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Journal of Dentistry

journal homepage: www.elsevier.com/locate/jdent





A systematic review of droplet and aerosol generation in dentistry

N. Innes^{a, *, 1}, I.G. Johnson^a, W. Al-Yaseen^a, R. Harris^c, R. Jones^d, S. KC^e, S. McGregor^f, M. Robertson^b, W.G. Wade^g, J.E. Gallagher^e

^a Applied Clinical Research and Public Health, School of Dentistry, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK

^b Child Dental and Oral Health, School of Dentistry, University of Dundee, Dundee, UK

^c Department of Public Health, Policy and Systems, Institute of Population Health, University of Liverpool, Liverpool, UK

^d Education, Scholarship and Innovation, School of Dentistry, College of Biomedical and Life Sciences, Cardiff University, UK

^e Faculty of Dentistry, Oral & Craniofacial Sciences King's College London, London, UK

f Library & Learning Centre, University of Dundee, Dundee, UK

^g Centre for Host-Microbiome Interactions, Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, London, UK

A R T I C L E I N F O

Keywords: Aerosol generating procedures Evidence-based dentistry Systematic reviews Infection control COVID-19 Aerosols

ABSTRACT

Objectives: This review aimed to identify which dental procedures generate droplets and aerosols with subsequent contamination, and for these, characterise their pattern, spread and settle.

Data resources: Medline(OVID), Embase(OVID), Cochrane Central Register of Controlled Trials, Scopus, Web of Science and LILACS databases were searched for eligible studies from each database's inception to May 2020 (search updated 11/08/20). Studies investigating clinical dental activities that generate aerosol using duplicate independent screening. Data extraction by one reviewer and verified by another. Risk of bias assessed through contamination measurement tool sensitivity assessment.

Study selection: A total eighty-three studies met the inclusion criteria and covered: ultrasonic scaling (USS, n = 44), highspeed air-rotor (HSAR, n = 31); oral surgery (n = 11), slow-speed handpiece (n = 4); air-water (triple) syringe (n = 4), air-polishing (n = 4), prophylaxis (n = 2) and hand-scaling (n = 2). Although no studies investigated respiratory viruses, those on bacteria, blood-splatter and aerosol showed activities using powered devices produced greatest contamination. Contamination was found for all activities, and at the furthest points studied. The operator's torso, operator's arm and patient's body were especially affected. Heterogeneity precluded inter-study comparisons but intra-study comparisons allowed construction of a proposed hierarchy of procedure contamination risk: higher (USS, HSAR, air-water syringe, air polishing, extractions using motorised handpieces); moderate (slow-speed handpieces, prophylaxis, extractions) and lower (air-water syringe [water only] and hand scaling).

Conclusion: Gaps in evidence, low sensitivity of measures and variable quality limit conclusions around contamination for procedures. A hierarchy of contamination from procedures is proposed for challenge/verification by future research which should consider standardised methodologies to facilitate research synthesis.

Clinical significance: This manuscript addresses uncertainty around aerosol generating procedures (AGPs) in dentistry. Findings indicate a continuum of procedure-related aerosol generation rather than the common binary AGP or non-AGP perspective. The findings inform discussion around AGPs and direct future research to support knowledge and decision making around COVID-19 and dental procedures.

1. Background

SARS-CoV-2 is the highly infectious coronavirus which causes COVID-19 [1]. Transmission is thought to be primarily via respiratory droplets (similar to other coronaviruses and circumstantial evidence from outbreaks during the current pandemic) with the highest viral load detected in the respiratory tract, just before symptoms are apparent and for the next 5 days [2,3]. Individuals are therefore most infectious when

https://doi.org/10.1016/j.jdent.2020.103556

Received 25 August 2020; Received in revised form 28 November 2020; Accepted 8 December 2020 Available online 23 December 2020

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Review article



^{*} Corresponding author at: Head of School of Dentistry, Professor and Honorary Consultant, Paediatric Dentistry, College of Biomedical & Life Sciences, Cardiff University, Heath Park, Cardiff, CF14 4XY, UK.

E-mail address: InnesN@cardiff.ac.uk (N. Innes).

¹ Web: https://www.cardiff.ac.uk/dentistry

they are pre-symptomatic or have mild, often non-specific symptoms, although even the relative importance of this in transmission is unclear [4]. Laboratory studies have been criticised for not being representative of real-life situations and there is ongoing controversy around the extent to which direct contact and fomite routes, and airborne transmission [5, 6] are responsible for viral spread [7,8].

Dental care involves close patient contact for prolonged periods leading to concern over transmission through aerosol generation during dental procedures [9,10], with the detection of SARS-CoV-2 in saliva [11] and the high viral load during the pre- and early symptomatic periods. In dentistry, universal precautions have been standard practice, based on evidence-informed infection control. These evolve as evidence emerges, particularly in response to blood and water borne infections and prion transmission [12–14].

The term Aerosol Generating Procedure (AGP) has been described as, "any procedure on a patient that can induce the production of aerosols of various sizes" although there is currently no agreed definition and a confusing lack of consistency in terminology. The UK National Emerging Respiratory Virus Threats Advisory Group has described "dental procedures (using highspeed devices such as Ultrasonic scalers and highspeed drills)" [15] as posing an increased risk of respiratory infection transmission. New terms such as aerosol generating exposure (AGE) have been suggested [16]. Policy documents have focused on ultrasonic scalers (USS), high-speed air-rotors (HSAR), air-water syringes (also known as triple or 3-in-1), and air polishers as sources of aerosols, with rubber dam and high-volume suction as mitigating measures [17–19].

To manage transmission risk of SARS-CoV-2, the extent and contamination of droplets and aerosols involved in dental procedures need to be identified. Similarly, the pattern, and timing, associated with spread and settle of droplets and aerosols in the context of clinical dentistry need to be understood to inform policy on surgery fallow times between patients. Globally specified patient spacing times for AGPs vary from none to 120 min [20].

An aerosol is defined as a suspension of liquid or solid in air [21,22]. When an aerosol is created with a liquid, a wide range of droplet sizes are produced. Particle size is a continuum, from larger heavier droplets, $> 5\,\mu\text{m}$ in diameter that fall rapidly to the ground, typically within 1 m of the source as splatter. Aerosols are composed of droplet nuclei $\leq 5\,\mu\text{m}$ in diameter and can remain suspended in air for many hours and be moved by air currents. At present, dental procedures are categorised dichotomously as either aerosol producing or non-aerosol producing. The former refers to procedures considered to produce smaller droplets of $\leq 5\,\mu\text{m}$ and the latter referring to procedures that are considered to produce few or no smaller droplets but may still produce larger droplets (> 5 μm). For the purposes of this review, aerosol will refer to suspensions of particles $\leq 5\,\mu\text{m}$ in diameter.

This review aims to critically assess existing knowledge and reduce uncertainty around dental procedures that generate droplets and aerosol, supporting policy making and local IPC protocols.

