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What is the evidence that medical procedures which induce coughing or involve respiratory suctioning are associated with increased generation of aerosols and risk of SARS-CoV-2 infection? A rapid systematic review

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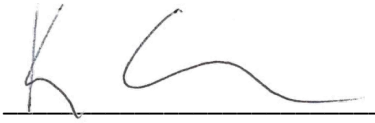

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Response to reviewer comments

Reviewer #1:

The "evidence" in medicine is often difficult to estimate. And even worser may it be if a mixture of processes, investigations, procedures, measures, patients/not-patients are included in a material of 6 very different groups - tables - of few studies in each group.

Four different types of infections are included in addition to noninfectious healthy volunteers and cadaveric stimulations. This heterogenous material is very difficult to evaluate for "evidence" of a) aerosol production from medical procedures and b) transmission of infectious materials between the source and eventually secondary cases.

We agree the evidence is complex to synthesize. However, a unique feature of this review is that we have attempted to consider the full range of evidence in order to answer the questions. We have indicated the limitations of the data in our analysis. We have also included an additional paragraph in the Methods section under Inclusion/ exclusion criteria that addresses these points.

The status of the patient/object may also be of importance - for instance given sedatives, sleeping etc. **We accept this might be a factor but we were only able to use the data available and we indicated in the evidence table where potential patient confounders were not accounted for.**

Surgery per se -9 studies- should be studied separately and compared with other surgical procedures liberating a lot of tissue and blood particles as aerosols.

We consider that it is important to evaluate the epidemiological and surgical evidence together as each contribute to answering the questions. It would be difficult to compare different types of surgical procedure as the nature of the procedure would have a major effect on the extent and type of contamination. Our question was focused on the risks associated with nasendoscopy procedures only.

Table 1. SARS-1, -the HCW- were exposed via multiple ways during SARS-1, and there was even a reuse of masks without disinfection between use. This table is very uncertain concerning transmission of virus via medical procedures in airways - per se.

We have acknowledged the uncertainties of these data in the analysis but because they are the only epidemiological data available we felt it important to include.

Table 2. Is a single study on lung function test on healthy volunteers- should include more studier here--?

This was the only study identified by the searches that addressed this procedure.

Table 4. Only 4 studies of outpatients, including volunteers –

These were the only studies identified by the searches. We have recognised differences in study participants within the text.

Table 5. 6 studies on a heterogenous material of healthy volunteers and HCW and in addition on

patients with and without Covid- 19 and SARS-1 - and influenza. The mixture of study materials seem unclear.

The studies were identified by our searches and meet the criteria for inclusion. They illustrate that suctioning is not a homogenous procedure and the limtiations of the vevidence associating it with the generation of aerosols. Given the lack of robust data avialable for a new virus, we believe it is reasonable to use data captured in relation to other similar respiratory viruses whilst acknowledging there may be differences in transmission characteristics

Conclusion: procedures, study materials and results are difficult to evaluate because of few studies in each group and missing information concerning: "aerosol generation" and/or "transmission". The basic for having an opinion on evidence- or not evidence at all, is not present.

In the manuscript we have discussed the limitations in available evidence and believe that our conclusion that there is an absence of evidence to demonstrate risk is therefore reasonable.

Reviewer #2:

This paper is a report of a review of a number of publications reported between 1st January 2003 and 6th October 2020. The studies examined whether nasogastric tube insertion, lung function tests, nasoendoscopy, dysphagia assessment or suction for airway clearance were aerosol generating practices (AGP) which could lead to transmission of SARS-CoV-2 infection. In all 20 papers were studied two of these were systematic reviews and the majority were primary studies. Broadly the studies were inconsistent in their results but it is likely that the simulation experiments differed in various respects. I would suspect that there are few such studies because of the difficulty involved in setting up a study that is reproducible. Furthermore the concept of aerosol transmission has been taken for granted ever since people became aware of the possibility. The authors suggest in their conclusion, that "There was an absence of evidence to suggest that the procedures included in the review were associated with an increased risk of transmission of respiratory infection. In order to better target precautions to mitigate risk, more research is required to determine the characteristics of medical procedures and patients that increase the risk of transmission of SARS-CoV-2."

The paper is full of detail and well-written but requires concentration. It is impossible not to agree with their conclusions. (There are some small grammatical errors such as 'compared to' and 'in comparison to' rather than 'compared with' or 'in comparison with')

Thank you. These errors have been corrected.

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Running title: Rapid review procedures associated with aerosols

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What is the evidence that medical procedures which induce coughing or involve respiratory suctioning are associated with increased generation of aerosols and risk of SARS-CoV-2 infection? A rapid systematic review

Summary

The risk of transmission of SARS-CoV-2 from aerosols generated by medical procedures is a cause for concern. This rapid systematic review aimed to evaluate the evidence for aerosol production and transmission of respiratory infection associated with procedures that involve airway suctioning or induce coughing/sneezing.

The review was informed by PRISMA guidelines. Searches were conducted in PubMed for studies published between 1/1/2003 and 6/10/2020. Included studies examined whether nasogastric tube insertion, lung-function tests, nasoendoscopy, dysphagia assessment or suctioning for airway clearance result in aerosol generation or transmission of SARS-CoV-2, SARS-CoV, MERS, or influenza. Risk of bias assessment assessed robustness of measurement, control for confounding and applicability to clinical practice.

Eighteen primary studies and two systematic reviews were included. Three epidemiological studies found no association between nasogastric tube insertion and acquisition of respiratory infections. One simulation study found low/very low production of aerosols associated with pulmonary lung function tests. Seven simulation studies of endoscopic sinus surgery suggested significant increases in aerosols but findings were inconsistent, two clinical studies found airborne particles associated with the use of microdebriders/drills. Some simulation studies did not use robust measures to detect particles and are difficult to equate to clinical conditions.

