 1.23; Table 5a). The heterogeneity 18.1 (7df, $P = 0.011$) was substantial but could not be explained by any of the study characteristics included in the meta-regression models.

Age

Fifteen studies ([1]Strindberg 1956, Seltzer *et al.* 1963, [1]Ingle *et al.* 1965, Harty *et al.* 1970, Barbakow *et al.* 1980a,b, 1981, Nelson 1982, Oliet 1983, Swartz *et al.* 1983, [1]Ørstavik & Hörsted-Bindslev 1993, Sjögren *et al.* 1990, Smith *et al.* 1993, [2]Friedman *et al.* 1995, Benenati & Khajotia 2002, Cheung 2002, Hoskinson *et al.* 2002) had analysed the influence of patients' age on treatment outcome but found no statistically significant difference in SRs stratified by age. It is noted that the age groups were clustered into bands that varied between studies for the purposes of statistical analyses; direct comparison between studies therefore are required for some degree of intuitive interpretation.

Only 13 (Table 1) studies reported outcome data by age range. For the purpose of this review, the outcome data were pooled into three age bands: up to 25 years, 25–50 years and above 50 years. Although the differences were small, the pooled SRs decreased with increase in age regardless of whether strict or loose criteria for success were used (Table 2). Further meta-analyses showed no significant difference in the odds of success amongst the three age bands (Table 5b). No further meta-regression analyses were carried out as the heterogeneity was not significant.

General medical health

Only one study ([1]Storms 1969) had investigated the influence of the patient's general health on the outcome of root canal treatment and reported no statistically significant difference in SRs between healthy and unhealthy (with known systemic disease) patients. Three studies (Çalişken & Şen 1996, Trope *et al.* 1999, Peters & Wesselink 2002) reported that only healthy patients were included in their studies and three other studies ([1]Markitziu & Heling 1981, [1]Seto *et al.* 1985, Lilly *et al.* 1998) analysed patients who had received radiotherapy in the head and neck region. There was insufficient stratified raw data for calculation of the pooled SRs by this factor.

Tooth type

There was a wide variation in the manner of presentation of outcome data by tooth type in various studies; the descriptors or classification used were: upper/lower teeth, anterior/posterior teeth, anterior/premolar/molar, 1/2/3 roots, 1/≥2 canals or each tooth type.

Thirteen studies ([1]Ingle *et al.* 1965, Heling & Tamshe 1970, 1971, Adenubi & Rule 1976, [1]Selden 1974, Jokinen *et al.* 1978, Barbakow *et al.* 1980a,b, 1981, Oliet 1983, Morse *et al.* 1983a–c, Swartz *et al.* 1983, Pekruhn 1986, [1]Ørstavik & Hörsted-Bindslev 1993, Peak 1994, Peretz *et al.* 1997, Benenati & Khajotia 2002, Cheung 2002, Hoskinson *et al.* 2002) had compared the outcome of treatment between tooth types, statistically. Three studies (Swartz *et al.* 1983, Benenati & Khajotia 2002, Cheung 2002) found statistically significant differences in SRs between tooth types. The former two found that mandibular molars had the lowest SR compared with other tooth types. Smith *et al.* (1993) reported that teeth in the mandibular right quadrant were associated with the lowest SR.

Thirteen studies (Table 1) presented the outcome data by tooth type (maxillary incisor and canine, maxillary premolar, maxillary molar, mandibular incisor and canine, mandibular premolar and mandibular molar); the differences in pooled success between different tooth types were small, the mandibular premolar teeth had the highest SRs whilst the mandibular molar teeth had the lowest SRs based on strict criteria (Table 2). When estimating the pooled effect of tooth type, the outcome data from maxillary and mandibular teeth of the same morphological type were pooled together. The results showed that there was no significant difference in the odds of success amongst the three types of teeth: incisors/canines, premolars and molars (Table 5c). The statistical heterogeneity could be partly explained by the 'criteria of success', 'unit of measure', 'geographic location of the study' and 'year of publication' (Table 6).

Pulpal and periapical status

Comparison of pre-operatively vital and nonvital teeth. Fourteen studies had analysed the influence of

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Table 2 Weighted pooled success rates (SRs) by patient factors and pre-operative factors related to the tooth/root

Factor/categories	Total no. of studies[a]	Strict radiographic criteria No. of studies	No. of units	Weighted pooled SR[c] (%)	Loose radiographic criteria No. of studies	No. of units	Weighted pooled SR[c] (%)
Gender							
Male	8	5	2200	65.7 (48.3, 83.1)	6	2667	84.9 (75.9, 94.0)
Female	8	5	3044	65.1 (49.9, 80.2)	6	3537	85.2 (75.8, 94.6)
Age							
Below 25	13	7 (6)[b]	2873	68.3 (52.2, 84.4)	8	2243	86.9 (83.2, 90.7)
Between 25 and 50	11	5	2336	66.8 (50.5, 83.2)	7	1813	86.8 (83.2, 90.4)
Above 50	12	5	1159	65.6 (49.8, 81.4)	8	1880	84.1 (78.5, 89.7)
Tooth type							
Upper incisors and canines	13	9	2021	70.6 (54.7, 86.5)	7	2021	85.6 (75.5, 95.7)
Lower incisors and canines	12	8	523	66.6 (47.7, 85.5)	7 (6)[b]	512	85.1 (72.0, 98.3)
Upper premolars	12	8	918	70.1 (56.6, 83.6)	5	711	80.7 (70.4, 91.1)
Lower premolars	10	7	674	76.8 (64.9, 88.6)	5	490	86.2 (76.2, 96.1)
Upper molars	12	8	1327	75.0 (63.6, 86.5)	6	906	83.3 (75.1, 91.5)
Lower molars	11	7	1222	64.2 (47.4, 81.1)	6	1220	81.7 (73.1, 90.3)
Pulpal/periapical (pa) status							
Vital pulp	22	13 (12)[b]	3027	82.5 (74.0, 91.0)	11 (10)[b]	1911	89.6 (83.1, 96.2)
Nonvital pulp	37	23	6343	73.1 (66.1, 80.0)	23	5928	84.7 (80.2, 89.2)
Nonvital pulp without pa lesion	15	9 (8)[b]	1699	82.1 (72.7, 91.6)	7	1141	90.1 (86.9, 93.3)
Nonvital pulp with pa lesion	48	28	4724	69.6 (61.1, 78.1)	29 (28)[b]	6844	81.4 (76.2, 86.6)
Size of periapical lesion							
≤5 mm	6	4	488	80.2 (70.4, 90.0)	3	343	91.0 (84.6, 97.5)
>5 mm	5	3	308	78.8 (74.2, 83.3)	3	362	79.9 (66.1, 93.8)

[a]Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported SRs based on both criteria.
[b]Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% rates by the respective factor under investigation have been excluded.
[c]Weighted pooled SRs were estimated using random-effects meta-analysis (where there was only one study, its reported SR and confident intervals were presented).

pre-operative pulpal status on the treatment outcome, statistically. Four studies (Grahnén & Hansen 1961, [1]Storms 1969, Smith *et al.* 1993, Hoskinson *et al.* 2002) reported that vital teeth had significantly higher SRs than nonvital teeth, but eight studies (Heling & Tamshe 1970, 1971, Adenubi & Rule 1976, Barbakow *et al.* 1980a,b, 1981, Nelson 1982, Morse *et al.* 1983a–c, Oliet 1983, [1]Ørstavik & Hörsted-Bindslev 1993, [2]Friedman *et al.* 1995) had found no such statistical difference. In contrast, [1]Strindberg (1956) & [1]Teo *et al.* (1986) had reported that nonvital teeth had significantly higher SRs than vital teeth with pulpitis. The majority of the studies exploring this variable ($n = 51$; Table 1) provided the SRs by pulpal status of the teeth. The pooled SRs for vital teeth were higher than those for nonvital teeth by 5% (loose criteria) or 9% (strict criteria; Table 2).

Out of the 63 studies reviewed, 19 had stratified SRs for both pre-operative vital and nonvital pulpal states but one study (Morse & Yates 1941) was excluded from the meta-analyses because of the absence of root canal treatment failure in the vital pulp group. The odds of success of vital teeth were 1.77 (95% CI: 1.35, 2.31) times higher than those for nonvital teeth (Table 5d). The heterogeneity in the data was substantial but could not be explained by the covariates investigated in meta-regression models (Table 7a).