1.1. Research question

When performing a specific dental procedure within a dental setting, what is known or still unknown regarding the level and spread of aerosol/droplet contaminants for that procedure and the outcomes/ outcome measures used?

Objectives:

- 1 To identify and catalogue activities within clinical dentistry and the dental surgery that generate aerosols and droplets
- 2 For these activities, to:
 - a Characterise the pattern of droplet and aerosol spread and settle relevant to the dental surgery and dental laboratories
 - b Identify whether there is evidence of an association with exposure, infection and transmission of pathogenic micro-organisms
 - c List micro-organisms that have been studied

d Record outcomes and outcome measures

3 To identify gaps in the evidence related to aerosols and droplets relevant to clinical dentistry

2. Methods

2.1. Protocol and registration

This review has been conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(Appendix 2) [23], registered under the International Prospective Register of Systematic Reviews ID number CRD42020193058 and Appendix 1 gives full details.

2.2. Eligibility criteria for study selection

2.2.1. Inclusion criteria

- Study methodology including but not limited to; trials, observational, experimental (including those using manikins, modelling studies, etc.), qualitative studies, non-clinical reports and other relevant studies;
- Topic of study investigate activities that generate aerosols etc. relevant to clinical dentistry;
- Where there is a measure of aerosols and droplets;
- Types of settings: dental practices and hospital settings, including simulated environments where they are relevant to the conduct of dental procedures and investigations; and
- English language and also literature written in Chinese if indexed in the searched database platforms.

2.2.2. Exclusion criteria

- Studies that measure bioaerosol generation but where these are not related to single procedures and are carried out at an environmental or broader level (i.e. measure bacterial counts over a day in a surgery)
- Non-English language articles, apart from Chinese journal articles (insufficient resources)
- Aspects of the dental environment which may increase risk of infection and transmission e.g. waiting rooms, high throughput, reception areas, bathrooms (these are generic issues which may be covered elsewhere)
- Grey literature

2.3. Information sources

Medline (OVID), Embase (OVID), Cochrane Central Register of Controlled Trials, Scopus, Web of Science and LILACS databases were searched for studies meeting the inclusion criteria and ClinicalTrials.gov was searched for recently completed, ongoing, or recruiting trials from the start of the databases to May 2020. The search was updated on 11 August 2020 to identify new studies published since the original search was conducted.

2.4. Search

The search strategy (Fig. 1) comprised controlled vocabulary and keywords. The references of all reviews, policy documents and included studies were screened for eligible studies.

2.5. Screening and selection of studies

Titles and abstracts were deduplicated and screened in Rayyan [24] independently and in duplicate by two reviewers. Where either reviewer considered a paper potentially eligible for inclusion, the full text was

1. Dental Care/	1. 27.13 or 14 or 15 or 16 or 17 or	30. viruses/
2. Dental Clinics/	18 or 19 or 20 or 21 or 22 or 23 or	31. Air Microbiology/
3. Dental Offices/	24 or 25 or 26	32. Viral.mp
4. Dental Equipment/	2. 28. Dent\$.mp.	33. Viridae.mp.
5. Dental Instruments/	3. 29. 27 and 28	34. Droplets.mp.
6. Dentistry/	 1 or 2 or 3 or 4 or 5 or 5 or 7 or 	35. "Droplet nuclei".mp.
7. Dentists/	8 or 9 or 10 or 11 or 12 or 29	36. Cough\$.mp.
8. Dental Hygienists/	5. Cross Infection/	37. Gag\$.mp.
9. Dental surger\$.mp.	6. Coronavirus Infections/	38. Sneez\$.mp.
10. Dental practice\$.mp.	7. Disinfection/	39. 59. 31 or 32 or 33 or 34 or 35
11. Dental Scaling/	8. Infectious Disease Transmission,	or 36 or 37 or 38 or 39 or 40 or
12. Dental Plaque/	Patient-to-Professional/	41 or 42 or 43 or 44 or 45 or 46
13. Ultrasonic.mp.	Occupational Diseases/	or 47 or 48 or 49 or 50 or 51 or
14. Ultrasound.mp.	10. Occupational Exposure/	52 or 53 or 54 or 55 or 56 or 57
15. Instrumentation.mp.	11. Infection Control/	or 58
16. Handpiece\$.mp.	12. Infection Control, Dental/	60. Aerosols/
17. Turbine.mp.	13. Risk Factors/	61. Bipaerosol\$.mp.
18. Drill.mp.	14. Risk Management/	62. "aerosol transmission".mp.
19. "Air line".mp	15. Particulate Matter/	63. "aerosolised transmission".mp.
20. "\Vater line".mp.	16. Air Pollutants, Occupational/	64. "aerosolized transmission".mp.
21. "Air polishing".mp.	17. Air Pollution, Indoor/	65. "aerosol generating
22. "Air abrasion" mp.	18. Blood-Borne Pathogens/	procedures".mp.
23. Extraction \$.mp.	19. Spatter.mp.	66. Aerosol\$.mp.
24. Cavitation.mp.	20. Saliva.mp.	67. "bio-aerosol generating
25. Preparation.mp.	21. Blood particles.mp.	procedures".mp.
26. Filling\$ mp.	22. Blood borne pathogens mp	68. "inhalation transmission".mp.
	23. Nosocomial mp	69. "contact transmission".mp.
		70. "nosocomial transmission".mp.
		71. emissions.mp.
		72. 72. 60 or 61 or 62 or 63 or 64
		or 65 or 66 or 67 or 68 or 69 or
		70 or 71
		73. 73. 30 and 59 and 7

Fig. 1. Outline of the search strategy, adapted for each database.

sought. Full texts of potential articles were retrieved and assessed independently and in duplicate. It was prearranged that screening of any Chinese language literature would be carried out in consultation with an external researcher who speaks Chinese.

Full texts were exported into Endnote and a database created in Excel. Differences were resolved by consensus involving at least one other research group member.

2.6. Data extraction

A standardised data extraction form was developed a priori and refined based on repeat pilot testing with a minimum of five publications and three data extractors. Eight reviewers were trained in data extraction form completion. Reviewers extracted data into an excel spreadsheet singly but consulted another reviewer where data reporting was unclear. Key missing data items were managed by contacting study investigators where possible. For studies where an intervention was measured for its ability to alter droplet and aerosol spread, only data relating to the baseline or control (i.e. without the intervention effect) was extracted.

2.7. Data items

The items of data extracted included: study demographics; dental procedures investigated; methodology; findings – (related to the reviews' outcomes). Detection methods for contamination were categorised as microbial, blood and other (non-microbial/non-blood)

methodologies.