There was an absence of evidence to suggest that the procedures included in the review were associated with an increased risk of transmission of respiratory infection. In order to better target precautions to mitigate risk, more research is required to determine the characteristics of medical procedures and patients that increase the risk of transmission of SARS-CoV-2.

Key words: aerosol generating procedure, respiratory infection, SARS-CoV-2, rapid systematic review, aerobiology, epidemiology, cough, suction, nasoendoscopy, nasogastric tube, lung function test

Background

Available evidence suggests that SARS-CoV-2 is emitted from an infected person's mouth or nose in small liquid particles as they breathe, speak, cough or sneeze. Particles range in size from larger respiratory 'droplets' (>10 um) to smaller 'aerosols' (<10 um) and fine particles (<1 um). Transmission mainly occurs during close contact when the virus is inhaled or inoculated onto the mouth, nose or eyes of a susceptible person and depends on the amount of viable virus present and the infection control measures that are in place.[1] Current World Health Organisation (WHO) and United Kingdom (UK) advice is that contact and droplet precautions, with the use of fluid-resistant surgical masks for close contact, are recommended for care of patients with SAR-CoV-2 infection. Airborne precautions (including the use of N95, FFP2 or FFP3 respirators) are recommended when aerosol generating procedures (AGPs) are being performed. Although not supported by evidence, the WHO recognises that some healthcare workers may place high value on the potential benefits of respirators and wish to use them in settings without AGPs.[1,2]

Historically, respiratory particles have been categorised as droplets which are deposited rapidly because of their mass and aerosols which are smaller and travel over longer distances.[3,4] However, it is now recognised that there is a continuum of particle sizes and aerosols which can be generated by breathing, speaking and coughing and can be present at both short and long distances.[5] The risk that aerosols are able to transmit infection is influenced by a range of other factors including the amount of virus in the particle, the speed and turbulence of emission, and properties of the ambient environment.[6] Although particles < 10 um can remain airborne for longer than larger respiratory droplets (>10 um), in typical particle size distributions a relatively small portion of total volume are in this range. Establishing the risk of transmission of SARS-CoV-2 associated with respiratory aerosols therefore requires evidence derived from different study designs. Laboratory-based studies can only provide evidence for part of the transmission process and demonstrate potential

rather than actual routes of transmission, while clinical studies can provide evidence of actual transmission although are more difficult to conduct and interpret.

Some medical or patient care procedures are thought to increase the generation of respiratory aerosols. Following the SARS epidemic in 2003, the WHO defined 'high-risk AGP' as medical procedures that 'have been reported to be aerosol-generating and consistently associated with an increased risk of pathogen transmission' and recommended the application of enhanced precautions for staff performing them.[8] The SARS-CoV-2 pandemic has raised concerns about a range of other medical procedures that have the potential to generate respiratory aerosols either as a result of the procedure or because of its propensity to induce coughing or sneezing in the patient.

We undertook this review to evaluate whether medical procedures which induce coughing/sneezing or involve respiratory airway suctioning, generate infectious aerosols and are associated with a risk of transmission of respiratory infection, including SARS-CoV-2. The procedures under consideration have not been previously defined as high-risk aerosol generating procedure (HR-AGP) but have been highlighted by clinicians as procedures of concern.[9] This review sought to evaluate evidence to determine if these procedures generate infectious aerosols and are associated with a risk of transmission of respiratory infection in order to inform guidance for healthcare professionals caring for patients with SARS-CoV-2. Two main questions were addressed:

1. Does evidence suggest that medical procedures which induce coughing/sneezing or involve respiratory airway suctioning result in infectious aerosol production?
2. And if yes, what is the associated risk of transmission of SARS-CoV-2?

Methods

As the assessment of evidence was required urgently to underpin guidance for use by healthcare professionals we adopted a rapid review approach, meaning that there was some deviation from standard systematic review procedures.[10] For example, although we produced a protocol, we were not able register it on Prospero as data extraction began before the protocol was finalised (Prospero requires registration before data extraction

commences); the protocol has been published elsewhere for transparency.[11] This rapid systematic review was informed by PRISMA guidelines. However, it should be noted that specific rapid review guidelines are not currently available.[12] Therefore, to ensure transparency we provide a full account of the review procedures below.

Search strategy

Searches were conducted by an information specialist (CS) in PubMed for studies published between 1st January 2003 and 6th October 2020. The search terms are detailed in web-appendix 1 and included terms reflecting aerosol generation and transmission from droplets and /or aerosols, respiratory secretions, coughing, sputum, and aerosols plus the set of procedures of interest (Table 1). In addition, the references of included articles were examined to identify any additional studies.

Inclusion/ exclusion criteria

The population of interest was adults and children with or without clinically suspected or confirmed COVID-19 or other respiratory infection (SARS, MERS, and influenza) or a simulated exposure model (e.g. using human volunteers, cadavers etc). The exposure of interest was one or more of the 'procedures of concern' shown in Table 1. The outcome of interest was the number and size of respiratory particles generated during the procedure and/or rate of infection with respiratory pathogens among exposed staff.

Study designs eligible for inclusion were case reports, case series, case control, outbreak studies, intervention studies (all designs) and systematic reviews reporting a search strategy involving multiple databases and explicit inclusion criteria. Studies were included if published in English from 2003. Only studies that reported original data were included, correspondence or comment pieces, in vitro and vaccine studies and predictive modelling studies were excluded.

The underlying evidence is heterogeneous, including different types of studies, both surgical and epidemiological, some with limited numbers of studies and others without potentially confounding factors. However, because of the limited amount of evidence, the full range of study types has been considered.