Comparison of pre-operatively vital and nonvital teeth without periapical lesion When comparing the pooled

Table 3 Weighted pooled success rates (SRs) by intra-operative factors (a) excluding those related to root fillings and (b) related to root filling

		Strict radiographic criteria			Loose radiographic criteria		
Factor/categories	Total no. of studies[a]	No. of studies	No. of units	Weighted pooled SR[c] (%)	No. of studies	No. of units	Weighted pooled SR[c] (%)
(a)							
Use of rubber dam isolation							
Yes	31	22	6353	78.0 (72.2, 83.8)	14	3729	84.4 (78.9, 90.0)
No	2	1	335	79.0 (74.6, 83.4)	2	400	82.5 (74.1, 96.4)
Apical size of canal preparation							
Small (ISO 20 – 30)	1	1	351	78.6 (76.4, 80.8)	0	–	–
Large (ISO 35 – 90)	1	1	53	69.8 (63.5, 76.1)	0	–	–
Taper of canal preparation							
Narrow	2	1	200	75.5 (72.5, 78.5)	1	534	82.2 (80.5, 83.9)
Wide	2	1	289	75.1 (72.6, 77.6)	1[b]	287	88.2 (86.3, 90.1)
Irrigant							
NaOCl	20	12	3374	79.3 (72.1, 86.6)	12 (11)[b]	3050	87.8 (82.4, 93.1)
Iodine	1	–	–	–	1	211	96.0 (93.4, 98.6)
Chloramine	1	–	–	–	1	104	63.0 (53.7, 72.3)
H_2SO_4	1	1	1277	82.0 (79.9, 84.1)	0	–	–
Water	2	1	1139	90.0 (88.3, 91.7)	1	42	83.0 (71.6, 94.4)
Saline	3	2	1189	64.4 (18.1, 100)	2	1136	90.3 (84.4, 96.1)
EDTA	3	2	258	72.2 (66.7, 77.6)	1	202	81.0 (75.6, 86.4)
Biosept	1	1	55	94.0 (88.0, 100)	0	–	–
Medicament							
Antibiotics	1	1	859	88.0 (85.8, 90.2)	1	859	95.1 (93.7, 96.6)
Antiseptics excluding calcium hydroxide	9	6	1356	70.2 (55.5, 84.8)	4	671	85.6 (78.0, 93.1)
$Ca(OH)_2$	8	7	1106	75.0 (66.3, 83.8)	4	342	91.0 (86.3, 95.8)
Steroid	3	3	2221	67.5 (41.0, 94.0)	1	2142	67.0 (65.0, 69.0)
Culture before obturation							
Negative	13	9	1523	81.9 (71.6, 92.2)	6	2757	88.2 (83.3, 93.1)
without periapical lesion	*5*	*3*	*372*	*88.6 (85.4, 91.8)*	*3 (2)*[b]	*1142*	*90.9 (86.2, 95.7)*
with periapical lesion	*10*	*7*	*578*	*73.1 (46.3, 100)*	*5*	*1555*	*86.8 (78.2, 95.5)*
Positive	8	4	99	68.5 (58.9, 79.5)	5	793	81.7 (79.0, 84.4)
without periapical lesion	*3*	*2*	*54*	*63.7 (51.0, 76.4)*	*2*	*284*	*91.6 (88.3, 94.8)*
with periapical lesion	*5*	*3*	*45*	*73.6 (61.0, 86.2)*	*3 (2)*[b]	*437*	*75.6 (71.5, 79.6)*
Apical disturbance							
No	4	3	1114	87.0 (82.4, 91.5)	3	1168	88.2 (78.9, 97.5)
Yes	5	3	1043	79.1 (65.5, 92.8)	3	173	72.6 (50.3, 94.9)
No. of visits							
Single	11	6	1077	77.2 (63.8, 90.6)	7 (6)[b]	538	89.5 (86.8, 92.1)
Multiple	30	18	8373	77.4 (69.3, 85.5)	19	7361	85.5 (80.7, 90.2)
(b)							
Root filling material/technique							
Chloropercha	14	11	5766	80.0 (70.3, 91.4)	5	3136	86.9 (72.3, 99.2)
Lateral compaction of GP	23	13 (12)[b]	2986	76.0 (66.6, 85.4)	13	2556	85.8 (81.9, 89.7)
Single GP point	6	2	128	64.4 (56.2, 72.6)	5	2657	84.7 (79.7, 89.7)
Silver point	7	3	220	81.0 (67.0, 94.9)	3	1485	88.4 (83.6, 93.2)
Amalgam	1	–	–	–	1	162	85.2 (79.7, 90.7)
Sealer							
Zinc oxide eugenol-based	13	8	3991	75.3 (63.9, 86.6)	8	3724	86.5 (83.1, 89.9)
Resin-based	8	5	976	70.7 (52.6, 88.7)	5	785	87.3 (76.3, 98.2)
Calcium hydroxide-based	2	2	239	80.2 (75.2, 85.3)	2	239	90.8 (84.9, 96.7)
Glass–ionomer-based	1	1	250	82.4 (77.1, 86.9)	1	250	94.4 (90.8, 96.9)
Endomethasone	1	1	52	60.0 (46.7, 73.3)	1	52	90.0 (81.8, 98.2)

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Table 3 (*continued*)

Factor/categories	Total no. of studies[a]	Strict radiographic criteria: No. of studies	No. of units	Weighted pooled SR[c] (%)	Loose radiographic criteria: No. of studies	No. of units	Weighted pooled SR[c] (%)
Apical extent of root filling (RF)							
Teeth with any periapical status							
Short RF	25	13	2106	76.8 (71.3, 82.3)	15	4112	82.5 (78.2, 86.7)
Flush RF	23	13	2874	77.3 (69.6, 85.0)	13 (11)[b]	4305	85.2 (80.0, 90.3)
Long RF	28	16	2599	65.8 (54.1, 77.5)	16 (15)[b]	2567	74.5 (67.9, 81.2)
Teeth with no periapical lesion							
Short RF	5	2	187	93.2 (89.6, 96.8)	3	673	89.9 (82.1, 97.7)
Flush RF	5	2	102	90.4 (77.0, 100)	3	682	92.3 (89.5, 95.2)
Long RF	5	2	180	83.2 (54.4, 100)	3	169	74.2 (67.6, 80.8)
Teeth with periapical lesion							
Short RF	10	4	234	69.9 (61.5, 78.3)	6	801	74.9 (66.1, 83.7)
Flush RF	8	4	331	83.7 (72.7, 94.7)	4 (3)[b]	844	84.2 (78.7, 89.6)
Long RF	11	5	290	73.6 (64.3, 83.0)	6	558	80.8 (70.2, 91.5)
Quality of root filling							
Teeth with any periapical status							
Satisfactory	7	5	2173	87.0 (82.3, 91.7)	3	1076	82.9 (70.4, 95.4)
Unsatisfactory	7	5	427	61.1 (50.4, 71.8)	3	116	64.2 (46.2, 82.1)
Teeth with periapical lesion							
Satisfactory	2	1	193	86.5 (81.7, 91.3)	1	169	63.9 (56.7, 71.1)
Unsatisfactory	2	1	11	81.8 (59.0, 100)	1	23	69.6 (50.8, 88.4)

EDTA, ethylene-diamine-tetra-acetic acid; RF, root filling; GP, gutta-percha.
[a]Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported SRs based on both criteria.
[b]Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% rates by the respective factor under investigation have been excluded.
[c]Weighted pooled SRs were estimated using random-effects meta-analysis (where there was only one study, its reported SR and confident intervals were presented).

Table 4 Weighted pooled success rates (SRs) by post-operative restorative status of the tooth

Factor/categories	Total no. of studies[a]	Strict radiographic criteria: No. of studies	No. of units	Weighted pooled SR[b] (%)	Loose radiographic criteria: No. of studies	No. of units	Weighted pooled SR[b] (%)
Quality of coronal restoration at recall							
Unsatisfactory	6	4	402	60.4 (53.8, 67.1)	2	601	75.6 (56.3, 95.0)
Satisfactory	8	6	763	77.9 (69.7, 86.1)	3	763	85.1 (69.2, 100)
Treated tooth being used as abutment for prosthesis							
Yes	1	–	–	–	1	11	45.5 (30.5,60.5)
No	1	–	–	–	1	74	79.7 (75.0,84.4)

[a]Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported SRs based on both criteria.
[b]Weighted pooled SRs were estimated using random-effects meta-analysis (where there was only one study, its reported SR and confident intervals were presented).

SRs between vital and nonvital teeth without pre-operative periapical lesion, the difference was <1% regardless of whether strict or loose criteria were used (Table 2).

Out of the 63 selected studies, 11 studies had presented stratified outcome data for both of these pre-operative conditions and were included for estimation of the pooled OR. The odds of success for vital teeth was similar to those for nonvital teeth without periapical lesion (OR = 1.08; 95% CI: 0.69, 1.67; Table 5d). The heterogeneity 33.5 (10 df) was significant. Meta-regression analyses showed that the covariate 'geographic location of study' and 'duration after treatment' were responsible for some of the heterogeneity (Table 7b).