2.8. Study quality assessments/ Risk of bias

The quality of the papers/ risk of bias was assessed. There were no standard quality tools for methodologies used in these papers or for assessing the quality of their reporting. We therefore took a pragmatic approach and assessed quality measures we considered important that are commonly measured in other study types (industry funding; conflict of interest; relevance, adequate description of equipment / procedure; sample size; controls; confounders; outcome reporting) (Table 1). Rather than assign an arbitrary numerical value to these which may be misleadingly summated, we used a traffic light system to show a pictorial representation of the quality of key aspects for each study, allowing the overall quality for items to be seen as well as the quality for each study. For each item we assigned red where the study does not meet standard and green for meeting standard. For standards where we considered it possible for them to be partially met, an amber colour was assigned. The study protocol in Appendix 1 has further detail.

2.9. Detection sensitivity of contamination assessment tool

The sensitivity of the detection methods used to assess contamination were evaluated using a schema tailored to the individual methodologies: microbial measures; blood measures; other [non-microbial/ non-blood measures) (Table 2). These are presented overall for all studies and grouped by procedure to allow a picture of the detection

Table 1

Description of criteria used to assess the methodology/reporting quality of included studies.

	Red (low quality)	Amber (moderate quality/ no mention)	Green (high quality)		
Was the study industry funded (related to the study materials being investigated)?	Yes, industry funded	Not mentioned	Statement that not industry funded		
Was there a conflict of interest?	Conflict of interest declared (related to the topic or study materials being investigated)	Not mentioned	Clearly states not industry funded or no conflict of interest statement		
Relevance to routine clinical dentistry	Low – mannikin or simulation study not involving human participants Medium – human participant study but involving procedures e.g. closed usual dentistry		High – undertaken in dental operatories with huma participants		
Procedure description	Inadequately described	Adequately described to be able to understand what was done but could not be reproduced and could be reproduced	Described in detail and could be reproduced		
Equipment used in Procedure	Not mentioned	Mentioned but not adequately described (type of item e.g. air rotor)(but no further detail	Adequately described in detail and could be reproduced		
Sample size	Not mentioned	Mentioned but not described in enough detail to reproduce	Adequately described in detail and could be reproduced		
Controls (for microbial studies)	No control measures described	Control measures described for example leaving a plate out for an hour before the procedure	Not applicable		
Sensitivity of measurement for contamination measure (separate for microbiological, blood and visual for spatter)(Further details found on Table 2)	Low sensitivity	Medium sensitivity	High sensitivity		
Outcome	Outcome reporting do not meet standard i.e. not expressed or statistical tests were not appropriate, not reported	Outcome reporting partially meets standard	Outcomes clearly stated with appropriate descriptive statistics to express contamination for areas as point estimates and include measures of distribution (e.g. standard deviation, standard error and range) and if statistical tests are used to analyse associations, these are appropriate, and include confidence intervals and the probability levels (p value)		

Table 2

Sensitivity of measurement for contamination measure (separate for microbiological, blood and visual for spatter).

	Blood agar used?	Incubation environment	Incubation duration (days)
Measureme	nt of microbial contamination		
Low	The study did not use blood agar as growth media.	Aerobic environment was used.	Incubation time $(1-3 \text{ days})$ was unsatisfactory for cultivating a wide range of bacteria with different replication rate.
	Not stated.	Not stated	Not stated.
Moderate	The study used blood agar as growth media.	Aerobic or anaerobic (in consideration to other parameters).	The study used a moderate incubation time for cultivating a moderate range of bacteria with different replication rate.
High	The study used blood agar as growth media.	Anaerobic environment was adopted that allowed.	Incubation time (7 days or more) was satisfactory for cultivating a wide range of bacteria with different replication rate.
Measureme	nt of blood contamination	unowed.	bacteria with different replication face.
Low	Visible detection with no other equip	oment used.	
Moderate		bility of enhancers (e.g. fluorescent dye).	
High		detection such as DNA detection with PCR.	
Measureme	nt of non-microbial and non-blood con	tamination	
	Visible detection with no other equip	pment used.	
	Used test with no consideration of di	ilution effect of blood in interpretation (false n	egatives).
Low	Used test with no consideration of in	npact of hypochlorite in interpretation	
	of surfaces in dental settings (false p	ositives at higher dilutions which is relevant for	or surfaces
	rather than gowns/masks/drapes)		
Moderate	Visible detection with the use of visi	bility of enhancers (e.g. fluorescent dye).	
	Direct testing;		
	Used agents appropriately, these age		
		phenolphthalein followed by hydrogen peroxic	le 3 %
	5	ent followed by hydrogen peroxide 3 %	
High	 Luminol 		
		n interpretation as suggested by (2014; 2006))	
		³ Gives 100 % positive results (less sensitivity	
			with more dilution but still 33.3% at 10^{-7}); and
	Considered impact of hypochlorite in	n interpretation of dental settings (relevant for	surfaces rather than gowns/masks/drapes).

sensitivity of the methods used, and therefore accuracy of the results in reflecting actual contamination. This allowed a judgement on the likelihood of under- or over-reporting of contamination for each study, and by procedure.

2.10. Relative contamination of procedures

Where methodology was similar enough to compare contamination levels or studies included multiple procedures, the relative contamination levels between procedures were examined and a visual map represented by a network diagram was constructed to clarify where there were comparisons between different procedures and how many, and to identify where there were gaps.

3. Results

There were 83 studies (Appendix 3) which met the inclusion criteria and for which we could obtain full manuscripts. All included studies were published in English (see PRISMA flow chart Fig. 2.).

Studies originated from 24 countries, the majority conducted in the USA (n = 26) and India (n = 21). They were published between 1963–2020 with 43/83 (52 %) of the studies published in the last decade (Fig. 3.)

A full description of the studies' characteristics and the data extracted can be found in Appendix 4.

The extracted data were heterogeneous across key characteristics, including; aims, methodology and outcomes. A narrative summary was undertaken and within study comparisons of relative contamination made. Whilst there were no studies showing a direct association between dental procedures with exposure, infection and transmission of pathogenic micro-organisms (outcome 2b), there was evidence of contamination of persons in the dental surgery and the surgery environment (surfaces, equipment etc.) and air from all procedures investigated although the levels of contamination varied (Appendix 4).

Approaches to the investigation varied: some studied procedures, some instruments and some both. Data were separated into the following categories: USS (n = 44 studies), HSAR (n = 31); oral surgery (n = 11), slow-speed handpiece (n = 4); air-water syringe (n = 4), air polishing (n = 4), prophylaxis with cup and pumice (n = 2) and hand scaling (n = 2.

Settle plates were used in 48 studies, 12 used visual inspection and 23 used air samplers (specific for aerosol). The main findings for each of the instruments/ procedure categories is summarised below (n = number of studies), with further detail provided in Table 3 and Appendix 4.