Study selection

Search results were screened using EPPI-Reviewer software.[13] One reviewer (JT) screened all titles and abstracts assisted by machine learning to prioritise potentially relevant papers. A second reviewer then independently screened the titles and abstracts provisionally included by JT and the excluded titles and abstracts that machine learning identified as most likely to have been erroneously excluded. Disagreements were resolved by discussion. Two reviewers (GC, JW) then independently screened the full reports of included references (n=68) and there was no disagreement. Reference checking of papers flagged by the full-text screeners as potential sources of further evidence was undertaken by KS.

Risk of bias, data extraction and synthesis

In line with best practice, available time and consistency requirements of a rapid review, one reviewer (KS) extracted all the data and a sample of 20% of papers were checked by a second reviewer (AO).[10,14] An independent panel reviewed all the papers and evidence tables to check the accuracy of the data and interpretation of the evidence.

Risk of bias

Since high quality evidence was unlikely to be available, evidence would be drawn from both experimental laboratory-based studies (such as cadaveric simulation studies) and observational studies of clinical practice. Therefore, in line with recommendations for rapid reviews the quality assessment for each study was focused on factors most important for decision-making.[10] AO, KS, JT and AS developed a bespoke risk of bias tool to assess each study according to a) the robustness of measurement, b) control for confounding and c) applicability to clinical practice. These dimensions are illustrated in Figure 1 below. Details of the assessment for each study are provided in the Evidence Tables (Tables 2 - 6) in the column 'Study contribution/limitations'.

Data extraction and synthesis

A standardised data extraction form was developed in order to produce a summary of each study. These summaries were then collated in evidence tables for each of the procedures of interest (nasogastric tube insertion, pulmonary lung function testing, suctioning for airway clearance, dysphagia assessment and nasoendoscopic procedures). Data were extracted on the following dimensions:

- *Study details:* Country, aim, design.
- *Procedures and measures:* procedures performed (on, by, where, number of repetitions) outcome measure type (e.g. virus transmission, aerosol size, spread, density) and method (e.g. virus transmission confirmed by antibody test, or aerosols captured by photodocumentation, particle sizer).
- *Findings:* Key conclusions and detailed findings e.g. relative risk of virus transmission with 95% confidence intervals, mean change in particle concentration etc.
- *Risk of bias assessment:* as described above.

The synthesis of study findings was organised according to each of the procedures of interest. Findings were narratively synthesised to examine if consistent patterns in the direction of effect could be identified. An overview of findings from systematic reviews involved examining the extent of relevant evidence and authors conclusions.

Findings

A total of 913 documents were identified in the search of which six were duplicates. A further three papers were identified from reference-checking and a further rapid systematic review published after the search was conducted. Following application of the inclusion criteria, 20 relevant papers were identified; 18 primary studies and two systematic reviews Figure 2).

Overview of primary studies

Nine of the 18 studies provided evidence on endoscopic sinus surgery[15-23], six studies focused on suctioning for airway clearance[23-28], four outpatient endoscopy[22,23,30,31], two nasogastric tube insertion[26,27] and one lung function testing[32]. None of the primary studies focused on procedures or testing for dysphagia. Most studies focused exclusively on one or

more of the six procedures of interest; the remainder included evidence on a wider range of procedures. For this review we only extracted data on the procedures of interest.

All studies aimed to determine whether procedures put healthcare workers (HCW) at risk, either by examining whether procedures generate aerosols or droplets[15-25,28-32] or whether procedures are associated with infection risk.[25,26,27] Some studies also evaluated whether one or more patient actions generated aerosols or droplets. Patient actions measured included coughing[22,24,29,30,32], sneezing[22,23,30], speech[22,30], heavy breathing[22], swallowing[30], tongue protrusion[30] and vomiting.[29] Finally, several studies evaluated whether a range of devices are effective in reducing the spread of aerosols or droplets during procedures. Devices included masks[23,24,25,29], drapes[15], smoke evacuation system[19] and suctioning.[19,20,21]

Fewer than half of the primary studies were clinically-based involving actual patients[15,18,25-28,31]; the remainder were simulations of procedures under experimental conditions and involved volunteers[30,32,22]; cadavers[17,19,20,21,22,23] ; human patient simulators[24,29] or porcine tissue[16].

Measurement of outcomes

Of three studies measuring transmission, one employed a measure of the presence or viral genome (PCR test), one a test for antibodies, and one antibody tests or case definitions. Of the 15 studies measuring aerosols / droplets almost half used an optical particle counter or sizer to capture data[18,19,21,22,28,31,32]. The remainder used a method to enhance visualisation of aerosols or droplets so that they could be captured using video or camera technology, including fluorescein dye[15,17,20 ,23,29], smoke[17,24] or green laser[30]. One study used both smoke and fluorescein dye[17].

Findings on nasogastric tube insertion (2 studies)

Both studies employed a retrospective cohort design and examined the association between performing nasogastric tube insertion and SARS infection among HCW in Canada (Table 2). One study[26] found that there was no evidence of an association between nasogastric tube insertion and SARS infection based on data from 32 nurses who were involved in the treatment of three infected patients of whom eight acquired SARS. Of 23 nurses who

undertook high risk procedures and consistently wore N95 or fluid resistant surgical masks (FRSM), three (13%) acquired SARS compared with five of the nine nurses who did not consistently wear a mask (56%) (RR 0.23; 95% CI 0.07 to 0.78, p = 0.02). Only three procedures were associated with a significant risk of SARS acquisition - intubation and suctioning prior to intubation (RR 4.2; 95%CI 1.58 – 11.4; p = 0.04) and manipulation of oxygen mask (RR 9.0; 95%CI 1.25 – 64.9; p<0.01). The second study[27] of 625 healthcare workers who provided care to 45 patients with SARS who underwent intubation also found no evidence of an association between nasogastric tube insertion and SARS infection. This was based on a multivariate analysis of a range of clinical procedures performed by 624 HCW who cared for 45 patients with SARS. Most staff wore FRSM (82%), only 4% wore N95 and 8% wore no mask. Twenty-six healthcare workers acquired SARS and the factors that were significantly associated with SARS acquisition were being a paramedic, having less infection control training, wearing less personal protective equipment and participation in administering non-invasive, fibreoptic or manual ventilation.

