# Risk of Transmitting COVID-19 During Nebulizer Treatment: A Living Ultra-Rapid Review

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## WHAT'S NEW

**Updated January 6, 2021**

**Search current as of December 1, 2020**

**Next update expected April 9, 2021**

This review is up to date as of December 1, 2020. No new eligible studies have been identified in MEDLINE.

U.S. Department of Veterans Affairs
Veterans Health Administration
*Health Services Research & Development Service*

# PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program comprises three ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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# ABSTRACT

**Objectives**: Patients with viral respiratory infections often benefit from the administration of aerosolized medications by nebulizer. However, it is uncertain if receipt of nebulized medications increases droplet or aerosol production with associated transmission of viruses such as SARS-CoV-2. Health care systems and providers have an urgent need to understand the risk of viral transmission during nebulizer treatments for patients presenting with presumed or confirmed cases of COVID-19. To that end, we conducted this ultra-rapid review to address the following key question: *What is the risk of transmitting SARS-CoV-2, SARS, MERS, and influenza with administration of drugs via nebulizer?*

**Methods**: We followed standard systematic review methodology adapted for the rapid (*ie*, 7 days) timeline of this review. In conjunction with expert medical librarians, we originally conducted 2 PubMed searches: the first for SARS-CoV-2, SARS, and MERS (April 3, 2020), and the second for influenza (April 4, 2020). We have updated the SARS-CoV-2 update through December 1, 2020. We then translated these search principles for SARS-CoV-2 to additional databases: the China National Knowledge Infrastructure, Wanfang, and the Chinese Network Journal Network. To identify emerging literature, we also conducted a hand-search of multiple pre-print online databases, and clinicaltrials.gov. We abstracted relevant study characteristics and outcomes and considered risk of bias using existing measures, but did not formally complete a risk of bias or GRADE assessment. We synthesized eligible studies narratively.

**Results**: We identified 22 articles: 1 systematic review, 7 cohort/case-control studies, 7 case series, and 7 simulation-based studies. Eight individual studies involved patients with SARS, 5 involved MERS, and 1 involved SARS-CoV-2. The 7 cohort/case-control studies (4 high risk of bias, 3 unclear risk of bias) found mixed results (median odds ratio 3.91, range 0.08 to 20.67) based on very weak data among a small number of health care workers with variable use of personal protective equipment. Case series had multiple potential contributors to transmission. Simulation studies found evidence for droplet dispersion after saline nebulization and measurable influenza viral particles up to 1.7 meters from the source after 10 minutes of nebulization with a patient simulator. Study heterogeneity prevented meta-analysis.

**Conclusions**: Case series raise concern of transmission risk, and simulation studies demonstrate droplet dispersion with virus recovery, but specific evidence that exposure to nebulizer treatment increases transmission of coronaviruses similar to COVID-19 is inconclusive. Tradeoffs balancing health care worker safety and patient appropriateness can potentially minimize risk, including choice of delivery method for inhaled medications (*eg*, nebulizer vs metered dose inhaler) and personal protective equipment (*eg*, N95 vs surgical mask).

# BACKGROUND

More than 7,000 health care workers (HCWs) have died worldwide from COVID-19, more than 14% in the United States alone.[1] Similar patterns were seen in the 2003 SARS outbreak during which 20% to 40% of infected individuals were HCWs.[2,3] A large case series study during the 2003 SARS outbreak raised concerns that nebulizer treatments administered to infected patients might have facilitated nosocomial spread.[2] Thus, reduction in transmission risk to HCWs has been a priority during this pandemic. One focus of transmission risk reduction has been around the delivery of therapeutic agents via nebulizer. Nebulizers are of particular concern due to the risk of aerosol generation and dispersion leading to potential transmission of infection.[4] Viral aerosols pose a significant risk as they can remain in the air for up to 3 hours and travel distances farther than droplets due to their smaller size (<5µm).[5-7] Because multiple professional organizations have identified nebulization as an aerosol-generating procedure (AGP),[8,9] its use in clinical care has been significantly restricted and, when used, requires high levels of personal protective equipment (PPE) (*ie*, fit-tested particulate respirators). These requirements for higher levels of PPE lead to increased equipment and personnel time costs.[10]

Yet the administration of inhaled therapeutics remains a core component of the management of multiple acute respiratory conditions.[9] Nebulization offers particular benefits, such as delivery of medications directly to the site of action, reduced systemic availability, and faster onset of action.[11] Nebulizers are often the preferred delivery mechanism when a patient is unable to perform the required technique for metered dose inhalers (MDIs) (*eg*, poor coordination, agitation, or exacerbation severity[12]). Because of the potential infection risk, many providers are currently opting to use alternative, and presumed safer, modalities for patients with COVID-19, such as MDI or dry powder inhalers (DPI). MDIs and DPIs have less aerosolization risk but require training for proper patient administration.[11] However, the actual risk of infection transmission for COVID-19 with nebulization of therapeutic medications—and the necessity of current precautions—is unknown.