3.1. USS (n = 44 studies)

All 37 studies with measures for droplet contamination (splatter) and where samples were collected from the air (n = 7) had positive findings including those that used high volume and standard suction. There was greater droplet contamination within 1 m distance of the patient (n = 8) [25–32]. The operator's face (mask and visor area) were heavily contaminated (n = 10) as were areas closer to the patient (operator's nearest arm) (n = 2) [31,33]. When assessed, contamination was identified on the assistant's face and arm (n = 4). The patient's body was heavily contaminated and their chest one of the most heavily contaminated areas. Contamination levels reduced with increasing distance from the mouth. At the maximum measured distance of 3 m, contamination was identified. Air sampling (n = 3) found contaminated aerosol

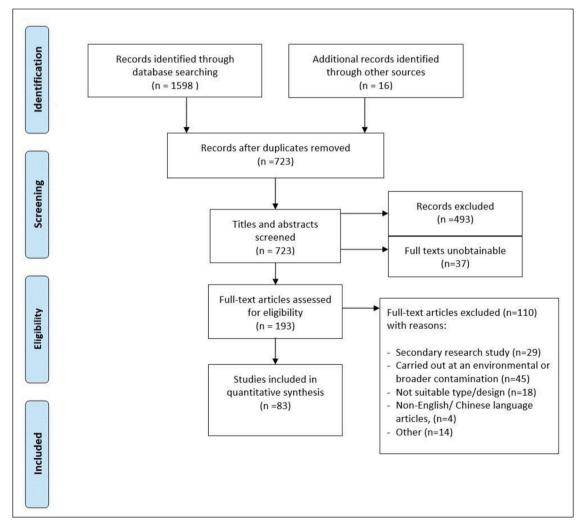


Fig. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2009) flow chart. A full description of study characteristics can be found in Appendix 4.

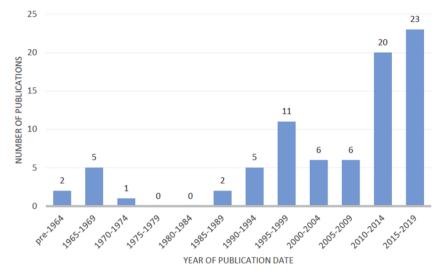


Fig. 3. Publications by date (n = 81; 2 publications from 2020 were not included).

was generated during treatment [31,34,35] with a small proportion detectable at four feet before returning to baseline two hours post-treatment [34].

3.2. HSAR (31 studies)

There was wide variability in the procedures investigated: Restorative (n = 27); cavity preparation, gaining endodontic access, fixed prosthesis tooth preparation; and Orthodontic (n = 4); cement removal [following fixed appliances]; and procedural time (10 s to four hours). Contamination was detected on settle plates on surfaces across all (n = 15) areas measured up to three meters from patient mouth [27,36]. Contamination levels were highest in front of the patient and reduced with increasing distance from the mouth [25,36,37] and the lowest areas of contamination levels were behind the patient [37]. One study found approximately 80 % of aerosol settled immediately following the procedure and reached baseline levels after two hours [34]. The operator, assistant and patient were consistently contaminated, most heavily on the operator's head and patient's chest. One study directly compared both single and multi-surgeries and found that contamination was detected over a larger distance when there were multiple dental chairs in an area [34].

3.3. Oral surgery (n = 11)

Oral surgery involving removal of teeth, generally third molars, used motorised handpieces of variable speeds (n = 10; 1 assumed), reporting the use of irrigation (n=6), intra-oral suction/aspiration (n=5) in single and multiple chair dental settings, found risk of contamination (mostly blood, with evidence of anaerobic bacteria). Contamination was present on the patient (chest and face), operator (face/head, arm/glove/ cuff, chest, abdomen, leg) and assistant (face/head, arm/glove/cuff, body) as well as the dental operatory and air environment (< 1 m). Surgeons and assistants wore surgical PPE including gowns and the research was conducted in a range of settings, mainly dental hospital outpatient facilities (n = 10). Most evidence was of blood spatter (visible and imperceptible) whilst microbiological examination was limited to aerobic testing. Imperceptible blood splatter was significantly higher than visible stains. Very limited evidence on extractions (n = 2) suggests lower risk but not without risk of contamination. Risk increased with time, type of procedure and decreased with distance.

3.4. Slow-speed handpiece (n = 5)

Three studied removal of excess material following fixed orthodontic appliance treatment [38–40] with air sampling equipment (to detect aerosol). Findings varied but could be related to study design differences. Dawson et al. [40] and Day et al. [39] found a marked increase in bacterial load during debonding and enamel cleaning compared to baseline levels. Ireland et al. [34] detected particles (2 μ m to >30 μ m diameter) demonstrating facilitation of aerosol and droplets.

With denture polishing and trimming [41,42] microbiological contamination was highest 2 feet from the operatory position compared to 1 ft and 3 ft [41] and microorganisms such as yeasts and Gram-negative bacteria were in the aerosol generated [42].

3.5. Air-water syringe (n = 4)

All studies identified contamination following use [25,43-45]. However, the extent of contamination varied widely (n = 3). Air and water used together (spray) generated more than air alone and water alone the least [25,43,44]. Smaller particles remained in the air for more than 6 h [45]. Bacterial contamination from droplets was detectable at 4 feet from the patient [43] and 6 feet from patients [25]. These were the maximum points sampled

3.6. Air polishing (n = 4)

Air polishing demonstrated contamination of, in ascending order, the operator's forehead, operator's mouth and patients' chest. Contamination from air polishing was found nine feet from the treatment area even in a surgery with 13 air changes/hour [46].

3.7. Prophylaxis (n = 2)

Prophylaxis with cup and pumice (n = 2), [25,44] produced less contamination than air-polishing (n = 4). It produced a higher rate of contamination than washing teeth with a water stream, but lower than drying teeth with an air spray or using a high turbine with water coolant, as measured using the same closed test chamber (n = 1).

3.8. Hand scaling (n = 3)

Hand scaling produced minimal contamination (two artificial environments; patients' head in a closed experimental test chamber with side glove ports for the operator (n = 1), and a mannequin in a closed box

Table 3

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Main characteristics of the included studies categorised by dental procedure/ instrument use (n = 83). Please note that the numbering in this table refers to the list of references (included studies) in Appendix 3 and are not the same numbering system as found in the main text.