The evidence from these studies relates to patients with SARS and there may therefore be differences in terms of risk of transmission to SARS-CoV-2. In one study[26] the exposure to three patients with SARS occurred during a period of 6 to 14 days between admission and death, which reflects the period of peak viral load associated with SARS.[35] The second study was focused on high-risk exposure to healthcare workers who provided care to SARS patients in the period 24 hours before to 4 hours after intubation. Intubation is likely to present similar risks in patients with SARS-CoV-2.[27] Whilst these studies contribute evidence about infection risk in real-world clinical practice, there are several limitations. Firstly, the studies do not provide evidence about whether the procedures generate airborne particles. Secondly, the studies used case records and participant recall; whilst case records may be robust it remains unclear which type of data are used to substantiate tube insertion and where the evidence relies on recall it may be at risk of recall bias. Thirdly, the design used in both studies is at high risk of confounding; in each study HCWs performed multiple procedures (not just nasogastric tube insertion) and it is unclear which (if any) are responsible for the infection and it cannot be ruled out that HCWs may have acquired the infection from another source including the community.

Findings on pulmonary lung-function testing (n=1 study)

A study by Greening *et al* used a simulation design involving healthy volunteers to examine aerosol / droplet production following pulmonary lung-function tests (tidal breathing, forced expiratory volume, slow vital capacity (SVC) following inspiration from functional residual capacity, and SVC following inspiration from residual capacity) and association with coughing (see Table 3).[32] The study found very low particle emission in tidal volume and SVC from functional residual capacity, and low emission during forced expiratory volume. Coughing resulted in the highest mass of exhaled particles compared with all other manoeuvres, with a 640% (95%CI 230-1570, P < .01) increase compared with SVC following inspiration from functional residual capacity.[32]

Whilst the study provides evidence about aerosol / droplet generation from pulmonary lung-function tests there are several limitations. Firstly, the study used 'healthy volunteers' and it is unclear how aerosol production might be affected in those with lung conditions or with a viral infection. Secondly, in-line filters, which would be routinely used in lung function laboratories, were not used during these tests and these would effectively filter airborne particles. Thirdly, it is unclear how appropriate the Particles in Exhaled Air particle sizer / counter system used in this study was for measuring aerosols / droplets in patients with a virus; the authors note that it registers mostly small droplets from the small airways, and virus are likely to be present in droplets from both upper and lower respiratory tract.

Findings on endoscopic sinus surgery (n=9 studies)

Two studies were observations of clinical practice, examining aerosol / droplet generation among patients whose SARS-Cov-2 infection status is unknown[15] or patients who have received a negative test result.[18] Of the remaining seven studies, most were cadaveric simulations[17,19,20,21,22,23], and one used porcine tissue[16] (see Table 4). The findings from these studies were not consistent.

Of the two clinical observations, one[18] found that non-powered instrumentation was not associated with a significant increase in concentration of airborne particles compared with the pre-instrumentation level (mean change = 0.0253 particles/cm^3 p = 0.34) but the increase was significant for drilling and microdebrider use (mean change 0.0853

particles/cm^3, p=0.001; 0.0644 particles/cm^3, p=0.001). 70.3% of all particles measured were at the smallest reported size of detection (0.3µm). The second clinical observation[15] found minimal contamination beyond the immediate surgical field.

All seven simulation studies evaluated drilling, of which six reported that it resulted in significant increase in aerosol generation[16,17,19-23] and one reported that it did not[20]. In contrast to Murr et al[18], microdebriders evaluated in five simulation studies all reported no aerosol / droplet generation[17,19,20,22,23] . Of five studies evaluating non-powered instruments, one reported significant aerosol / droplet generation compared with baseline (mean change 1.29 particles/cm^3, p=0.001) and increase in smaller particles (0.30-0.37µm)[19]. The other four reported no aerosol / droplet generation[16,20,22,23] . Of three simulation studies evaluating electrocautery, all concluded that it resulted in a significant increase in aerosol / droplet generation[16,19,22] . Three simulation studies examined external activation of powered instruments[17,20,23] with all three reporting some increase in generation of aerosols or droplets. Nasal suctioning did not generate significant airborne aerosols in range 1-10µm[22] and using suction mitigated the increase in aerosols generated by drilling[19,20,21] and a negative pressure masks technique was reported to eliminate large droplets and reduce small aerosol particle concentration by 98%[17].

None of the studies provide evidence in relation to patients with COVID-19 or other respiratory infections and each of the studies has some limitations. One clinical observation study[18] appears to use robust measures and account for potential confounders, but the study by David *et al* 2020[15] does not. The cadaveric and porcine simulation studies do not account for patient factors such as breathing coughing, nasal secretions, etc and whilst some of these simulations appear to use robust measures and account for potential confounders many do not (see Table 4).

Findings on outpatient nasendoscopyendoscopy (n=4 studies)

One study conducted in the USA used a clinical observation design and examined aerosol / droplet generation among patients who have received a negative SARS-Cov-2 test result. The remaining three studies were simulations (one cadaveric and two healthy volunteers). The findings from these studies were not consistent. One clinical observation[31] found that

diagnostic nasal endoscopy with a rigid endoscope was not associated with increased particle aerosolization, but that sinonasal debridement, endonasal non-powered and suction instrumentation were associated with increased particle aerosolization compared with pre-procedure levels (mean increase 0.0869 particles/cm^3, 95%CI 0.029-0.144, p=0.005; 0.105 particles/cm^3, 95%CI 0.050-0.1599, p=0.001). The three simulation studies[22,23,30] all found evidence of droplet or aerosol formation during nasendoscopy and associated patient behaviours such as sneezing (see Table 5).