Understanding whether nebulizers pose sufficient infection transmission risk to require current stringent precautions is critical to delivering high-quality care while minimizing risk to HCWs and optimizing the use of potentially scarce resources. Thus, we sought to synthesize the evidence about the risk of transmitting SARS-CoV-2 with nebulizer use. Because of the likely limited literature on risk associated with COVID-19, we also considered infections caused by related coronaviruses such as SARS and MERS, as well as more a common and long-standing human viral infection, influenza.

# KEY QUESTION

The key question for this rapid review is:

**What is the risk of transmitting SARS-CoV-2, SARS, MERS, and influenza with administration of drugs via nebulizer?**

# METHODS

This review was originally requested as an ultra-rapid, living review[13,14] by the US Department of Veterans Affairs (VA) operations leadership managing COVID-19 clinical care procedures and policies. We made the following modifications to streamline the systematic review processes: (1) our *a priori* protocol was not published prior to conducting the review because the original report was completed in 7 days, (2) we performed a single review at title-and-abstract level, and (3) we conducted a single-reviewer data abstraction with second reviewer verification. While there are no agreed-upon reporting guidelines for rapid reviews, we followed PRISMA reporting guidelines for systematic reviews.[15] Note that the original report was completed and published online on April 11, 2020. Since that date, we have conducted monthly search updates and provided updates to the original report on May 15, 2020 and July 27, 2020.

## SEARCH STRATEGY

### Search Terms

For our initial search in early April 2020, we conducted a broad search including COVID-19 search terms and terms for additional respiratory viruses in anticipation of limited published data related to the emergent outbreak. In consultation with expert medical librarians, we initially conducted 2 searches in MEDLINE (via PubMed): the first search for SARS-CoV-2, SARS, and MERS (last updated on July 17, 2020); and a second search for influenza (last updated on April 16, 2020) (Appendix A). Searches had no restrictions by study design or language. The developed search strategy was applied with adjustments to additional databases: China National Knowledge Infrastructure and Wanfang. We hand-searched pertinent clinical guidelines (*eg*, Surviving Sepsis Campaign), systematic reviews,[16,17] and all eligible studies and select excluded studies to identify potentially relevant articles not identified otherwise.[2,3,6,10,16,18-28] the China National Knowledge Infrastructure and Wanfang database searches have been limited to COVID-19 terms and were updated through September 1, 2020. We also reviewed multiple online databases for rapid reviews related to COVID-19.[13,29-43] To identify relevant work on COVID-19 in the Chinese-language resources, we hand-searched the Chinese Medical Journal Network. To identify emerging literature, we reviewed in April and conducted a search of the preprint server collections within the NIH iCite from inception through September 1, 2020. In addition, we reviewed clinicaltrials.gov for all studies involving SARS or SARS-CoV-2 to check for studies not identified by our other methods and that could provide additional data for this review once completed (August 31, 2020).

### Inclusion/Exclusion Criteria

Study selection was based on the eligibility criteria listed in Table 1.

**Table 1. Study Eligibility Criteria**

| Study Characteristic | Include Criteria | Exclude Criteria |
|---|---|---|
| Population | • Adults, children, or simulated patients with probable or confirmed COVID-19 (SARs-CoV-2), SARS, MERS, or influenza | Animal studies |

| Study Characteristic | Include Criteria | Exclude Criteria |
|---|---|---|
| | • For experimental studies (simulation studies) examining effects of nebulization on droplet dispersal, these studies may include non-patients or patient simulators | |
| Intervention | Nebulized delivery of a medication (*eg,* albuterol) or placebo solution (*eg*, saline). Nebulizers include pneumatic jet compression, ultrasonic, vibrating mesh/horn, and microprocessor-controlled breath actuated types. | • Noninvasive ventilation (*eg*, BiPAP, CPAP)<br>• High-flow nasal oxygen<br>• Large-volume nebulizers |
| Comparator | None or other drug delivery (*eg*, metered dose inhalers, dry powder, or slow-mist inhaler) | None |
| Outcomes | • Confirmed and probable cases of the specific viral infection (*ie,* measures of transmission risk)<br>• For experimental/simulation studies, virus recovery (*eg,* by RNA sequencing) or droplet dispersion at different distances/time points | None |
| Setting | Any inpatient setting, emergency department or outpatient setting. Experimental/simulation studies may take place in nonclinical settings. | None |
| Timing | Any | None |
| Designs | Systematic reviews, trials (randomized and nonrandomized), cohort studies, case-control studies, case series, case reports, experimental/simulation studies of droplet/virus dispersion | None |