Procedure category (no of studies)	Procedures investigated (e.g. cavity preparation) and type of investigation (clinical/ laboratory, patient/ mannequin)	Investigated contamination of operator, assistant, patient	Area within dental surgery investigated*	Different timepoints sampled (hours, minutes, seconds)	Detection sensitivity scores for outcome methodologies
	Ultrasonic scaling (n=44)	Operator (n=18) 5,8,9,10,16,21,31,44,45,55,59,60,63, 65,70,72,83,85	Environmental surfaces < 1m (n=15) 8,16,21,33,37,45,52,54,61,66,71,73,74,76,78 ⁾	During procedure (n=28) 8,9,22,23,24,25,32,48,90,52,54,59,60,61,62,64,65,66,69, 70,72, 73,74,76,78,80,85,87	High detection sensitivity (n=5)
	Simulation Mannequin (n=3) ^{8,25,83}	Head/face (n=13) 8,9,10,16,21,31,44,53,59,65,72,83,85	>1m (n=3) ^{25,44,64}	During and after combined (n=8) ^{10,16,21,31,41,44,45,} 71	Moderate detection sensitivity (n=3)
		Body (n=8)5,8,10,31,60,70,83,85	$< 1m \text{ and } > 1m (n=9)^{10,41,48,69,90,70,80,83,87}$	After procedure(n=3)	Low detection sensitivity
USS (n=44) ^a		Assistant (n=4)		0-30 min ^{29,37,83}	(n=34)
	Simulation Typodont	Head (n=2)16,83		30 min-1 hr ^{29,37,83}	Uncategorized detection sensitivity
	Laboratory (n=3) ^{33,34,66}	Body $(n=3)^{31,70,83}$ Patient $(n=14)$	Air Samples (n=7) ^{6,22,23,24,29,32,87}	1–2 hr ^{29,83}	(n=2)
		Chest (n=14)5,8,16,21,31,44,60,61 62,65,70,71,73,85		2–4 hr ²⁹	
	Tooth/cavity preparation (clinic) (n= 24)	Operator (n=10)	Using settle plate within 1m of operating area	Within the first 30 minutes after the procedure $(n=4)^{8, 29,51, 94}$	High detection sensitivity (n=4)
man (and	Mannequin/ Typodont (clinic) (n=3) ^{8,36,42}	Head/face $(n=9)^{96,95, 20,8,81,59,63,55,3}$, Body $(n=2)8,60$	$(n=12)^{93,8,92,42,48,59,63,90,60,81,94,87}$	Between (30 min -1 hr) after procedure $(n=2)^{29,51}$	Moderate detection sensitivity (n=6)
HSAR $(n=31)^{\circ}$	Mannequin/ typodont simulation (laboratory) (n=4) ^{13,30,51,89}	Assistant (n=3) Head/face (n=3) ^{8,81,63} , Body (n=1) ⁸ Patient (n=6) Intra-oral (n=1) ²⁰ , Head/face (n=1) ⁹⁵ , Body (n=4) ^{92, 20, 8, 94}	Using settle plate 1m or more from operating area $(n=9)^{93,48,90,56,63,94,\ 60,63,\ 81}$	1-2 hr (n=2) ^{29,51} , 2-4 hr (n=2) ^{29,51} , > 4 hr (n=1) ⁵¹	Low detection sensitivity (n=21)
	Surgical removal of teeth (clinic) (n=8) ^{4, 17, 38,39,84, 43, 87, 98}	Operator (n=5) Head/ face/neck (n=4) 4 , 38 , 40 , 98	Environment and surfaces within 1m from operating area $(n=4)^{17,32, 39, 46, 87}$	Up to 30 min during procedure $(n=2)^{17,43}$	High detection sensitivity (n=3)
	Implants (clinic) (n= 1) 98	Arms/ Cuffs/ hands	Environment and surfaces 1m or more from		Moderate detection sensitivity (n=2)
Oral surgery	Extraction (clinic) (n=2) 32,98	(n= 3) ⁴ , ³⁸ , ⁴⁰	operating area (n=0)		
(including Other: rest extractions) periodonta (n=11) ^c (clinic) (n= Not verifie	Other: restorative and periodontal procedures (clinic) $(n=1)^{87}$	Abdomen/ shoes $(n=3)^{4, 38, 4}$ Nearby operator $(n=1)^{43}$ Assistant $(n=3)$ Head/ face/neck $(n=2)^{4, 98}$ Arms/ Cuffs/ hands, $(n=1)^{4}$ Other body parts $(n=1)^{4}$	Sampled at mouth (n=0)	During treatment with agar plates replaced every 10 min $(n{=}1)^{32}$	Low detection sensitivity (n=6)
	Not verified/ unclear (clinic) (n=2) ^{40, 46}	Nearby assistant $(n=1)^{43}$ Patient: (n=3) Head/ face, $(n=1)^4$ Chest $(n=2)^{4, 17, 43}$			
Slow-speed handpiece (n=5) ^d	Removal of excess material following fixed orthodontic appliance removal $(n=3)^{14,15,97}$		Air sampler 30cm from patient's mouth $(n=2)^{14,15}$		High detection sensitivity (n=3)
		Operator (n=1) ² (thorax and abdomen area of technician)	Air sampler 10cm from patient's mouth $(n=1)^{97}$	Not specified (n=5)	Moderate detection sensitivity (n=0)
	Polishing and trimming of denture (n=2) ^{2,47}		Settle plates at 1ft, 2ft and 3ft from the motor $n=1^{47}$		Low detection sensitivity $(n=2)$
Air-water syringe (n=4) ^e	ucinuit (II-2)	N/A	Experimental Simulation-Air Samples Human aerosol test chamber ⁸⁹	During procedure $(n=3)^{89,90,93}$	High detection sensitivity (n=0) (continued on next page)

Procedure category (no of studies)	Procedures investigated (e.g. cavity preparation) and type of investigation (clinical/ laboratory, patient/ mannequin)	Investigated contamination of operator, assistant, patient	Area within dental surgery investigated*	Different timepoints sampled (hours, minutes, seconds)	Detection sensitivity scores for outcome methodologies
	Air-water syringe with air and water used together (n=3) ^{89,90,95}			After procedure $(n=1)^{51}$: at 2 min, 35 min, 2 hr, 4 hr and 6 hr.	
	Air-water syringe with air alone $(n=4)^{51,89, 90,93}$		Quartz crystal microbalance cascade impactor (QCMCI) ⁹⁵		Moderate detection sensitivity (n=1)
	Air-water syringe with water alone $(n=4)^{51,89,90,93}$		Clinical (splatter plate) 90,91 0–1m90,91 1–2m90,91		Low detection sensitivity (n=3)
	Air polishing (clinic) $(n=3)^{18,49,53}$	Operator Head/face $(n=3)^{18,49,53}$	Air sampled 12 inches from patients' mouth at 50° angle ⁵³	30 min including procedure of 2 $\min^{49,53}$	High detection sensitivity (n=0)
Air polishing (n=4) ^f	Mannequin/ typodont simulation (laboratory) $(n=1)^{35}$	Patient Body (n=1) ¹⁸	Air sampled $< 1m$ of operating area ³⁵ Surface $< 1m$ operating area $(n=1)^{49}$ Surface $> 1m (n=1)^{49}$	During procedure (n=2) ^{18,35}	Moderate detection sensitivity (n=1) Low detection sensitivity (n=3)
Prophy: cup and	Prophy on patient's head in closed experimental test chamber with side glove ports (clinic) $(n=1)^{89}$	N/A	Air sampling of the closed chamber around the patient's head ⁸⁹	During the procedure (10–120 sec) with 4 min clearance period of quiet breathing before and after ⁸⁹	High detection sensitivity (n=0)
pumice (n=2) ^g	Prophy (clinic) (n=1) ⁹⁰		Air sampled 3 ft from floor and 1 ft from patients' mouth (in front) to the sides and end of the surgery ⁹⁰	During procedure (30 sec) ⁹⁰	Moderate detection sensitivity (n=0) Low detection sensitivity (n=2)
Hand scaling (n=2) ^h	Hand scaling patient head in closed test chamber with side glove ports (clinic) $(n=1)^{89}$	N/A	Air sampling of the closed chamber around the patient's head ⁸⁹	During procedure (10–120 sec) with 4 mins clearance period of quiet breathing before and afterwards ⁸⁹	High detection sensitivity (n=0) Moderate detection sensitivity (n=0)
	Mannequin/typodont simulation (laboratory) (n=1) ³⁴		Air sampled around mouth distance not specified ³⁴	During procedure (2 sec) ³⁴	Low detection sensitivity sampling/ measuring approach (n=3)

Unique study identification numbers.