None of the studies provide evidence in patients with COVID-19 or other respiratory infections and each of the studies had some limitations. The measuring device (an optical particle sizer) used in the clinical observation was not able to detect the smallest particles and this study provided limited information about the experimental setup and sampling location with respect to ventilation. The cadaveric and healthy volunteer simulation studies did not account for patient factors such as nasal secretions, fever etc. and not all used robust measures or accounted for potential confounders (see Table 5).

Findings on suctioning for airway clearance (n=6 studies)

Three studies used a retrospective cohort design, of which one evaluated SARS-Cov-2 transmission among healthcare workers in the USA, and two SARS transmission among health care workers in Canada. Two simulation studies (one from Hong Kong[24] and one from the USA[29]) used non-human simulators to evaluate aerosol / droplet production and the final study involved a clinical observation of aerosol / droplet production among H1N1 patients in the UK. Heinzerling et al[25] found that among seven HCW who performed airway suctioning on an infected patient without applying transmission-based precautions (e.g. use of mask) none developed SARS-Cov-2 infection. In the retrospective studies on SARS patients[26] Loeb *et al* found that critical care nurses who assisted with suctioning before intubation of SARS patients were four times more likely to become infected than nurses who did not perform suction (RR 4.2 95%CI 1.58- 11.14, p=0.04). However, Raboud *et al* 2010 found no evidence of association of suction for airway clearance with SARS infection in a study of exposure of 624 nurses. In the two simulation studies[24,29] Chan et al found that coughing during oro-tracheal suctioning could produce substantial dispersion of potentially infected exhaled air[24]. A simulation study using fluorescein to evaluation contamination

associated with a range of healthcare activities, found that suctioning was not associated with increased concentration of fluorescein in air relative to other general care activities e.g. bathing, intravenous access, physical examination and no contamination was found on face or face shield during suctioning.[29] Finally, a clinical observation study on H1N1 pandemic patients found an increase in aerosol generation during respiratory/airway suctioning but this was not statistically significant (OR = 4.11 (0.50–34.0).[28] The particle size generated during suctioning were smaller than those collected during baseline but the difference was not significant.

Each study has limitations. The three transmission studies rely (at least in part) on participant recall to determine which procedures HCW performed, and as such are at risk of recall bias. These retrospective studies are also at high risk of confounding as HCW performed multiple procedures (not just suction for airway clearance) and it is unclear which (if any) are responsible for the infection, although Raboud *et al*[27] did adjust for this in a regression analysis, and HCW may have acquired the infection from another source. Second, two of the three studies on aerosol / droplet generation are simulations and as such it is not clear how these correspond to real-world conditions, for example breathing and nasal secretions, and there are also concerns about the appropriateness of measures used in these studies. Finally, the clinical observation on H1N1 patients provides no details on what type of respiratory suctioning was involved and there was considerable variation between and within individuals in the emission of aerosolised RNA.

Overview of systematic reviews

Two systematic reviews were identified that included primary research and addressed the review questions (Table 6).[33,34] One investigated the evidence for the risk of transmission of acute respiratory infections to healthcare workers caring for patient undergoing AGPs, including nasogastric tube insertion and suctioning.[33] Limited evidence was found, findings were based on the two studies already considered by this review[26,27] and it was conducted prior to COVID-19. The authors concluded that although both procedures might be associated with an increased risk of transmission the odds ratios were not statistically significant.

Thamboo et al[34] undertook a systematic review of potential AGPs in otolaryngology – head and neck surgery during the COVID-19 pandemic in order to inform clinical recommendations. The review found limited evidence in relation to nasoendoscopy and endoscopic surgery and identified some of the studies already included in this review. The authors made assumptions about the risk associated with different particles size, evidence was assessed and weighted and the limitations of basing recommendations on evidence from small, descriptive case-series experimental studies or retrospective cohort studies was recognised. The authors concluded that evidence for potential aerosols from nasal endoscopy was low and for treatment of epistaxis was moderate. Evidence for nasal electrocautery was not distinguished.

Interpretation

We identified and evaluated evidence for the generation of respiratory aerosols during nasogastric tube insertion, cardiopulmonary exercise and lung function tests, nasoendoscopy, swallowing assessment and oral suction and their association with risk of transmission of SARS-CoV-2 and similar respiratory infections.

The evidence is predominantly derived from experimental simulation studies which used optical particle counters or digital photography to measure respiratory particle dissemination or attempted to simulate droplets with fluorescein or aerosols with smoke. Some studies used cadavers or porcine tissue where the background effects of breathing and nasal secretions would not be accounted for, with only three studies[30,32,22] based on healthy volunteers where behaviour such as coughing and sneezing could be evaluated. These simulation studies had important limitations in terms of the reliability of the measurement method in accurately detecting a wide range of particle sizes, some did not adjust for background levels or position counters to capture exposure to the operator, and the extent to which the simulation reflects actual aerosol generation is unknown. Four studies based on clinical observation were more likely to reflect a real-life situation; one found a non-significant increase in aerosols associated with suctioning, two a significant increase in aerosols compared with baseline associated with sinonasal and endonasal

debridement, but another study found minimal spread of particles beyond the endonasal surgical field.

Although simulation studies provide some evidence of the potential for airborne respiratory particles to be generated from these procedures, the presence of aerosols does not prove an increased risk of transmission of respiratory viruses. In order to demonstrate a clinically significant risk of airborne infection, aerosols must contain enough infectious virus to enable an infective dose to reach the specific host cell tissue that the virus is able to infect.[36] The evidence needs to demonstrate a significant increase in aerosols compared with background levels and that the aerosols are able to carry virus and transmit infection.