Abbreviations: BiPAP=bilevel positive airway pressure; COVID=coronavirus disease; CPAP=continuous positive airway pressure; MERS=Middle East respiratory syndrome; RNA=ribonucleic acid; SARS=severe acute respiratory syndrome

## SCREENING PROCESS

We used Covidence (www.covidence.org), a web-based software, to screen title/abstracts for identified citations, then full-text articles for inclusion. Citations/abstracts were screened by a single reviewer unless an article was flagged as uncertain, in which case a second reviewer was consulted. At full text, articles identified as excludes were screened by a second reviewer. At all steps of eligibility determination, investigators maintained an open dialogue to clarify eligibility criteria (as needed) and to discuss articles when eligibility was uncertain.

## DATA ABSTRACTION

We collected the following study characteristics: author/year, location/setting, study date, number of patients, patient characteristics, intervention characteristics (nebulizer type such as pneumatic jet compression vs ultrasonic vs vibrating mesh/horn vs microprocessor-controlled breath activated), volume of medication, use of HEPA filter in system, and duration of a treatment episode. We next abstracted outcomes including the rate of COVID-19 transmission for cohort, case-control, or case series studies, or distance to aerosolized viral particles from simulation studies. Data elements were abstracted into a shared document by a single investigator and verified by a second investigator.

## RISK OF BIAS ASSESSMENT

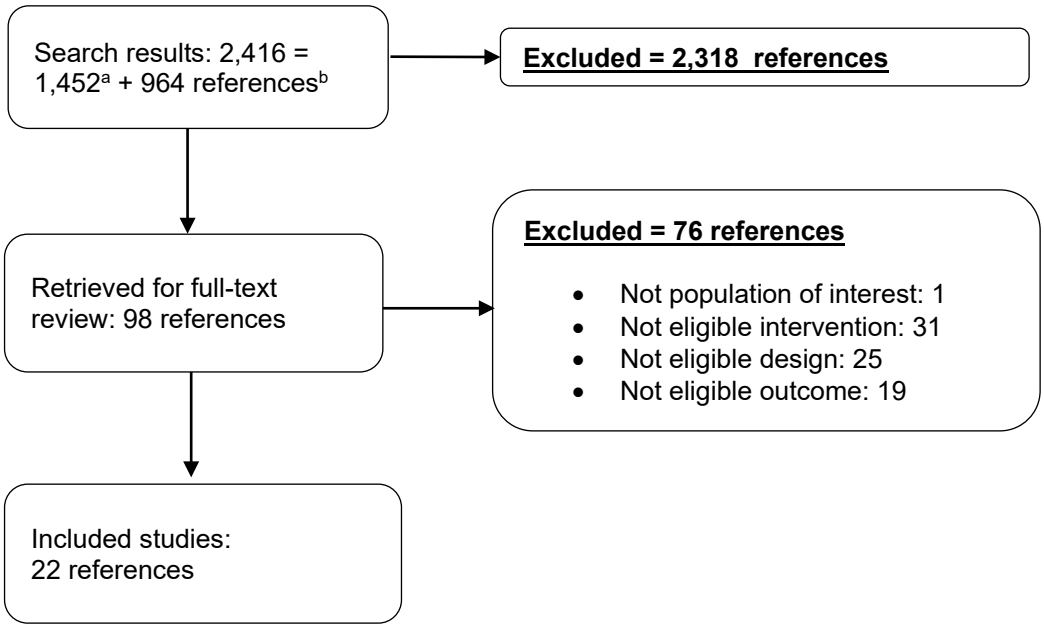
We considered the risk of bias and study limitations based on standardized measures (*eg*, Newcastle-Ottawa Scale for Cohort Studies) as available but did not formally complete them. Instead, for each study, we identified the most important strengths and limitations and made a judgment about the overall strength of the evidence it provided.