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Table 5 Summary of meta-analyses for the effects of clinical factors on success rates of root canal treatment

Comparisons (test versus reference categories)	No. of studies	Odds ratio	95% CI	Heterogeneity	
				χ^2 value	*P* value
(a) Gender					
Male versus female	8	1.01	0.827, 1.23	18.1	0.011
(b) Age					
<25 vs. 25–50	10	0.95	0.84, 1.08	11.8	0.226
<25 vs. >50	10	0.96	0.82, 1.12	9.8	0.371
(c) Tooth type					
Premolars versus incisors	10	1.16	0.86, 1.57	29.5	0.001
Molars versus incisors	11	0.92	0.56, 1.51	98.0	<0.001
(d) Effects of pulpal and periapical (pa) status					
Vital versus Nonvital	18	1.77	1.35, 2.31	61.6	<0.001
Vital versus nonvital without pa lesion	11	1.08	0.69, 1.67	33.5	<0.001
Vital versus nonvital with pa lesion	17	2.35	1.77, 3.13	53.6	<0.001
Nonvital without versus with pa lesion	13	1.95	1.35, 2.81	45.8	<0.001
Small versus large pa lesion	5	1.55	0.85, 2.84	11.9	0.018
(e) Effects of pre-obturation culture results					
−ve versus +ve culture results (any pa status)	6	1.17	0.95, 1.44	6.1	0.294
−ve versus +ve culture results (teeth with no pa lesion)	3	1.04	0.65, 1.64	0.9	0.651
−ve versus +ve culture results (teeth with pa lesion)	3	2.12	0.81, 5.53	4.0	0.135
(f) Effects of apical extent of root filling					
Flush versus short (any pa status)	21	1.27	0.93, 1.73	125.0	<0.001
Flush versus short (teeth with no pa lesion)	5	0.83	0.55, 1.23	8.8	0.067
Flush versus short (teeth with pa lesion)	7	1.56	1.26, 1.94	12.0	0.061
Flush versus long (any pa status)	21	2.34	1.87, 2.93	56.1	<0.001
Flush versus long (teeth with no pa lesion)	5	3.72	2.48, 5.60	4.8	0.304
Flush versus long (teeth with pa lesion)	7	1.74	1.36, 2.21	10.2	0.117
Short versus long (any pa status)	24	1.80	1.34, 2.42	117.6	<0.001
Short versus Long (teeth with no pa lesion)	5	2.89	0.89, 9.08	26.3	<0.001
Short versus long (teeth with pa lesion)	9	1.06	0.84, 1.33	14.3	0.075
(g) Quality of root fillings					
Satisfactory versus unsatisfactory	7	3.92	2.26, 6.78	27.6	<0.001
(h) Number of treatment visits					
Single versus multiple (seven studies)	7	1.16	0.82, 1.64	4.43	0.619
Single versus Multiple (three randomized controlled trials)	3	1.89	0.99, 3.63	0.027	0.986
Single versus multiple (three RCTs after excluding cases without pa lesion or not dressed with $Ca(OH)_2$ in multiple visit group)	3	1.35	0.63, 2.88	1.88	0.391
(i) Quality of coronal restorations					
Satisfactory versus unsatisfactory	7	1.82	1.48, 2.25	11.87	0.065

Comparison of pre-operatively vital and nonvital teeth with periapical lesions. The results for this group were in stark contrast to the previous groups; the pooled SRs of vital teeth were 8% (loose criteria) and 13% (strict criteria) higher than those of nonvital teeth with pre-operative periapical lesions (Table 2).

Out of the 63 studies, 18 studies had stratified outcome data by both pre-operative vital teeth versus nonvital teeth with periapical lesion. The paper by Morse & Yates (1941) was not included in the meta-analyses because of the absence of failed cases amongst the vital teeth group, leaving 17 studies in the meta-analysis (Table 5d). The results showed that the odds of success of vital teeth was 2.35 (95% CI: 1.77, 3.13) times higher than nonvital teeth with pre-operative periapical lesion (Table 5d). The heterogeneity 53.6 (16 df) was substantial. However, none of the explored covariates was found to be responsible for the remaining heterogeneity as they neither reduced the I^2 or the *tau*2 values when they were

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Table 6 Meta-regression analyses to account for heterogeneity in analysing the effects of tooth type on the success rate of root canal treatment

Covariate included	Proportion of variation because of heterogeneity (I^2)	Estimate of between-study variance (*tau2*)
(a) Comparison of premolars versus incisors (n = 10)		
None	0.70	0.11
Criteria for success (loose or strict)	0.58	0.07
Unit of measure (root or tooth)	0.55	0.08
Geographic location of study (USA, Scandinavian or other countries)	0.20	0.01
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.74	0.16
Duration after treatment (≥4 years or not)	0.70	0.12
Year of publication (before 1970s, 1970–1989, 1990–2002	<0.001	<0.001
(b) Comparison of molars versus incisors (n = 10)		
None	0.90	0.36
Criteria for success (loose or strict)	0.87	0.28
Unit of measure (root or tooth)	0.79	0.20
Geographic location of study (USA, Scandinavian or other countries)	0.15	0.04
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.90	0.37
Duration after treatment (≥4 years or not)	0.90	0.42
Year of publication (before 1970s, 1970–1989, 1990–2002	0.32	0.42

entered separately into the meta-regression models (Table 7c).

Comparison of pre-operatively nonvital teeth with or without periapical lesion. Ten studies ([1]Engström *et al.* 1964, [1]Heling & Tamshe 1970, 1971, Adenubi & Rule 1976, Selden 1974, Jokinen *et al.* 1978, Morse *et al.* 1983a–c, Swartz *et al.* 1983, Sjögren *et al.* 1990, [2]Chugal *et al.* 2001, Hoskinson *et al.* 2002) had compared the SRs of nonvital teeth/roots with and without periapical lesion statistically, most found the former were associated with significantly lower SRs than the latter. Only Morse *et al.* (1983a–c) could not find a statistical difference.

The above findings are consistent with some studies ([1]Strindberg 1956, Nelson 1982, Matsumoto *et al.* 1987, Halse & Molven 1987, [1]Ørstavik & Hörsted-Bindslev 1993, Smith *et al.* 1993, [2]Friedman *et al.* 1995) that investigated the periapical status without stratifying the pulpal status. [1]Teo *et al.* (1986) and Peak (1994), however, reported no significant difference in SRs between teeth/roots with or without periapical lesion.

Of the nonvital teeth, the pooled SRs for those without periapical lesions were 9% (loose criteria) and 13% (strict criteria) higher than for those with periapical lesion pre-operatively (Table 2).

Of the 63 studies, 14 studies provided stratified outcome data by both nonvital teeth with and without periapical lesion. The paper by Sjögren *et al.* (1990) was not included in the meta-analysis because of the absence of failed cases amongst the teeth without pre-operative periapical lesion, leaving 13 studies for the meta-analysis (Table 5d). It was evident that nonvital teeth without periapical lesion had approximately 1.95 (95% CI: 1.35, 2.81) times higher odds of success than nonvital teeth with periapical lesions (Table 5d). The heterogeneity 45.8 (12 df) was substantial and could be partly explained by the 'geographic location of studies' and 'year of publication' (Table 7d).

Size of periapical lesion

Ten studies had statistically compared the SRs of teeth with pre-operative, large or small periapical lesions; six ([1]Storms 1969, Selden 1974, Matsumoto *et al.* 1987, [2]Friedman *et al.* 1995, [2]Chugal *et al.* 2001, Hoskinson *et al.* 2002) found that teeth with smaller lesions were associated with significantly higher SRs than those with larger lesions. In contrast, [1]Strindberg (1956), Byström *et al.* (1987) and Sjögren *et al.* (1990, 1997) found no statistical difference.

Only six reviewed studies (Table 1) provided the outcome data by the size of lesion. By pooling the data for lesion size into <5 or ≥5 mm in diameter, the pooled SR for small lesions was 11% (loose criteria) and 1% (strict criteria) higher than that for large lesions (Table 2). The estimated pooled odds of success for small lesions was higher but not statistically significant when compared with the pooled odds of success for large lesions (OR = 1.55; 95% CI: 0.85, 2.84; Table 5d). The heterogeneity 11.9 (4df, P = 0.018) in the estimate was substantial and could be partly

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Table 7 Meta-regression analyses to account for heterogeneity in analysing the effects of pulpal and periapical status on the success rate of root canal treatment

Covariate included	Proportion of variation because of heterogeneity (I^2)	Estimate of between-study variance (*tau*2)
(a) Comparison of vital versus nonvital teeth (*n* = 18)		
None	0.72	0.22
Criteria for success (loose or strict)	0.74	0.19
Unit of measure (root or tooth)	0.74	0.24
Geographic location of study (USA, Scandinavian or other countries)	0.68	0.26
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.71	0.35
Duration after treatment (≥4 years or less)	0.70	0.23
Year of publication (before 1970s, 1970–1989, 1990–2002	0.71	0.27
(b) Comparison of vital versus nonvital without pa lesion (*n* = 11)		
None	0.70	0.19
Criteria for success (loose or strict)	0.67	0.24
Unit of measure (root or tooth)	0.72	0.24
Geographic location of study (USA, Scandinavian or other countries)	0.58	0.21
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.61	0.17
Duration after treatment (≥4 years or less)	0.53	0.11
Year of publication (before 1970s, 1970–1989, 1990–2002	0.70	0.21
(c) Comparison of vital versus nonvital with pa lesion (*n* = 17)		
None	0.70	0.34
Criteria for success (loose or strict)	0.69	0.23
Unit of measure (root or tooth)	0.72	0.39
Geographic location of study (USA, Scandinavian or other countries)	0.74	0.48
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.77	0.74
Duration after treatment (≥4 years or less)	0.72	0.41
Year of publication (before 1970s, 1970–1989, 1990–2002	0.62	0.62
(d) Comparison of nonvital teeth with or without pa lesion (*n* = 13)		
None	0.74	0.18
Criteria for success (loose or strict)	0.71	0.15
Unit of measure (root or tooth)	0.67	0.24
Geographic location of study (USA, Scandinavian or other countries)	0.65	0.26
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.80	0.33
Duration after treatment (≥4 years or less)	0.69	0.14
Year of publication (before 1970s, 1970–1989, 1990–2002	0.25	0.01
e) Comparison of small and large lesions (*n* = 5)		
None	0.66	0.27
Criteria for success (loose or strict)	0.65	0.28
Unit of measure (root or tooth)	0.32	0.07
Geographic location of study (USA, Scandinavian or other countries)	0.82	0.78
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	–	–
Duration after treatment (≥4 years or less)	0.32	0.07
Year of publication (before 1970s, 1970–1989, 1990–2002	0.65	0.28

explained by 'unit of outcome measure' and 'duration after treatment' (Table 7e).