Only one study on oral suctioning[28] set out to detect influenzas virus in respiratory particles but did not attempt culture to establish if the particles could transmit infection. Epidemiological evidence from studies that explored the risk of developing respiratory infection in personnel who performed the procedure is limited and only found for nasogastric tube insertion and suctioning. These studies did not demonstrate an association between performing these procedures and the risk of SARS, although the risk may be different in relation to SARS-CoV-2.

The potential for respiratory infections to transmit by an airborne route is dependent on a complex set of parameters which influence the generation and behaviour of respiratory particles. Conventionally, airborne particles have been distinguished as droplets which settle rapidly because of their mass, and aerosols which evaporate to form droplet nuclei and travel longer distances.[37,3] Droplets were perceived to be the primary risk of transmission when a susceptible person is in close proximity.[4,8]

However, it is now recognised that the dynamics are more complex and affected by a number of factors including force and volume of exhalation as well as humidity, temperature and airflow in the surrounding environment which affect the rate of evaporation and dissemination of particles.[6] Natural respiratory activities such as breathing and talking can generate a broad range of particle sizes, from submicron aerosols to large droplets. Using an expiratory droplet assessment kit (0.5 µm - 20 µm) on healthy volunteers,

Gregson et al (2020)[5] found an association between amplitude of speaking or singing and increased concentration of short-range aerosols but also a significant variation in particle emission between individuals. Indeed, results from different studies on the fluid dynamics of respiratory particles vary by orders of magnitude reflecting both the complexity of the phenomenon and approaches to measurement.[6]

One of the concerns related to the procedures included in this review was their tendency to induce coughing. The mechanism by which coughing generates respiratory particles involves high-speed airflow over the mucus lining the airway and this generates a higher concentration of respiratory particles compared with speaking.[7] The initial particle cloud has a high concentration of droplets which settle rapidly. The smaller particles remain in suspension and travel further. The evaporation of smaller droplets into droplet nuclei depends on the ambient temperature and relative humidity.[38] However, given the greater mass of droplets expelled by either coughing or speaking these particles contain a high proportion of the fluid, and therefore virus, expelled. The amount of virus expelled will also depend on the viral load which will vary depending on the severity of the infection and specific regions of the respiratory tract that are affected.[7]

The competing risks of more virus in larger droplets at lower concentration versus a higher concentration of smaller droplets with lower viral load have not been well studied for coughing. However, the risk of being exposed to an aerosol containing virus appears to be lower than the risk due to larger droplets at close range. The added risk of being exposed to a virus-containing aerosol particles from an aerosol generating medical procedure appears to be low relative compared with the general risk of exposure to expiration from a patient. In a light-scattering study the authors estimated that during 1 min of loud speaking at least 1,000 virion-containing droplet nuclei would be generated and remain airborne for more than 8 min. Nevertheless, at a saliva viral load of 7×10^6 copies per millilitre the probability that a 3µm droplet nucleus contains a virion is only 0.01%.[39] Viral emissions associated with coughing are likely to be considerably higher than for breathing[40] with more virus being contained in larger droplets, which present a greater risk during close contact rather than via longer range aerosols. Therefore, the risk of aerosol infection from patients in the

absence of AGPs is not fully understood and the additional risk posed by AGPs whether as aerosols or droplets, is difficult to distinguish from general patient interaction.

The generation of the aerosol is only one component of the chain of infection, with the quantity and stability of the virus and susceptibility of the host also being key to transmission.[6,36] The particle must be able to enter or be transferred onto the mucous membranes of the host and carry a sufficient number of viable virus to by-pass the host human defences, including the mucus coating the cell surface. Whilst experimental studies have explored the dynamics of respiratory particles, these viral and host parameters determining the risk of infection are less well understood. In addition, environmental factors such as the proximity of susceptible individuals and the duration of exposure, the size of the indoor environment and its ventilation, as well as hygiene practices and the presence of surfaces that play a role in indirect contact will also be important in transmission.

There are few other systematic evidence reviews that address these medical procedures. One was conducted prior to the COVID-19 pandemic. It informed the concepts of high risk AGPs and drew similar conclusions to our review in relation to nasogastric tube insertion and suctioning.[33] There is only one robust review related to SARS-CoV-2, this is focused on nas(o)endoscopy and, although did not identify all the evidence included in this review, drew similar conclusions.[34]

Overall, we identified an absence of evidence to suggest that these procedures are associated with additional risk of transmission of respiratory viruses beyond standard patient interactions. For pulmonary function tests, very low levels of particle emission were detected in the one study on lung function tests. Coughing was associated with emission of large particles which are more likely to equate to droplets than aerosols. Similarly, two simulation studies found no significant increase in aerosol generation or contamination of the face associated with suctioning of the respiratory tract. Findings from simulation studies on nasoendocopy suggested a significant increase in aerosols but findings were inconsistent, probably reflecting the use of different models (cadaveric, porcine or human volunteer) and lack of robust measures to detect particles, and absence of baseline

measures in some cases, and uncertainty about whether fluorescein and smoke are adequate surrogates for the generation of human respiratory particles. In addition, these simulation studies are difficult to equate to clinical conditions and did not account for patient factors such as coughing and were vulnerable to confounding. The limited evidence available from studies of virus emission or evidence of transmission associated with conducting these procedures did not demonstrate a risk of transmission, although their retrospective design makes them vulnerable to bias and confounding. Given the absence of evidence it is not possible to establish a clear absence of risk associated with these procedures.