## SYNTHESIS

We narratively synthesized the evidence and used reported odds ratios with 95% CI or calculated odds ratios and 95% CI from the primary data to generate a forest plot using RevMan 5.3. We did not calculate a pooled estimate due to limited data and heterogeneity.

# RESULTS

**Figure 1. PRISMA Literature Flow Diagram**




[a] Search results from MEDLINE (1,041), iCite (388), and identified from relevant articles (23) were combined.
[b] CNKI-China National Knowledge Infrastructure (382), Wanfang (108), and Chinese Medical Journal Network (474).

We identified 2,416 publications through our systematic database searches of published literature and hand-searches of the literature. We also identified 542 studies through the literature searches. Of these, we retrieved 98 references for full-text review. Of the 22 included studies, 1 was a systematic review, 7 were cohort or case-control studies, 7 were case series, and 7 were simulation-based studies (Figure 1). Eight individual studies involved patients with SARS, 5 involved MERS, and 1 involved SARS-CoV-2. We screened titles from the preprint servers bioRxiv and medRxiv, 5 of which were reviewed at full text. One was included.[44] In addition, we reviewed LitCOVID and found no additional studies. We reviewed the collection of 474 articles on COVID-19 within the Chinese Medical Journal Network, screened 4 articles at full text, and included none. We also did not identify any relevant completed COVID-19 evidence syntheses. There were no relevant systematic review under way. Similarly, our clinicaltrials.gov search found no relevant studies.

# INCLUDED STUDIES

## Current Guidance

We reviewed 3 current guidelines for the public health and clinical management of patients with COVID-19, specifically the World Health Organization (WHO),[45] Centers for Disease Control and Prevention (CDC),[8] and Society of Critical Care Medicine (SCCM).[9] The key recommendations from these guidelines are highlighted in Appendix B. Key findings are that the CDC and SCCM guidelines cite nebulizer treatments as aerosol-generating procedures and

recommend that health care workers (HCWs) wear appropriate personal protective equipment (PPE) (*ie*, fit-tested particulate respirators) during nebulizer treatment administration to a patient with known or suspected COVID-19. The WHO guidelines do not list nebulizer treatments as an aerosol-generating procedure or make specific recommendations about PPE during their administration. However, the WHO guidelines do discuss other forms of aerosol-generating procedures, the importance of using appropriate PPE during these procedures, and the preference that these procedures be performed in a negative pressure room in an intensive care unit.

## Prior Systematic Review

A 2012 systematic review addressed aerosol-generating procedures (AGPs) and the risk of transmitting acute respiratory infections to health care workers (HCWs).[16] Multiple databases were searched through October 2010. Authors identified 3 eligible retrospective cohort studies that addressed risk of nebulizer treatments for HCWs, all judged to be very low quality.[23-25] A pooled estimate showed no increased risk (OR 0.9; 95% CI 0.1 to 13.6) with high statistical heterogeneity. A sensitivity analysis excluded the study by Wong and colleagues[25] on the basis that lack of training/description of infection control measures may have introduced bias, and showed an increased risk for transmission with nebulizer treatments (OR 3.7; 95% CI 0.7 to 19.5). However, PPE use was not well documented in any of the 3 studies, so the sensitivity analysis that excludes Wong et al on the basis of poorly described infection control measures is not well justified and, in our opinion, the observed heterogeneity is not well explained. This review was protocol driven and used a comprehensive search and other standard systematic review methods. Important weaknesses were misapplication of GRADE quality ratings to individual studies, nonstandard approach to judging risk of bias, reporting a pooled estimate for highly heterogeneous studies (methodologically and statistically), and using a statistical approach that has subsequently been shown to generate 95% CIs that are often too narrow.[46]

## Primary Literature

In this section, we describe results by study type:

- Cohort and case-control studies
- Case series studies
- Experimental and simulation studies