Intra-operative factors

Use of rubber dam isolation during treatment

None of the studies on primary root canal treatment had analysed the influence of use of rubber dam isolation on outcome of root canal treatment. Thirty-one studies reported the routine use of rubber dam during treatment whilst only two studies reported that rubber dam was not used. Twenty-eight studies did not mention the use of rubber dam isolation in their treatment protocol. There was no obvious difference in the pooled SRs between the treatments carried out under rubber dam isolation or not (Table 3a). The effects of use of rubber dam isolation could not be analysed further because of insufficient data.

Apical size of canal preparation

Only three studies ([1]Strindberg 1956, [1]Kerekes & Tronstad 1979, Hoskinson *et al.* 2002) have analysed

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Table 8 Meta-regression analyses to account for heterogeneity in analysing the effects of apical extent of root filling (RF) on the success rate of root canal treatment

Covariate included	Proportion of variation because of heterogeneity (I^2)	Estimate of between-study variance (*tau*2)
(a) Comparison of flush versus short RF ($n = 21$)		
None	0.84	0.45
Criteria for success (loose or strict)	0.84	0.47
Unit of measure (root or tooth)	0.83	0.47
Geographic location of study (USA, Scandinavian or other countries)	0.80	0.47
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.71	0.25
Duration after treatment (≥4 years or less)	0.85	0.48
Year of publication (before 1970s, 1970–1989, 1990–2002	0.86	0.62
(b) Comparison of flush versus long RF ($n = 21$)		
None	0.64	0.18
Criteria for success (loose or strict)	0.64	0.18
Unit of measure (root or tooth)	0.65	0.17
Geographic location of study (USA, Scandinavian or other countries)	0.60	0.17
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.37	0.07
Duration after treatment (≥4 years or less)	0.64	0.16
Year of publication (before 1970s, 1970–1989, 1990–2002	0.65	0.18
(c) Comparison of short versus long RF ($n = 24$)		
None	0.80	0.43
Criteria for success (loose or strict)	0.81	0.46
Unit of measure (root or tooth)	0.77	0.39
Geographic location of study (USA, Scandinavian or other countries)	0.75	0.36
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.78	0.38
Duration after treatment (≥4 years or less)	0.77	0.42
Year of publication (before 1970s, 1970–1989, 1990–2002	0.79	0.42
(d) Comparison of satisfactory versus unsatisfactory RF ($n = 7$)		
None	0.78	0.53
Criteria for success (loose or strict)	0.82	0.64
Unit of measure (root or tooth)	0.82	0.64
Geographic location of study (USA, Scandinavian or other countries)	0.78	0.64
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.75	0.40
Duration after treatment (≥4 years or less)	0.80	0.53
Year of publication (before 1970s, 1970–1989, 1990–2002	0.62	0.11
(e) Comparison of satisfactory versus unsatisfactory restoration ($n = 7$)		
None	0.50	0.09
Criteria for success (loose or strict)	0.57	0.12
Unit of measure (root or tooth)	Insufficient data	
Geographic location of study (USA, Scandinavian or other countries)	0.54	0.11
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.54	0.11
Duration after treatment (≥4 years or less)	0.53	0.11
Year of publication (before 1970s, 1970–1989, 1990–2002	0.41	0.07

the effect of apical size of canal preparation on treatment outcome. Although none of them found any significant influence, both [1]Strindberg (1956) & Hoskinson *et al.* (2002) reported that the SRs decreased with increase of apical size of preparation. The raw data from Hoskinson *et al.*'s (2002) study showed that SR of small (ISO 20–30) apical preparations (77%) was higher than that of large (ISO 35–90) preparations (70%; Table 3a). The effects of size of preparation could not be analysed further because of insufficient data.

Taper of canal preparation

Two studies (Smith *et al.* 1993, Hoskinson *et al.* 2002) analysed the influence of taper of canal preparation on treatment outcome. Smith *et al.* (1993) using loose criteria for determination of success, found that a 'flared' (exact degree of taper was not reported) preparation (wide taper) resulted in significantly higher SRs compared with a 'conical' preparation (narrow taper). In contrast, Hoskinson *et al.* (2002) using strict criteria, did not find any significant difference in

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treatment outcome between narrow (0.05) and wide (0.10) canal tapers. The SRs stratified by taper of canal preparation are presented in Table 3a. The effect of taper of canal preparation could not be analysed further because of insufficient data.

Canal obstruction and other technical errors

Four studies ([1]Strindberg 1956, [1]Engström *et al.* 1964, Cvek *et al.* 1982, Sjögren *et al.* 1990) have investigated the influence of canal obstruction and other procedural errors on treatment outcome. [1]Engström *et al.* (1964), Cvek *et al.* (1982) and Sjögren *et al.* (1990) found that the presence of canal obstruction resulted in significantly lower SRs, in complete contrast to the findings of [1]Strindberg (1956). Cvek *et al.* (1982) and Sjögren *et al.* (1990) reported that root canal treatment with iatrogenic perforations resulted in significantly lower SRs, whilst [1]Strindberg (1956) found that instrument separation during treatment reduced the SR significantly. None of the studies presented stratified outcome data for the effect of canal obstruction.

Irrigant

Different types of irrigants have been used singly or in various combinations in the studies reviewed, including solutions of: sodium hypochlorite, iodine, chloramine, sulphuric acid, water, saline, ethylene-diamine-tetra-acetic acid (EDTA) solution, hydrogen peroxide, organic acid, Savlon®, Biosept® and quaternary ammonium compound. Some studies ($n = 32$) standardized the use of irrigant, whilst others (10 studies) used a combination of irrigants; 20 studies did not present any information on irrigants. None of the studies has systematically investigated the effect of irrigant on SRs. [1]Cvek *et al.* (1976) found that using 0.5% sodium hypochlorite solution was associated with better healing than using 5% solution after a 3-month canal dressing with $Ca(OH)_2$, but the difference was not statistically significant. The pooled SRs by different irrigants are presented in Table 3a. There was no obvious trend in pooled SRs by the type of irrigant used. The effect of type of irrigant could not be analysed further because of insufficient data.

Medicament

Most studies did not standardize the type of root canal medicament during treatment but the use of a number of medicaments has been reported. In descending order of frequency of reported use, they are: calcium hydroxide ($n = 15$), phenolic compound ($n = 8$), iodine ($n = 4$), creosote ($n = 3$), cresatin ($n = 3$), formaldehyde-based compounds ($n = 3$), corticosteroid ($n = 3$), antibiotics ($n = 2$), Grossman's solution ($n = 1$) and eugenol ($n = 1$). Four studies (Adenubi & Rule 1976, Jokinen *et al.* 1978, Trope *et al.* 1999, Cheung 2002) have investigated the influence of canal medicament on treatment outcome. Adenubi & Rule (1976) found no difference between chloromycetin and neomycin as canal medicament. Jokinen *et al.* (1978) reported that roots treated with a medicament containing corticosteroid had significantly better outcomes than those treated without corticosteroid. Trope *et al.* (1999) found that teeth dressed with calcium hydroxide had significantly higher SRs than those with no dressing. Cheung (2002) concluded that treatment using calcium hydroxide as intra-canal dressing was associated with longer mean survival times than those treatments using Ledermix® or those without medicament dressing at all.

Twenty studies (Table 1) presented the outcome data based on the type of medicament. The pooled SRs of teeth dressed with steroid were lower than those dressed with antibiotics or antiseptics, regardless of whether strict or loose criteria were used (Table 3a). No further analysis was carried out because of insufficient data.

Root canal bacterial culture test results (positive or negative) prior to obturation

Comparison of pre-obturation root canal culture test results regardless of periapical status. Twelve studies have investigated the influence of bacterial culture (prior to obturation) results on treatment outcome; six studies (Buchbinder 1941, [1]Frostell 1963, [1]Engström *et al.* 1964, Engström & Lundberg 1965, [1]Oliet & Sorin 1969, Sjögren *et al.* 1997) found that canals with negative culture results prior to obturation were associated with significantly higher SRs than those with positive culture results. In contrast, the other six studies (Seltzer *et al.* 1963, Bender *et al.* 1964, [1]Storms 1969, Heling & Shapira 1978, Matsumoto *et al.* 1987, Peters & Wesselink 2002) detected no significant difference.

Fourteen studies (Table 1) provided information on treatment outcome related to the bacterial culture test results prior to root canal obturation. The pooled SRs for teeth with negative culture results were higher than those with positive culture results by 7% (loose criteria) and 13% (strict criteria), respectively (Table 3a).

Of the 63 studies initially identified, six studies presented SRs by both positive and negative pre-obturation root canal culture results. The meta-analyses

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showed the odds of success of teeth with pre-obturation negative culture were not significantly different from those of teeth with a positive culture (OR = 1.17, 95% CI: 0.95, 1.44; Table 5e). The heterogeneity [6.1 (5 df)] was not significant, therefore, no further meta-regression analysis was carried out.