Coughing may be a risk factor for transmission. However, although this has been investigated experimentally in terms of aerosol generation, an association with infection transmission has not been demonstrated. Aerosol generation (<10um) associated with coughing appears to be at a relatively low level but is highly variable. Epidemiological evidence suggests that the specific characteristics of the patient are a critical factor in driving transmission as a large proportion of transmission to both other patients and staff appears to be related to only a small number of patients.[42,43] Exposure during early stage in infection when viral load is highest is a key factor in driving risk and needs to be considered in terms of identifying risk to healthcare workers.[43]

The most recent WHO guidance on the use of masks in healthcare settings acknowledged that whilst respirators are recommended primarily for settings where AGPs are performed, some healthcare workers have strong preferences about having the highest perceived protection. However, whilst personal protective equipment such as N95/FFP3 respirators have a role to play in protecting against inhalation of aerosolised particles, administrative and engineering controls remain priority components of infection prevention and control. Strategies to ensure that patients with SARS-CoV-2 are segregated to allow non-urgent procedures to be conducted when no longer infectious and that procedures are conducted in well ventilated areas are key to mitigating the potential risk from aerosols.[2]

Evidence suggests that the risk of transmission of SARS-CoV-2 to healthcare workers may be determined by a more complex range of factors than purely the generation of aerosols.[33,44]

Aerosols have been assumed to be the explanation for the association between a small number of respiratory tract procedures such as tracheal intubation, non-invasive and manual ventilation, and risk of transmission to healthcare workers performing them.[33] This potential route of transmission has subsequently been applied to a wider set of procedures, for which expert consensus has assumed a similar risk of exposure to respiratory aerosols, and these are defined as high risk AGP.[1,45] However, evidence for aerosols being generated during some procedures designated as AGP is absent or equivocal.[41,44] It is therefore possible that other factors such as very close and prolonged contact with respiratory secretions might play a role in increasing the risk of transmission.[33,44] Uncertainty about the link between medical procedures and risk of transmission to healthcare workers is demonstrated by the significant inter-country variation in designation of medical procedure as AGPs.[46]

The paradigm for AGPs needs further consideration to better combine evidence from aerosol and infection prevention and control science. More research is required to determine the characteristics of both medical procedures and patients that increase the risk of transmission in order to better target precautions to mitigate the risk.

Limitations of review

This review was limited in scope and because undertaken within a short timeframe was restricted to publications in PubMed. However, this would be expected to capture the main publications on this topic and references from the included studies and other systematic reviews were assessed to help mitigate this. Findings related to other respiratory viruses may not be comparable with SARS-CoV-2 because of difference in transmission dynamics.

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Figure legends

Figure 1: Elements considered in the risk of bias evaluation

Notes. AG = aerosol generating; AGPs = aerosol generating procedures; AGB = aerosol generating behaviours; PPE = personal protective equipment. The rectangles labelled RQ1 and RQ2 show the parts of the model that were explored by research question 1 and research question 2, respectively. The orange area of overlap between these rectangles indicates the intersection of the foci of the two research questions in relation to aerosol production. RQ1: Does evidence suggest that medical procedures which induce coughing or involve respiratory airway suctioning result in infectious aerosol production? RQ2: If yes, what is the associated risk of transmission of SARS-CoV-2? The grey box labelled “Not covered in the literature” refers to the evidence base at the time of the searches were conducted (Oct, 2020).

Figure 2: PRISMA diagram

Table Click here to access/download;Table;Table 1.docx

Table 1: Procedures of concern in relation to generation of infectious aerosols

Nasogastric tube insertion
Cardiopulmonary and lung function tests, cardiopulmonary exercise test, spirometry, cardiac physiology procedures
Swallowing assessment related to dysphagia including endoscopic and fluoroscopy
Suction of the upper airway in the context of airway clearance
Endoscopic sinus surgery, cautery and nasoendoscopy (nasendosocopy)

Figure 1

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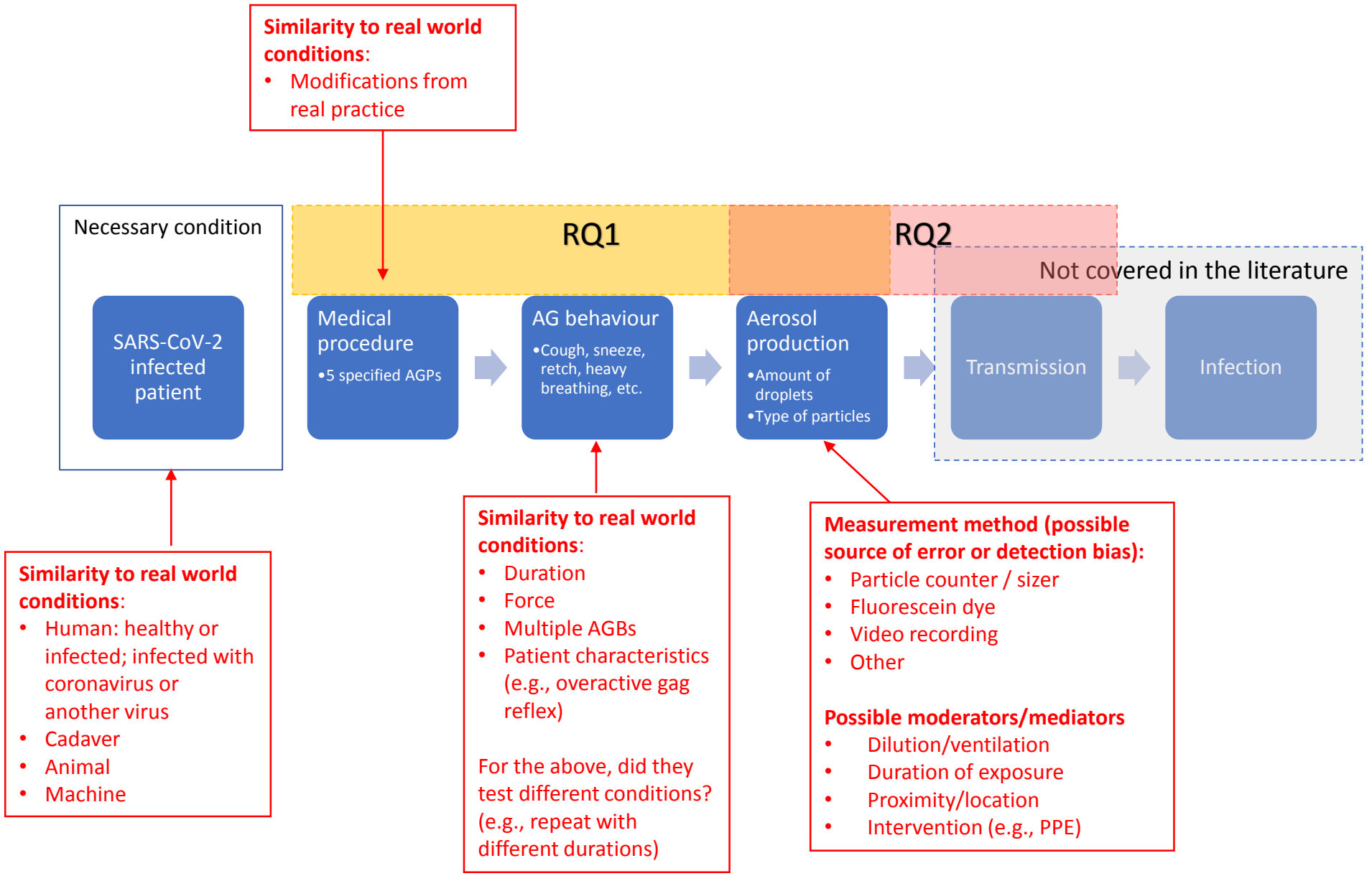