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Table 2 (continued)

Dos Santos 2014¹⁸, Harrel 1999³⁵, Logothetis 1995⁴⁹, Muzzin 1999⁵³.

* m = metre(s); ft - foot/feet; in = inch(es); cm = centimetre(s); hr = hour(s); min = minute(s); sec = second(s).

^a Balcos 2019⁵, Barnes 1998⁶, Bentley 1994⁸, Choi 2018⁹, Chuang 2014¹⁰, Devker 2012¹⁶, Feres 2010²¹, Fine 1992²², Fine 1993 a²³, Fine 1993b²⁴, Graetz 2014²⁵, Grenier 1995²⁹, Gupta 2014³¹, Hallier 2010³², Harrel 1998³⁴, Harrel 1996³³, Holloman 2015³⁷, Jawade 2016⁴¹, Kaur 2014⁴⁴, King 1997⁴⁵, Labaf 2011⁴⁸, Miller 1971⁹⁰, Mohan 2016⁵², Narayana 2016⁵⁴, Nejatidanesh 2013⁵⁵, Prospero 2003⁵⁹, Purohit 2009⁶⁰, Ramesh 2015⁵¹, Rao 2015⁶², Reddy 2012⁶⁴, Retamal-Valdes 2017⁶⁵, Rivera-Hidalho 1999⁶⁶, Sadun 2020⁶⁹, Saini 2015⁷⁰, Sawhney 2015⁷¹, Serban 2013⁷², Sethi 2019⁷³, Shetty 2013⁷⁴, Singh 2016⁷⁶, Swaminathan 2014⁷⁸, Timmerman 2004⁸⁰, Veena 2015⁸³, Watanabe 2013⁸⁵, Yamada 2011⁸⁷. ^b Al-Amad 2017³, Belting 1963⁹³, Bentley 1994⁸, Cochrane 1989⁹², Dahlke 2012¹³, Day 2008¹⁵, Earnest²⁰, Greco 2008²⁸, Grenier 1995²⁹, Grundy 1967³⁰, Hallier 2010³², Hausler 1966³⁶, Junevičius 2005⁴², Labaf

^b Al-Amad 2017³, Belting 1963⁹³, Bentley 1994⁸, Cochrane 1989⁹², Dahlke 2012¹³, Day 2008¹⁵, Earnest²⁰, Greco 2008²⁸, Grenier 1995²⁹, Grundy 1967³⁰, Hallier 2010³², Hausler 1966³⁶, Junevičius 2005⁴², Labaf 2011⁴⁸, Larato 1966⁹¹, Manarte-Monteiro 2013⁵⁰, Micik 1969⁸⁹, Miller 1971⁹⁰, Miller 1995⁵¹, Neiatidanesh 2013⁵⁵, Oliveira 2018⁵⁶, Prospero 2003⁵⁹, Purohit 2009⁶⁰, Rautemaa 2006⁶³, Samaranayake 1989⁸⁸, Stevens 1963⁹⁶, Tag El-Din 1997⁹⁴, Toroğlu 2001⁸¹, Toroğlu 2003⁸, Travaglini⁹⁵, Yamada 2011⁸⁷.

^c Al-Eid 2018⁴, Divya 2019¹⁷, Hallier 2010³², Ishiharma 2008³⁸, Ishiharma 2009³⁹, Janani 2018⁴⁰, Jimson 2015⁴³, Kobza 2018⁴⁶, Wada 2010⁸⁴, Yamada 2011⁸⁷, Aguilar-Duran 2020⁹⁸.

^d Agostinho 2004², Dawson 2016¹⁴, Day 2008¹⁵, Ireland 2003⁹⁷, Kritivasan 2019⁴⁷.

^e Belting 1963^{93,}, Micik 1969⁸⁹, Miller 1971⁹⁰, Miller 1995⁵¹.

⁸ Micik 1969⁸⁹, Miller 1971⁹.

^h Harrel 1998³⁴, Micik 1969⁸⁹.

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et a

(n = 1). Levels of air contamination in the test chamber were comparable to a clinical examination in the same experiment. When hand scaling with orthodontic treatment was compared to HSAR contamination was much lower when no powered instruments were used [37].

3.9. Relative contamination levels

Although there were 83 studies, the degree of heterogeneity in methodology meant it was not possible to compare data between them. The outcome of interest was contamination. It could be grouped as being microbial, blood and non-microbial/non-blood. However, within these, there were a large variety of outcome measures (Appendix 4). For example, even within those looking at colony forming units, the outcome measures encompassed; whole plate (CFU/mm²); (CFU/mm³); (CFU/cm²); (CFU/m3), volume of sampled air (CFU/cm²/min), Index of Microbial Air Contamination (CFU/m²/h) and rate of production (CFU/min).

However, it was evident that there was a hierarchy of contamination levels with some procedures generating more contamination than others. A network diagram (Fig. 4) illustrates where intra-study comparisons exist. Data from these 13 studies were tabulated (Appendix 5, Table 1) and compared for relative contamination levels within studies (Appendix 5, Table 2).

These studies and their data were then categorised as higher, moderate and lower relative contamination levels (Fig. 5). This is a proposed hierarchy model and it should be noted that positions denote relative positions along a spectrum rather than definitive cut-offs between the three levels.

3.10. Quality assessment/ risk of bias

The quality assessment (Table 4) for the studies showed a mixed picture for each of the seven domains; the majority of studies scored "high" quality for one domain (controls), "moderate" for four (study

Fig. 5. Proposed levels of contamination associated with different procedures, drawn from Appendix 5 showing levels of contamination within studies to minimize dissimilarities in methodology, procedures and outcomes that might account for differences. Note that this must be interpreted with caution and will need to be modified as further evidence becomes available. *Indicates very low certainty.