### *Cohort and case-control studies (n=7)*

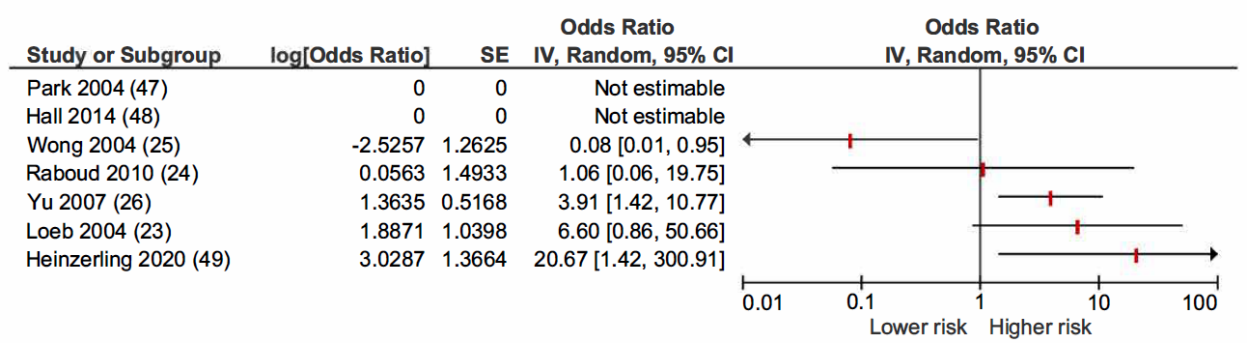
Of the 7 studies, 5 were retrospective cohorts[23-25,47,48] and 2 were case-control studies[26,49] (Table 2 and Figure 2). In addition to the 3 studies included in the prior review by Tran and colleagues,[23-25] we included 4 newer studies. Of the 5 cohort studies, 3 were judged high risk of bias (ROB)[23,47,48] and 2 were unclear ROB.[24,25] One case-control study examined experiences with SARS-CoV-2[49] and was found to be high ROB. The other case-control study had uncertain ROB.[26] Common contributing causes of ROB included exposure details that were typically acquired via unblinded interviews, rare comprehensive matching or controlling for confounders, small sample sizes, inconsistent data about use of PPE and comorbidities of at-risk HCWs, and lack of information about potential community exposures (Appendix C). Overall, these 7 case-control and cohort studies had weak methods and reported inconsistent findings, with 2 studies showing an association between nebulizer use and viral transmission, 3 showing no association, and 2 showing no association with wide confidence intervals.

The 1 study of transmission of COVID-19 was a high ROB case-control study of 121 hospital-based HCWs exposed to the first known case in the United States.[49] Authors report that 2 of the 3 COVID-positive HCWs were exposed to nebulizer treatment compared with 3 of 34 exposed HCWs who were COVID-negative (OR 20.7; 95% CI 1.4 to 300.9 by our calculation). None of the HCWs wore currently recommended PPE for COVID-19. The 3 HCWs with COVID-19 also had a higher median duration of contact than those without COVID-19 (120 minutes vs 25 minutes; p=0.06).

Five studies reported risk of transmission during the 2003 SARS outbreak. One uncertain ROB study compared nebulizer exposure during the 28 hours around patient intubation among HCWs who did, and did not, acquire SARS.[24] There were zero nebulizer exposures among 26 SARS cases and 9 exposures among HCWs who did not contract SARS (see Table 2 for additional study level details). The second uncertain ROB cohort study included 66 medical students who had visited the hospital ward of the index patient with SARS in China.[25] Medical school records were cross-referenced with nebulizer treatment timing to verify exposure. No association was found, though no students examined the index patient directly. Among a subset of 19 students with clear and limited exposures to SARS-infected patients, 6 of 10 who visited the ward before the patient started receiving nebulizer treatments contracted SARS compared to 1 of 9 students who visited the ward the day after treatment initiation (OR 0.08; 95% CI 0.01 to 0.95 by our calculation). One high ROB cohort study examined the SARS attack rate of 43 critical care nurses in 2 Canadian intensive care units.[23] Only 5 of 32 nurses who entered the room of an infected patient also had medical record validated nebulizer exposure with a relative risk of 3.24 (95% CI 1.11 to 9.42; p=0.09). The other high ROB cohort study of SARS included 110 HCWs from 8 of 9 facilities that cared for 6 U.S. patients with SARS.[47] Four of 110 HCWs with high-risk exposures to a SARS-positive patient also reported exposure while the patient received aerosolized medications, 1 without a respirator and 1 without gloves, gown, or eye protection. None of the 103 HCWs tested for convalescent antibodies were positive. The final study related to SARS was an unclear ROB case-control study that examined factors associated with nosocomial super-spreader events on adult inpatient wards in Hong Kong (n=38) and China (n=86).[26] In univariate analyses, the authors report an OR of 1.37 (95% CI 0.66 to 2.85; p=0.40) for nebulizer exposure as an environmental factor and for as a host factor an OR 3.91 (95% CI 1.42 to 10.78; p=0.006). Neither was significantly associated with a super-spreader event in the final multivariate analyses.