Comparison of pre-obturation root canal culture test results for teeth without periapical lesion. For those teeth without a pre-operative periapical lesion, the pooled SR of teeth with negative culture results was 1% lower (loose criteria) and 24% higher (strict criteria) than those teeth with positive culture (Table 3a).

Only three studies presented stratified SRs by both culture test results for teeth without periapical lesions. Meta-analysis results showed that there was no significant difference in SRs between teeth with negative or positive culture test results prior to obturation (OR = 1.04, 95% CI: 0.65, 1.64; Table 5e). The heterogeneity 0.86 (2 df) was not significant and therefore, no further meta-regression analysis was carried out.

Comparison of pre-obturation root canal culture test results for teeth with periapical lesions. Interestingly, Bender *et al.* (1964) found that culture results had a significant influence on the outcome of treatment when only the teeth associated with periapical lesions were considered. For those teeth with pre-operative periapical lesion, the pooled SRs of teeth with negative bacterial cultures prior to root filling were 11% higher (loose criteria) and 1% lower (strict criteria), respectively, than those of teeth with positive cultures (Table 3a).

Stratified outcome data were only available from three studies. Although the difference was not statistically significant, the odds of success of those teeth with pre-operative periapical lesion and negative culture were two times (OR = 2.12, 95% CI: 0.81, 5.53) higher than those teeth with periapical lesions and positive culture results (Table 5e). The heterogeneity 4.0 (3 df) was not significant, therefore no further meta-regression analysis was carried out.

Root filling material and technique (single-point gutta-percha, lateral condensation of gutta-percha, silver point, amalgam)

A number of root filling materials have been used in the studies, including: gutta-percha, silver points, amalgam, Hydron® (poly-hydroxyethyl methacrylate), Alytit®, and iodoform paste. Most of the studies obturated the canals using gutta-percha with various types of sealer (24 studies) or gutta-percha softened in chloroform (chloropercha; 14 studies); one study used iodoform paste for obturation of all their cases. Most others (13 studies) used a combination of obturation materials or techniques and ten studies did not present any information on root filling material/technique.

Most of the studies ([1]Strindberg 1956, Seltzer *et al.* 1963, Bender *et al.* 1964, Heling & Tamshe 1970, 1971, Adenubi & Rule 1976, Swartz *et al.* 1983, [1]Teo *et al.* 1986, Reid *et al.* 1992, Peak 1994, [2]Friedman *et al.* 1995) which have investigated the effects of root filling materials/techniques on treatment outcome, did not find any significant influence. There were however some exceptions; Reid *et al.* (1992) found that gutta-percha root fillings were associated with failure significantly less often than Hydron® root fillings. Smith *et al.* (1993) reported that root canals filled with apical amalgam followed by lateral compaction of gutta-percha coronally were associated with significantly higher SRs than those filled with apical amalgam only.

Stratified data on SRs associated with root filling material/technique could be extracted from 38 studies (Table 1) and the pooled SRs are presented in Table 3b. Teeth with chloropercha root fillings were associated with 1% (loose criteria) and 4% (strict criteria) higher pooled SRs than those teeth with lateral compaction of gutta-percha with sealer (Table 3b).

Different types of sealer have been used, including: Zinc oxide eugenol-based (Bioseal®, Grossman® cement, Procosol®, Roth's root canal sealer®), resin-based (AH26®), glass–ionomer-based (Ketac Endo®), calcium hydroxide-based (CRCS®, Sealapex®) and Endomethasone®. Zinc oxide eugenol-based sealers (14 studies) or AH26® (eight studies) were the most frequently used. Three studies did not standardize the use of sealer and 34 studies did not report this information. Four studies (Adenubi & Rule 1976, Nelson 1982, Ørstavik *et al.* 1987, Eriksen *et al.* 1988, [1]Waltimo *et al.* 2001) had compared the outcome of treatment using different sealers. Only Nelson (1982) reported that zinc oxide eugenol-based sealers were associated with significantly higher SRs than other sealers (KRI paste®, N2®, Endomethasone®, Spad®) and the others concluded that the type of sealer used had no significant effect on treatment outcome.

The pooled SRs for teeth filled with the resin based-sealer, AH26® had 0.8% higher (loose criteria) and 4.6% lower (strict criteria) SRs than those obturated with zinc oxide eugenol-based sealers (Table 3b). The effects of root filling techniques, materials and type of

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sealers were not investigated further because of insufficient data.

Apical extent of root filling

Sixteen studies had investigated the influence of apical extent of root filling on treatment outcome. Most of the previous studies classified the various extents into three categories for statistical analyses: >2 mm short of radiographic apex (short), 0–2 mm within the radiographic apex (flush) and extruded beyond the radiographic apex (long). Most found that this factor had significant influence on the SRs; flush root fillings were associated with higher SRs than short root fillings ([1]Strindberg 1956, [1]Storms 1969, Harty *et al.* 1970, Adenubi & Rule 1976, Nelson 1982, Morse *et al.* 1983a–c, Sjögren *et al.* 1990, [1]Ørstavik & Hörsted-Bindslev 1993, Smith *et al.* 1993) or long root fillings ([1]Strindberg 1956, Seltzer *et al.* 1963, Bender *et al.* 1964, [1]Engström *et al.* 1964, Harty *et al.* 1970, Adenubi & Rule 1976, Jokinen *et al.* 1978, Nelson 1982, Swartz *et al.* 1983, Klevant & Eggink 1983, Oliet 1983, Sjögren *et al.* 1990, [1]Ørstavik & Hörsted-Bindslev 1993, Smith *et al.* 1993); short root fillings in turn had significantly higher SRs than long root fillings (Seltzer *et al.* 1963, Bender *et al.* 1964, [1]Engström *et al.* 1964, Adenubi & Rule 1976, Jokinen *et al.* 1978, Nelson 1982, Klevant & Eggink 1983, Oliet 1983, Swartz *et al.* 1983, [1]Teo *et al.* 1986, Matsumoto *et al.* 1987, [1]Ørstavik & Hörsted-Bindslev 1993). Seven studies (Soltanoff 1978, Halse & Molven 1987, Byström *et al.* 1987, Peak 1994, [2]Friedman *et al.* 1995, Sjögren *et al.* 1997, Heling *et al.* 2001, Hoskinson *et al.* 2002) could not find any significant association.

The pooled SRs by apical extent of root fillings revealed the same trends as individual study findings (Table 3b).

Four studies (Bender *et al.* 1964, Halse & Molven 1987, Sjögren *et al.* 1990, Smith *et al.* 1993) had statistically analysed the influence of apical extent of root fillings in teeth with or without periapical lesion, separately. For teeth with no pre-operative periapical lesion, Bender *et al.* (1964) found that flush and short root fillings had similar SRs but had significantly higher SRs than long root fillings. In contrast, Smith *et al.* (1993) reported that the extent of root fillings had no influence on treatment outcome, in agreement with Sjögren *et al.* (1990).

For those teeth with pre-operative periapical lesion, Bender *et al.* (1964) found that flush root fillings had significantly higher SRs, followed by short and then long root fillings. Similarly, Sjögren *et al.* (1990) and Smith *et al.* (1993) also reported that flush fillings had significantly higher SRs than long or short root fillings. In contrast, Jokinen *et al.* (1978) reported that long root fillings had the highest SR followed by flush root fillings and then short root fillings; whilst Halse & Molven (1987) could not detect any significant difference.

The pooled SRs stratified by presence or absence of periapical lesion are presented in Table 3b. When there was no pre-operative periapical lesion, the pooled SRs of long root fillings were the lowest regardless of whether loose or strict criteria were used (Table 3b). When a periapical lesion was present, teeth with flush root fillings had the highest SRs whilst teeth with short root fillings had the lowest SRs (Table 3b).

Meta-analysis to compare flush and short root fillings. Twenty-one studies (Table 5f) presented SRs stratified by short or flush root fillings. The meta-analyses showed that there was no significant difference in the odds of success (OR = 1.27, 95% CI: 0.93, 1.73) between teeth with short or flush root fillings when teeth with or without pre-operative periapical lesion were considered together (Table 5f). The heterogeneity [125.0 (20 df)] was significant and could partly be explained by the 'qualification of operator'. Similarly, no significant difference in the odds of success (OR = 0.83, 95% CI: 0.55, 1.23) was found between flush and short root fillings in teeth without a pre-operative lesion. However, when considering teeth with a pre-operative periapical lesion, those with flush root fillings had 1.6 times the odds of success (OR = 1.56, 95% CI: 1.26, 1.94) compared with teeth with short root fillings. Although the heterogeneity was significant at 10% level, meta-regression analysis was not carried out to explore the source because of insufficient data.

Meta-analysis to compare flush and long root fillings. Twenty-one studies (Table 5f) presented stratified outcome data by long and flush root fillings. The meta-analysis showed that the odds of success for teeth with flush root fillings was significantly higher than those for teeth with long root fillings (OR = 2.34; 95% CI: 1.87, 2.93) when periapical status was not considered (Table 5e). The heterogeneity [56.1 (20 df)] was substantial and could be partly explained by the 'qualification of the operators' (Table 8b). Such a difference in the odds of success remained true even when teeth with or without pre-operative periapical

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lesions were considered separately in the meta-analyses (Table 5f).