Figure 2

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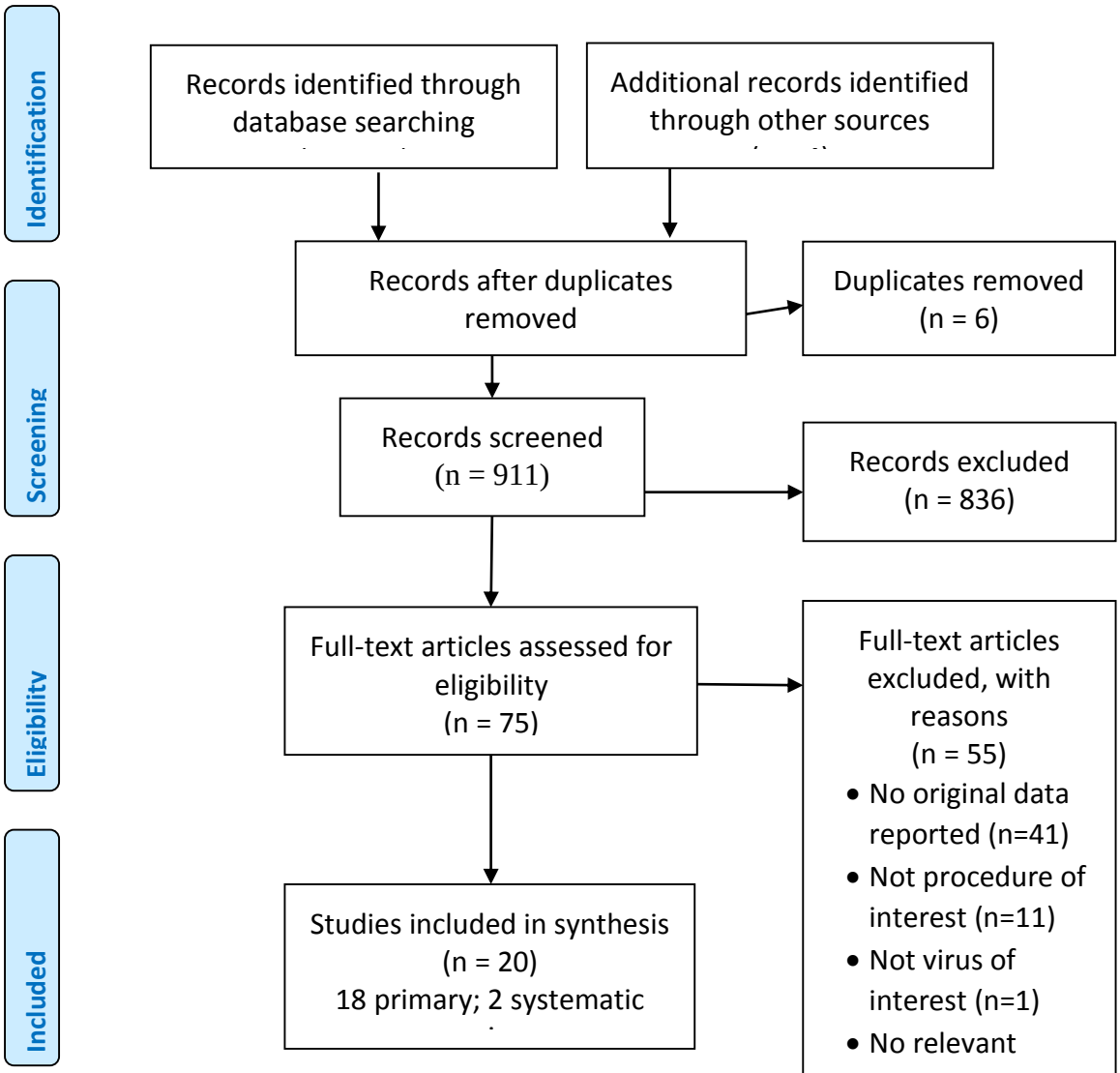

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