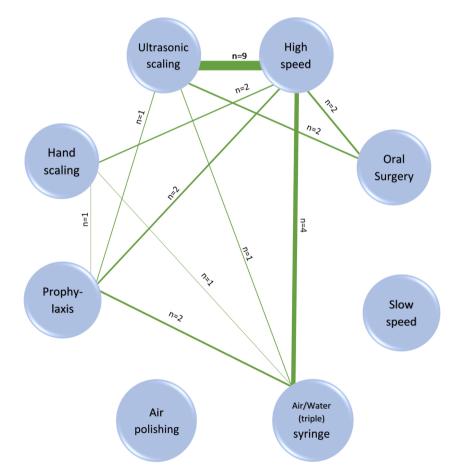


Fig. 4. Network diagram illustrating where studies included comparison between different procedures within them. (See also Appendix 5). The nodes represent the eight procedures and the lines between them show where a study compares them. The number of studies is shown by 'n=' and also the relative thickness of the lines. Where a node has no linkages, there are no studies comparing it with another procedure.

funding, conflict of interest, procedure description and outcome reporting) and "low" for two (equipment use and sample size).

Risk of bias was assessed across the cumulative evidence. It was not possible to carry out a statistical assessment of publication bias but the spread of evidence was considered through publications dates' analysis to look for increases in evidence production to see if these align to events such as infectious disease outbreaks.

3.11. Detection sensitivity

Across all studies, for detecting contamination, 59 were rated as low detection sensitivity, 11 were moderate and 11 as having a high detection sensitivity. Detection sensitivity gradings for each procedure and by study are detailed in Appendix 6.

4. Discussion

The 83 studies included in this review looked at eight different activities classified as; USSs, HSAR and slow-speed handpieces, oral surgery, air-water syringe, air polishing and hand scaling. There was heterogeneity between methodologies used to investigate contamination and a lack of consistency even when the same methodology was used by different studies. Few studies used a high detection sensitivity measure making under-reporting of levels of contamination a concern. Despite the variable methodology and broadly low detection sensitivity of the methods used, all activities and all studies identified contamination from droplets that had either settled (splatter) or droplet nuclei remaining in the air as aerosol and at the furthest points studied.

Contamination levels varied with some activities such as hand scaling generating contamination no greater than occurs during speaking [25]. The greatest levels of contamination were found with procedures involving powered devices and water (HSAR and USS). Devices that used air and water together also generated splatter and aerosol and highest nearest the patient. It was not possible to draw conclusions around the use of the slow-speed handpiece with any certainty because no study compared it with anything else for either use of carious tissue removal or orthodontic cement removal.

Although dental procedures are commonly categorised dichotomously as either aerosol producing or non-aerosol producing, this is an over-simplification, bearing in mind that while droplet nuclei $\leq 5 \,\mu m$ in diameter are categorised as aerosols, in reality droplet size lies on a continuum. Since SARS-CoV2 transmission has been reported up to 4 m from the source [47], aerosol transmission remains a possibility.

The majority of studies used a settle plate methodology which is limited to capturing droplets which can carry viruses. Settle plates can detect droplets that have fallen onto a surface. However, air turbulence caused by movement in the surgery may affect what is captured. Air samplers, most of which actively sample the air in the room, will therefore detect both aerosol and airborne droplets before they have fallen to ground (n = 23 studies). Many of the studies that stated they were detecting aerosols, did not use a methodology that investigated airborne transmission (i.e. droplets <5 μ m) such as air samplers. Most studies' findings related to droplet splatter detected on settle plates. However, both droplets and aerosols can carry viruses although the universal precautions currently in use will provide protection from droplet transmission.

Although we identified 83 studies investigating eight different procedures, it was difficult to draw definitive conclusions about relative droplet and aerosol generation between procedures. Firstly, because diverse methodologies had been used and secondly, because study quality was generally low, especially in relation to the sensitivity of measuring contamination. Low detection sensitivity could result in significant underestimates: for example, saliva cultured under highly sensitive conditions will yield c 10^8 CFU/ml but only $10^5 \cdot 10^6$ using low detection sensitivity methods. Thirdly, all studies found contamination as far as they measured it and most, for as long as they measured it –

which begs the question as to whether greater distances and times measured would have resulted in further positive findings. There was also insufficient data to explore differences according to environmental context such as ventilation or single/multi-chair surgeries (although where multi-surgery environments were studied this showed contamination over larger distances [34,48].

There has been growing research in this area with over half of the studies being published in the last decade. Most studies (n = 62) used microbes purported to be from the oral cavity to monitor contamination from procedures. All, apart from two looking at the bloodborne virus Hepatitis B [49,50] and three at fungi, investigated bacteria. None of the studies investigated contamination by respiratory viruses. This is despite several significant outbreaks of respiratory viruses where AGPs might have been a risk factor (Severe Acute Respiratory Syndrome (SARS) 2003; Swine flu 2009; Middle East Respiratory Syndrome in 2012). Viruses are difficult to culture, in comparison to bacteria, which may account for this. Most of the studies looked at easily cultured oral bacteria as surrogates of contamination from the droplets and aerosol generated from the procedure. However, viruses are small (typically between 20-300 nm in diameter) and can be carried in the same way as bacteria, therefore patterns of bacterial splatter and aerosol can provide some information to inform viral spread.

None of the studies directly explored exposure (for the dental team or patient) to potentially pathogenic micro-organisms. Studies did, however, identify significant contamination relating to the operator's head and the patient's body when powered devices (HSARs and USSs) were used. Visors, glasses and masks were often heavily contaminated, with a small number of ultrasonic studies finding contamination under the visor and mask. The body and operating arm of the operator were subject to significant contamination and studies of the assistant found less contamination (although this varied depending on the area of the mouth being worked on). Areas closest to the patient were most affected. This has implications for decisions about personal protective equipment and the coverage needed. The patient's face and body were significantly contaminated as a result of powered devices (HSARs and USSs). These were often measured in the oral surgery procedures and were also found to be contaminated. There were two studies, both oral surgery ones, that investigated the lower part of the operator body. One indicated contamination of the abdomen and upper leg areas [51], and another showing no contamination of shoe covers used by surgeons and their assistants [52]. Although these are only two studies, they have implications for infection control measures to reduce the chances of cross contamination in dental settings.

Beyond time, distances and settings there were further obvious gaps in the data as a whole. These include a lack of negative controls and baseline measures, clarity of reporting over specific procedure times and time periods during and following them to see when there was no longer contamination from the procedure. However, the most concerning gap may be the general failure across the studies to report the limits of contamination for distance and very few reporting on time for settle. Studies on mitigating interventions (such as high-volume evacuators, HEPA filters, air changes etc.) may be able to clarify this area further. However, it is encouraging to see more research in the field being undertaken, with three papers published since this search was undertaken, fitting the inclusion criteria [53–55] and one further paper [56] awaiting full text assessment at the time of submission, hopefully these will add to the body of well conducted research informing risk and risk mitigation in relation to AGPs.

A limitation of the study is that, as a result of the diverse nature of the study designs included, the experimental approach and the type of data extracted from those studies, it was not appropriate to use a standardised quality assessment tool."