Meta-analysis to compare short and long root fillings. Stratified outcome data by short and long root fillings were available from 24 studies (Table 5f). When teeth with different periapical status were considered together, the meta-analysis results showed that the odds of success for teeth with short root fillings were significantly higher than those for teeth with long root fillings (OR = 1.80; 95% CI:1.34, 2.42; Table 5f). The heterogeneity [117.6 (23 df)] was substantial but none of the tested covariates could account for it as they neither reduced the I^2 or the *tau*2 values when they were entered separately into the meta-regression models (Table 8c). When only teeth without pre-operative periapical lesion were considered, the OR increased to 2.89 (95% CI: 0.89, 9.08), with the difference being borderline significant ($P = 0.051$). In contrast, when only teeth with pre-operative periapical lesion were considered, there was no difference in the odds of success between teeth with short or long root fillings (OR = 1.06, 95% CI: 0.84, 1.33; Table 5f).

Quality of root filling

Nine studies had analysed this aspect statistically. Six studies (Harty *et al.* 1970, Adenubi & Rule 1976, [2]Heling & Kischinovsky 1979, Nelson 1982, [1]Teo *et al.* 1986, Halse & Molven 1987) found that satisfactory root fillings were associated with significantly higher SRs than unsatisfactory root fillings ('inadequate seal' or 'radiographic presence of voids'). Cheung (2002) found that voids in root filling present at the mid or apical thirds had significantly worse outcome than those with voids present in the coronal third or those without voids. In contrast, Sjögren *et al.* (1990) and Heling *et al.* (2001) reported that the quality of root fillings had no significant influence on SRs; however, only a small proportion (5–10%) of their cases had unsatisfactory root fillings.

Seven studies provided stratified data by the quality of root filling. The pooled SRs for teeth with satisfactory root fillings were higher than those for teeth with unsatisfactory root fillings by 18.7% (loose criteria) and 25.9% (strict criteria), respectively (Table 3b).

This observation could be confirmed by the large and significant estimated pooled effects (OR = 3.92; 95% CI: 2.26, 6.78; Table 5g). The heterogeneity 27.6 (6 df) in the estimate was substantial and could partly be explained by 'year of publication' (Table 8d).

Apical disturbance during root canal treatment

Various studies have investigated the effect of disturbance of the apical tissues during treatment. 'Apical disturbance' has however, been defined differently by different researchers. Some (Harty *et al.* 1970, Adenubi & Rule 1976, Nelson 1982) defined it as instrumentation beyond the apical foramen or extrusion of sealer/filling. Others only considered extrusion of calcium hydroxide (Çalişken & Şen 1996) or sealer (Boggia 1983, [2]Friedman *et al.* 1995) into the periapical tissue as apical disturbance. There are also conflicting results from their statistical analyses. Harty *et al.* (1970) reported that apical disturbance resulted in a significantly higher SR than absence of apical disturbance, but Adenubi & Rule (1976) reported the contrary. [2]Friedman *et al.* (1995) found extrusion of sealer reduced the SRs significantly. On the other hand, Çalişken & Şen (1996) found that extrusion of calcium hydroxide had no significant influence on the outcome of treatment. Only five studies (Table 1) have provided outcome data based on this factor. The pooled SRs for those cases without apical disturbance were higher than those with apical disturbance by 15.6% (loose criteria) and 7.9% (strict criteria), respectively (Table 3a). No further meta-analyses were carried out because of the difference in definition between studies.

Acute exacerbation during treatment

Sjögren *et al.* (1990) reported that acute 'flare-ups' during treatment had no effects on outcome. None of the studies reviewed has presented outcome data by this factor (Table 1).

Number of treatment visits

Twenty-five studies had carried out all treatments over multiple visits, whilst in four studies all treatment was completed in one visit. In 10 studies, the treatment had been completed in either one or multiple visits, whereas the remainder (22 studies) did not provide this information. All seven studies (Soltanoff 1978, Oliet 1983, Trope *et al.* 1999, Weiger *et al.* 2000, Deutsch *et al.* 2001, Cheung 2002, Peters & Wesselink 2002) comparing the outcome of treatment carried out over single or multiple visits, found no significant difference in SRs between the two approaches. Out of the seven studies, three (Trope *et al.* 1999, Weiger *et al.* 2000, Peters & Wesselink 2002) were randomized controlled trials. Outcome data related to this factor could be extracted from 34 studies (Table 3a). The pooled SRs for single-visit treatment were 4% higher (loose criteria) and

0.2% lower (strict criteria) than the SRs for multiple-visit treatment (Table 3a).

Meta-analysis was initially carried out by incorporating all the seven studies which provided SRs by number of visits. No significant difference in the odds of success (OR = 1.16, 95% CI: 0.82, 1.63) was found and the heterogeneity was not significant (Table 5h). The analysis was repeated after excluding the observational studies, the odds of success for single-visit treatment were higher than those for multiple visit treatment (OR = 1.89; 95% CI: 0.99, 3.63) and the difference was borderline significant (Table 5h). However, in one trial (Trope *et al.* 1999), some of the teeth were not associated with pre-operative periapical lesions and some cases treated over multiple visits had not been dressed with an inter-appointment calcium hydroxide dressing (the main biological purpose of multiple visit treatment). After eliminating such cases, the estimated pooled OR decreased to a statistically insignificant level (OR = 1.35, 95% CI: 0.63, 2.88; Table 5h). Meta-regression analysis was not performed as the heterogeneity was not significant.

Post-operative (root canal treatment) factors

Quality of coronal restoration after RCT

Eleven studies had analysed the influence of quality of coronal restoration on treatment outcome and reported contradicting conclusions. The studies had categorized the quality of restorations differently, for example, restored versus unrestored, satisfactory versus unsatisfactory or permanent versus temporary. Hoskinson *et al.* (2002) defined satisfactory restorations as those with no evidence of discrepancy, discoloration or recurrent caries at the restoration margin with absence of a history of decementation. Some found that root treated teeth with restorations (Heling & Tamshe 1970, 1971, Heling & Shapira 1978, [2]Friedman *et al.* 1995), satisfactory restorations (Swartz *et al.* 1983) or permanent restorations ([2]Heling & Kischinovsky 1979) were associated with significantly higher SRs than their contrary counterpart. In contrast, others ([1]Teo *et al.* 1986, Safavi *et al.* 1987, Ricucci *et al.* 2000, Heling *et al.* 2001, Cheung 2002, Hoskinson *et al.* 2002) found no significant differences.

Eight of the 63 studies (Table 1) had presented outcome data based on quality of coronal restoration after treatment. The pooled SRs for teeth with 'satisfactory' restoration were higher than those teeth with 'unsatisfactory' restorations by 10 and 18% based on loose or strict criteria, respectively (Table 4).

Meta-analysis (Table 5i) incorporating seven studies providing SRs by the quality of coronal restoration showed that the odds of success (OR = 1.82; 95% CI: 1.48, 2.25) were significantly higher in teeth with satisfactory restorations than teeth with unsatisfactory restorations. The heterogeneity 11.9 (6 df) was borderline significant (Table 5i) and could partly be explained by the 'year of publication' (Table 8e).

Use as abutment for prosthesis

Three studies ([1]Storms 1969, Matsumoto *et al.* 1987, Sjögren *et al.* 1990) had investigated the influence of this factor on treatment outcome; however, [1]Storms (1969) had included nonsurgical or surgical re-treatment cases in their analyses of this factor. Sjögren *et al.* (1990) and Matsumoto *et al.* (1987) reported that bridge and denture abutments had significantly lower SRs than individual units, but [1]Storms (1969) did not find such a significant difference. The data for this factor from Matsumoto *et al.*'s (1987) study is presented in Table 4. No further analysis was carried out because of insufficient data.

Discussion

In this study, the authors attempted, *via* a systematic review of observational studies and randomized trials, to explore the effects of individual clinical factors (prognostic and interventions) on the SRs of primary root canal treatment. An ideal clinical intervention outcome study design would include the features of randomization and a control group. The exposure to any prognostic factors and interventions should be easily quantified and recorded and additionally, in the case of interventions, easily delivered in a discrete and standardized manner. In the case of a drug trial, this is relatively easily achieved, the main problem being compliance in delivery. In stark contrast, 'root canal treatment' consists of a series of interdependent steps or procedures including: isolation, access, mechanical preparation of root canals (taper and size of apical enlargement), irrigation, medication and obturation. The mechanical and chemical preparations are delivered in parallel as well as in series, and most importantly, the probability of these factors interacting in their ability to influence outcome is extremely high. It is well known that even a detailed protocol fails to allow two operators to produce the same treatment under identical conditions (Gulabivala *et al.* 2000). Given the variation in pre-operative conditions, the diversity of the cases under treatment is likely to be enormous. The

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study of the effect of root canal treatment outcome therefore requires that all relevant factors are recorded or accounted for in detail. In the ideal scenario, the studies (randomized controlled trials) should provide sufficiently detailed data to enable the exploration of the effect of these individual factors and their interactions. In theory, therefore, the estimated weighted pooled ORs and sub-group analyses using the method of meta-analysis should give sufficient information on the effect of individual factors and their interaction on the outcome of treatment. This view is however countered by those who believe a perfect data set is impossible to achieve and mathematical approaches may simply average often incompatible data (Eysenck 1994). It is therefore necessary to include intuitive synthesis to derive an overview, regardless of scientific principles (Popper 1959).

The calculation of ORs requires paired data from the same studies. In the studies reviewed, however, estimated pooled ORs were only possible for 11 factors: 'gender', 'age', 'tooth type', 'pre-operative pulpal status', 'pre-operative periapical status', 'size of periapical lesion', 'pre-obturation culture results', 'number of treatment visits', 'apical extent of root fillings', 'quality of root fillings' and 'quality of coronal restorations'. A number of studies did not provide paired data and therefore in order not to lose these studies from the analyses, the present review included the estimation of *weighted pooled SRs* by each factor, which does not require paired data. In contrast to part 1 of this review, un-weighted pooled SRs were not estimated because they do not take account of the sample size and standard error of individual studies.

Whilst the quality of studies that may be included in meta-analyses has been amply discussed and described, there is an absence of strict guidelines on the minimum number of such studies that should contribute to valid meta-analyses. Some (Janket *et al.* 2003, Stokman *et al.* 2006) meta-analyses have included only two studies of an intervention. Although this is acceptable according to the criteria given by the Cochrane Oral Health Group (personal communication), this is equivalent to calculating variance on two observations, from a statistical point of view. As discussed in part 1 of this paper, the relatively small number of studies included in the meta-analyses to estimate weighted pooled SRs for some factors under investigation may have produced distorted results. For example, the estimated weighted pooled success for those teeth treated without rubber dam, using loose criteria data, had a narrow confidence interval, although the sample size was only two (Table 3a). The SRs reported by the two studies (Barbakow *et al.* 1980a,b, Shah 1988) were not significantly different and had small confidence intervals [90% (87%, 93%) and 78% (68%, 88%), respectively). The study with the larger sample size (Barbakow *et al.* 1980a,b; $n = 335$) and smaller confidence intervals carried more weight in the estimated pooled success value generated by the meta-analysis, thus explaining the final narrow confidence interval.

In general, the results of the meta-analyses showed that there was substantial heterogeneity in the data. Attempts were made to explain the heterogeneity using two approaches: (i) the study characteristics were entered into the meta-regression model as covariates to test their effect on the estimated pooled OR and to evaluate whether their inclusion reduced the proportion of variation because of heterogeneity and the estimate of between-study variance; (ii) sensitivity tests were carried out to test whether the exclusion of studies that did not provide stratified data for primary and secondary treatment would reduce the heterogeneity. The first approach was used to test the study characteristics, of which the following; geographical origin of the study, the decade of publication and qualification of the operators, were found to be responsible for some of the heterogeneity, although not consistently. The second approach was used to test the effect of exclusion of studies that had included re-treatment cases in their data; this did reduce the heterogeneity of the results in the case of studies evaluating the effect of culture results prior to obturation on outcome.

Interestingly, there were greater variations in the weighted pooled estimates of probability of success by each factor based on those outcome data where loose rather than strict criteria for success were used. It is possible that this is because of greater subjectivity in judging partial healing of a lesion than complete healing. It was therefore decided to base the following discussions on the pooled SRs estimated from the data based on the use of strict criteria together with the findings from the intuitive synthesis of individual studies and the estimated pooled effects of factors.

For the general patient factors (gender, age and general medical health), the results of all three analytical approaches were available and all concurred in their findings on the effect of 'gender' and 'age'. The results confirmed that there was no obvious difference in SR between male and female patients, consistent with the fact that there is no known difference in healing potential between genders. Given that presence or absence of pain may be a criterion in the judgement

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of treatment outcome, the documented difference in pain perception between genders, which has been ascribed to hormonal differences, may have an important bearing on this discussion (Macfarlane *et al.* 2002). Although there was no evidence of significant difference in pooled SRs by the age bands, a trend of pooled SRs decreasing with increase in age was noted. This observation is consistent with the hypothesis that older patients have poorer healing ability because of aging (Mogford *et al.* 2004), malnutrition (Chernoff 2004) or systemic diseases such as diabetes which are more prevalent in the older age group (Cowie *et al.* 2006, Forouhi *et al.* 2006). Although, the evidence for the influence of medical health on treatment outcome is weak based on this review, two studies (Fouad & Burleson 2003, Marending *et al.* 2005), which were published beyond the time-frame for inclusion in this review, reported that diabetes (noninsulin dependent/insulin dependent) or impaired nonspecific immune response had a significant influence on the SRs of root canal treatment on teeth with periapical lesions. Further comprehensive investigations on the effects of age and health as well as their interaction on treatment outcomes are therefore required.

Most studies did not show any significant difference in SRs by tooth type, which was confirmed by the pooled SRs estimated using the meta-analysis method. The results appear to infer that the complex canal anatomy associated with molar teeth does not negatively influence the outcome of root canal treatment. Perhaps more important is the issue of apical anatomy and its infection (Wada *et al.* 1998, Nair *et al.* 2005). The strength of this inference is undermined by the fact that the studies had not stratified the outcome data by pulpal or periapical status per tooth type.

Returning to the issue of absence of obvious improvement in SRs by the year of publication, reported in part 1, the refutation that the apparent lack of improvement in SRs was a function of more adventurous case selection in recent years, may be rebutted on the grounds that tooth type, age, gender and patient's health did not significantly influence outcomes of primary root canal treatment. The outcome of this systematic review may help to inform the designation of case complexity for referral (http://www.aae.org/dentalpro/guidelines.htm, http://www.rcseng.ac.uk/fds/docs/complexityassessment.pdf).

Many pre-operative factors associated with the teeth, such as history of trauma, presence of resorption, presence of fracture or cracks, or presence of swelling and/or sinus, may have an influence on treatment outcome but these have not been systematically investigated in the reviewed studies. Only three factors (pre-operative vitality of teeth, periapical status and size of periapical lesion) were well recorded and researched and results from all three approaches in analysis were available. As alluded to in the introduction, root canal treatment as a treatment intervention is used to manage two distinct biological entities; the diseased but vital pulp with an absence of periapical disease at the one extreme and the necrotic, infected pulp/space with an established periapical lesion, at the other extreme. The problem, however, is more complicated than this, because in reality, the clinician faces a continuous spectrum of pulpal/periapical conditions associated with teeth that can be very difficult to diagnose accurately because of limitations in the sensitivity and specificity of available methods (Dummer *et al.* 1980, Hyman & Cohen 1984). The importance of this lies in the fact that the pulpal and more importantly the periapical conditions have a profound effect on the treatment outcome.

The vitality of pulp was reported as a significant influencing factor by only a small proportion of studies (4/14 studies) that had analysed this factor statistically. Nevertheless, the meta-analysis confirmed that vital teeth had significantly higher SRs (5–9% or OR = 1.8) than nonvital teeth, consistent with the results of meta-analysis by Kojima *et al.* (2004). This demonstrates the value of meta-analyses in increasing statistical power by pooling data from individual studies.

The effect of the interplay between nonvitality and periapical disease on treatment outcome is demonstrated by the following observations. Elimination of data on 'nonvital teeth with periapical lesions' reduced the difference in SRs between 'vital' and 'nonvital teeth' to a negligible level (<0.5% or the OR to 1.1). In contrast, elimination of the data on 'nonvital teeth without periapical lesions', increased the difference in SRs between 'vital' and 'nonvital teeth' to 10% or the OR to 2.4. The important influence of the periapical status was further confirmed by the significant difference (9–13%, OR = 2.0) in SRs between nonvital teeth with and without periapical lesion. The explanation for these clinical observations evidently lies in the knowledge that nonvitality is not always associated with root canal infection (Bergenholtz 1974), whilst the presence of a periapical lesion always signifies the presence of root canal infection (Sundqvist 1976).

The size of the periapical lesion may influence the decision to intervene by both patients and clinicians (Reit & Gröndahl 1984). In this review, all three

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analytical approaches showed no significant difference in SRs between small and large lesions. Some of the heterogeneity of the data could be explained by 'unit of outcome measure' and 'duration after treatment'. On the basis of this review, it may be concluded that there is no difference in the outcome of treatment on teeth associated with large or small periapical lesions but the former require longer to heal completely; their evaluation therefore requires a longer follow-up period.

In contrast to the pre-operative data, that on intra-operative factors was comparatively deficient; the reviewers could usually only call on one or two of the three analytical approaches for most factors. Even when the results from two approaches were available, the synthesis was compromised by the small number of studies available. Definitive conclusions could therefore not be drawn on most of the following factors: use of rubber dam, canal obstruction and procedural errors, apical size and taper of canal preparation, type of irrigants, root filling material/technique, type of medicaments and sealer and apical disturbance during treatment. The treatment aspects on which reasonable data were available included: 'pre-obturation culture results', 'apical extent of root fillings', 'quality of root filling', 'quality of coronal restoration' and 'number of treatment visits'.