Since the COVID-19 pandemic began, much research effort has focussed on elucidating the modes of SARS-CoV-2 transmission to intervene and effectively reduce its spread. It is not disputed that COVID-19 is highly transmissible with the most common routes similar

Table 4

Quality assessment of included studies (n = 83). Studies were ranked as low (red), moderate (amber) or high (green) for each parameter (see protocol for full description in Appendix 1). There is no summation across fields.

Included studies (First author year)	Was the study industry funded? (related to study materials being investigated)	Was there a conflict of interest?	Relevance to routine clinical dentistry	Procedure description	Equipment used reporting	Sample size	Controls (for <u>microbial</u> <u>studies</u>)	Outcome (Contamination)
Balcos 2019							N/A	
Barnes 1998							N/A	
Bentley 1994	•				•			
Choi 2018								
Chuang 2014	-	•						
Devker 2012								
Feres 2010	•	•						
Fine 1992	•	-						
Fine 1993		•						
Fine 1993								
Graetz 2014	-	-					N/A	
Grenier 1995	-							
Gupta 2014		•						
Hallier 2010	-							
Harrel 1996	-						N/A	
Harrel 1998	-	-					N/A	
Holloman 2015								
Jawade 2016	-							
Kaur 2014	-							12
King 1997								
Labaf 2011	-		•					1
Miller 1971	-		•					1
Mohan 2016	2							
Narayana 2016	2			-				
Nejatidanesh 2013				-			N/A	
Prospero 2003					•			
Purohit 2009	•				•			
Ramesh 2015				•	•			•
Rao 2015	•	•						
Reddy 2012	•							
Retamal-Valdes 2017	•	•			•			•
Rivera Hidalho 1999	•	•	•	•			N/A	
Sadun 2020	•	•	•	•	•	•		•
Saini 2015					•			
Sawhney 2015					•	•		
Serban 2013		0		•	Ŏ			0
Sethi 2019		•	Ŭ.	0	Ó	Ó		0
Shetty 2013	•				•	•		
Singh 2016					•	•		
Swaminathan 2014		0	Ŭ.	0		Ŭ.	Ŏ	0
Timmerman 2004		0		0		0	Ŭ.	0
Veena 2015	•				Ó		N/A	0
Watanabe 2013				•	•			
Yamada 2011							N/A	
Al-Amad 2017								
Belting 1964	_							
Bentley 1994 Cochran1989							N/A	
Dahlke 2012							N/A	
Day 2008		-	Ĭ			i i i i i i i i i i i i i i i i i i i	N/A	
Earnest 1991	Ŏ	i i i i i i i i i i i i i i i i i i i	Ĭ	Ĭ	Ŏ	Ŏ	0	Ŏ
Greco 2008								
Grundy 1967							N/A	
Hausler 1966								+
Junevicius 2005 Larato 1966							N/A	+
Manarte-Monteiro			1	1	i i			1
2013	-	-	-		-		-	-
Micik 1969								
Miller 1995							N/A	
Oliverira 2018								
Rautemaa 2006								
Samaranayake 1989 Stevens 1963								+
Tag el-Din 1997	Ĭ	1	1	i 🎽	i i			1
Toroglu 2001		Ĭ	Ĭ	Ĭ	Ĭ	Ĭ	ŏ	Ĭ
Toroglu 2003	<u> </u>	Ö		Õ	Ó		Ū.	
Travaglini 1966								
Yamada 2011					•		N/A	
Aguilar-Duran 2020	•					1	N/A	
Al-Eid 2018	•						N/A	
Divya 2019							•	
Ishihama 2008							N/A	1
Ishihama 2009							N/A	
Janani 2018	•				•			1
Jimson 2015	2			-				1
Kozba 2018								
Wada 2010	•						N/A	
Agostinho 2004		•				•		
Dawson 2016	•	•						•
Ireland 2003	•	•					N/A	
Kritivasan 2019	•	•	•		•		•	
Dos Santos 2014					•			
BOS BUILTOS LOLA	-							
Harrel 1999	ĕ	•	•				N/A	•
	•	•	•	•	•	•	N/A	•

to other respiratory viruses: respiratory droplets and direct contact (although the role of fomites remains controversial) [4]. In addition, there is broad agreement, and evidence from outbreaks, that transmission via aerosols occurs [5]. In response to this evidence, dentists around the globe paused clinical practice and at the time of publishing this review, dental activity remains significantly reduced. However, the potential role that dental aerosols play in transmission of COVID-19 remains poorly understood. It is important to highlight that all included studies in this review were concerned with where aerosol/droplet spread reached in the dental setting, and/or the associated microbial load. None of these studies directly investigated infectious disease transmissibility from AGPs. Such studies focused on Covid-19 are needed but may be difficult to perform giving the challenges of working with live virus and the uncertain relevance of possible viral surrogates.

This review has focused on droplet and aerosol contamination relating to specific dental procedures, extending beyond previous work that looked at micro-organisms and hazards generated in dental practice [57]. This provides evidence which may be used to determine the baseline risks associated with dental procedures, helping dental professionals to identify clinical situations with increased aerosol transmission risks where mitigation would be strongly advisable.

5. Conclusion

Despite generally low detection sensitivity measures being used, there was evidence of contamination of surfaces around the surgery environment/ personnel or contamination in air from all procedures that were studied. There was evidence that this varied by procedure type. Most studies used microbial surrogate measures (mainly oral microbiota) and blood or colored water for detecting contamination following these procedures. None looked at respiratory viruses. The variability in methodology and variety of outcome measures thwarted attempts to synthesise across studies. By looking at comparisons of procedures within studies, blunt generalisations could be made over higher, moderate and lower risk procedures. There are significant gaps in the evidence and its quality that limit conclusions around all aspects of contamination for different procedures. These hamper evidence-based clinical recommendations and policy decision making, especially relevant for dentistry and COVID-19.

Funding

There are no external sources of funding for this research and it was supported by the authors' institutions

Authors contributions

NI, IJ, RH, JE had oversight of the study planning and execution, and to the conception, design, data acquisition, synthesis, visualization and interpretation, drafted and critically revised the manuscript. WW conception, design, data synthesis and interpretation, drafted and critically revised the manuscript WA, MR data acquisition, synthesis, visualization and interpretation, drafted and critically revised the manuscript. SKC, RH data acquisition, synthesis and interpretation, drafted and critically revised the manuscript. SM design of the study, provision of and management of study literature resources and critically revised the manuscript.

All authors gave their final approval and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

All of the authors confirm they have no conflict of interest with regard to this work, to report. There are no external sources of funding for this research and it was supported by the authors' institutions

Acknowledgments

We would like to thank library team at the British Dental Journal, for their quick response and dedication to try to supply the full text of papers we required where there was limited access to hard copies in the face of challenges imposed by the COVID-19 lockdown. A special thanks to the American Journal of Dentistry, who provided us a copy of one of their articles at no charge. This work was not externally funded and authors were supported by their institutions.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdent.2020.103556.

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