The pre-obturation culture was putatively designed to detect residual bacteria in the root canal system in the hope that it would be a good predictor for treatment outcome. In reality it is probably a better measure of the efficacy of bacterial removal from the *prepared part* of the root canal system. It is likely that the infection in the apical anatomy would be better correlated to treatment outcome (Goria *et al.* 2005, Nair *et al.* 2005). The root canal bacterial sampling and detection techniques have varied between studies and in their ability to detect residual apical infection. This may partly explain the inconsistent reports from individual studies with only half (6/12) of the studies finding that culture results had a significant effect on treatment outcome. In contrast, the pooled SRs of teeth with negative culture were 7–13% higher than those teeth with positive cultures. After excluding those studies that had not partitioned the re-treatment cases as well as those that had not provided paired sets of data, only 6 of the 12 studies remained to contribute to the estimation of the pooled effect of this factor on outcome. Although the results of both approaches of analyses (estimation of pooled SRs and pooled OR) were in favour of a negative pre-obturation culture result, the estimated pooled effect [OR = 1.2; 95% CI: 0.95, 1.44; chi-square for heterogeneity 6.1 (5 df) $P = 0.294$] was not statistically significant. This could however be attributed to a lack of statistical power. In order to formally justify the exclusion of studies that had not partitioned re-treatment cases, the meta-analysis was repeated by including this data ($n = 14$ studies). On doing so, the estimated effect of pre-obturation culture results (OR = 1.9, 95% CI: 1.4, 2.7) became highly significant ($P < 0.001$) but the heterogeneity also became substantial 30.7 (13 df, $P = 0.004$). This highlights the dilemma in where to set the boundary between inclusion and exclusion criteria for studies in systematic reviews. The use of strict inclusion criteria may reduce the number of incorporated studies and heterogeneity but also the statistical power in detecting significance of the factor under investigation as well as that of the heterogeneity. Attempts were made to further analyse the effect of culture results by teeth with or without pre-operative periapical lesion but the pooled SRs (Table 3a) and the ORs (Table 5e) gave contradictory results. This was because of the small number of studies incorporated in the analyses and a large discrepancy in the number of units in each category. This showed that the adopted principle of triangulation of outcomes through different analytical approaches has merit.

Apart from bacterial culture results, other treatment measures that may serve as surrogate measures of root canal treatment efficacy, include the apical extent of instrumentation and root fillings. Whilst the measure 'apical extent of root filling' was frequently measured, none of the selected studies had analysed the influence of apical extent of instrumentation. Therefore, in the absence of such information, the 'apical extent of root fillings' may serve as a crude and imprecise surrogate measure of the 'extent of instrumentation'. The use of the radiographic root apex as the reference point for measuring the apical extent of root filling in previous studies has been criticized because of the poor correlation between the location of this point and the actual canal foramen (Mizutani *et al.* 1992).

The effect of apical extent of root fillings on treatment outcome was profound and interacted with the periapical status. All three analytical approaches concurred that: teeth with flush root fillings had the highest SRs followed by short and then long root fillings, in agreement with Kojima *et al.* (2004). However, the difference between flush and short root fillings was small and not significant (OR = 1.27, 95% CI: 0.93, 1.73). The results of the analyses stratified by presence or absence of periapical lesion were compromised by

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the substantially smaller number of studies contributing to the data and have to be interpreted with caution. Nevertheless, the results showed that the difference in SRs between teeth with flush and short root fillings was not significant when the teeth were not associated with periapical lesions. In contrast, the difference in SRs between teeth with short and long root filling was not significant when the teeth were associated with periapical lesions. On the basis of these findings, it may be speculated that both the apical extent of instrumentation and root filling had significant effects on outcome. These two factors may interact with each other as it is generally normal practice to obturate the canal to the same extent as canal preparation. Explanation of these observations lie in the fact that a single measure 'apical extent of root filling' informs about both the apical extent of canal cleaning, as well as the potential extrusion of foreign materials into the surrounding tissues. Extrusion of cleaning, medication or filling materials beyond the apical terminus into the surrounding tissues may result in delayed healing or even treatment failure because of a foreign body reaction (Yusuf 1982, Nair *et al.* 1990, Koppang *et al.* 1992, Sjögren *et al.* 1995).

The radiographic measure of 'quality of root filling' could be used as an indicator of the ability of the root filling to prevent root canal system re-infection or as a surrogate measure of the quality of the entire root canal treatment delivered by the clinician. Unfortunately, the criteria for judging the quality of root fillings have not been well defined by the selected studies. Satisfactory root fillings were defined either as having 'adequate seal' or 'radiographic absence of voids'. This subjective assessment has not been standardized or calibrated, nor tested for variability in assessment by inter- and intra-observer agreement. Nevertheless, all three analytical approaches showed that 'unsatisfactory' root fillings had significantly lower SRs than those judged 'satisfactory'; so perhaps, the intuitively judged crude measure was adequate for the purpose.

There has been an on-going controversy, fuelled by debate between specialists arguing for single-visit treatment on the basis of cost-effectiveness and business sense against academics and some specialists arguing for multiple visit treatments, based on a biological rationale (Spångberg 2001). The main thread of argument for multiple visit treatments is the putative desirability of using an inter-appointment calcium hydroxide dressing for its antibacterial effect and to gauge the periapical response before root filling. The results of all three analytical approaches showed no significant difference in the SRs between treatments carried out over one or multiple visits, in agreement with the review by Sathorn *et al.* (2005). Their meta-analysis only included three randomized controlled trials and only those cases treated with calcium hydroxide were included in the multiple visit treatment dataset. They commented on the lack of power in the three studies as well as in the pooled data, as a sample size of 433–622 was deemed necessary for a difference in 10% SR in such a trial.

The importance of the post-root canal treatment coronal restoration was supported by two quantitative analytical approaches and showed that teeth with satisfactory coronal restorations had significantly better periapical healing (10–18%; OR = 1.82) compared with those with unsatisfactory restorations. On the basis of these results, the provision of the coronal restoration should be considered the final part of the root canal treatment procedure along with obturation to prevent post-operative re-infection.

Within the limitations of this systematic review, four factors have been identified as having a strong effect on the outcome of root canal treatment on the evidence from at least two of the three analytical approaches. These included: (i) presence of periapical lesion, (ii) apical extent of root filling, (iii) quality of root filling and (iv) post-treatment restorative status. The relative strength of effect of each factor and the potential interactions between them could not be precisely determined because of the lack of sufficient data. The interactions between the periapical status and each of the significant treatment factors have, however, been demonstrated to some degree. The main clinical inference is to focus canal preparation on obtaining and maintaining access to the apical anatomy (infection) particularly in the presence of a pre-operative periapical lesion. Once the access to the apical anatomy has been achieved, care should be taken to decontaminate the canal system and then to provide a filling extending from the terminus of the root canal system to the coronal access, in order to prevent re-infection. Although the quality of the root canal treatment should not be judged purely by the radiographic appearance of the root filling, it could be used as a surrogate measure of the extent and quality of the entire treatment. Instrumentation and obturation should be extended to the terminus of the root canal system without extruding materials into the surrounding tissues. The significant effects of the quality of the coronal restoration warrant its immediate placement or

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at least some sort of a permanent (antibacterial) seal in the access cavity.

There is, however, a lack of evidence to guide clinicians in the selection of the best decontamination and root canal obturation protocols. There is, therefore, a need to carry out further randomized controlled trials to identify the most appropriate size, taper and extent of canal preparation, irrigation regime (type of irrigant and method), medication regime (type and method) and root filling material and technique, in order to improve the probability of success of root canal treatment. Complete randomization of samples is often not effective in reducing imbalance of pre-operative prognostic factors but may be improved by stratified randomization (Lewsey 2004). The design of randomized controlled trials for root canal treatment is further complicated by the fact that not all sources of clinical heterogeneity (intra-operative factors) can be identified and quantified. Examples of immeasurable or nebulous factors include: the complexity of the root canal system and access to it; the clinical and technical skills of the operator; the logistical, organizational and delivery aspect of the care and the patient's healing capacity. In addition, the interactions between the treatment factors cannot be ignored. A number of examples may be cited: (i) the size and taper of the canal preparation influences the efficacy of the irrigation regime to remove a bio-molecular film from the root canal system (Ng *et al.* 2006), (ii) certain root canal obturation techniques require a larger apical size and taper of canal preparation (Schilder 1967); and (iii) the use of thermo-plasticized root canal obturation techniques may result in higher prevalence of root filling extrusion (Van Zyl *et al.* 2005). When designing an outcome study, a robust decision is therefore required on the potential confounding factors that would be controlled/standardized *versus* those that would be recorded. The statistical analyses used should also respect the hierarchy that is often inherent in clinical data, and should partition the total variation within the data across 'levels' accordingly. For the endodontic treatment dataset, the individual roots (level 1) are nested within the tooth (level 2), and the individual teeth are nested within the patient (level 3). These issues have never been addressed in previous endodontic outcome studies. Last but not least, further root canal treatment outcome studies should standardize the pre-operative pulpal and periapical status of teeth and account for known confounders, such as quality and apical extent of root fillings and quality of coronal restorations, review all the treatments for at least 3 years, report the stratified SRs by strict and loose criteria, and use more than two pre-calibrated radiographic observers with intra- and inter-observer agreement tests. The inference is that a complex treatment intervention such as root canal treatment requires a complex system for recording the procedure characteristics. Unfortunately, no automated recording system exists and requires at least a two-step (observation followed by recording) system that has to be manually operated. This can have unfavourable effects on compliance in data recording (Saunders *et al.* 2000); it is therefore important to rationalize and prioritize essential data for collection. The present review outcomes should help inform both study design and prioritization of factors for recording.

In conclusion, the results of this review should be interpreted with caution and cannot be considered to give definitive conclusions because of the retrospective and heterogeneous nature of the data. It does, however provide strong clues about the factors likely to dominate outcomes and inform the design of future randomized controlled trials.

Notes

1. Studies excluded for reasons given in Table 1.
2. Re-treatment cases were included in the stratified data by potential influencing factors.

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