One high ROB cohort examined 48 HCWs with and 48 HCWs without contact with an index patient infected with MERS.[48] Fourteen (29%) of HCWs with index-patient contact also had exposure via nebulizer treatment. No HCWs with index-patient contact developed MERS (exposed or unexposed).

**Figure 2. Odds Ratios of Viral Transmission after Nebulizer Treatment Exposure**




Abbreviations: IV=inverse variance; SE= standard error

### *Case series studies (n=7)*

We identified 3 case series of patients with SARS[2,3,50] and 4 with MERS[51-54] (Table 3). Two of the 3 case series reported on the nosocomial transmission of SARS from the same index patient in China[2,3] and a third described the nosocomial outbreak in Canada.[50] The MERS case series described nosocomial transmissions in Saudi Arabia,[53] the United Arab Emirates,[54] and South Korea.[51,52] All case series described hospitals with widespread nosocomial transmission and index cases who received nebulizer treatments, but in none of the studies were HCWs clearly using appropriate PPE. Overall, these studies raise the possibility that nebulizer treatment contributed to viral transmission. However, no conclusions about the risk from the nebulizer treatments in these cases can be drawn.

### *Experimental and simulation studies (n=7)*

There were 2 experimental studies on live human patients and 5 human simulation studies (Table 4). Overall, these studies support the concept that nebulizers could increase transmission of viral infection as evidenced by the presence of aerosols in the vicinity of a patient (or patient simulator) receiving nebulizer treatments, and 1 study found recovery of virus measured by PCR from viral transport medium.

One experimental study exposed 3 groups of live adult patients (11 healthy, 11 with coryzal symptoms, and 21 with acute exacerbations of chronic respiratory illness) to a series of respiratory procedures in variable order including nebulization in a standard ward room without an external window or ventilation system.[55] Droplet dispersion was measured during each procedure with an optical particle sizer at 20cm and 1m from the patient (Table 4). The authors reported a significant increase ($p<0.0001$) in mean pre/during intervention droplet counts (normalized difference) at sizes 0.3-0.5, 0.5-1, 1-3, and 2-5 microns across all patient groups at both distances. None of the included subjects had documented viral infections, nor was the presence of viral particles measured. A second experimental study, identified through a preprint server, sought to characterize the pattern of droplet dispersion with human participants of unknown clinical status receiving selected common airway management procedures during routine care, one of which was nebulization.[44] Droplet patterns were captured by high-speed camera of illuminated droplets against a black background. They found no evidence of droplet dispersion during nebulization, though they noted that fine aerosols were detected but not quantified due to “abundance.”

We found 5 publications describing simulations of patients undergoing nebulizer treatment.[20,21,56-58] First, Tang and colleagues used live-attenuated influenza vaccine as a surrogate virus tracer in a simulation model with nebulized, distilled water from a portable home nebulizer.[56] They used biosamplers collecting into viral transport medium (VTM) over 10 minutes of nebulization within a mock isolation room at distances of 0.4m, 1.1m, and 1.7m from the manikin's nose. They found decreasing average viral loads at samplings as distance increased: $7.34 \pm 0.28 \times 10^4$ copies/ml VTM (0.4m), $2.09 \pm 0.41 \times 10^4$ copies/ml VTM (1.1m), and $1.41 \pm 0.23 \times 10^4$ copies/ml VTM (1.7m). Second, McGrath and colleagues characterized aerosol emissions during the administration of albuterol sulfate using a jet nebulizer with an open facemask compared with a vibrating-mesh nebulizer with a valved facemask. The authors then compared each nebulizer type (jet vs vibrating mesh) according to the use of a mouthpiece with and without a filter.[57] Aerosol emissions were measured via UV spectrophotometry during 3 trials of all combinations. Open facemask jet nebulizers had greater total aerosol emissions than valved facemask vibrating-mesh nebulizers. Further, same-type nebulizers with an unfiltered mouthpiece displayed greater aerosol emission than their filtered mouthpiece counterpart. Taken together, those with an open facemask jet nebulizer had the greatest level of aerosol concentration while those with a filtered mouthpiece vibrating-mesh nebulizer had the lowest aerosol emission. The vibrating-mesh nebulizer combined with a filtered mouthpiece showed no increase in aerosol concentration at 0.8m over baseline. Third, Blood and colleagues measured particles inside and outside a patient isolation system placed over a manikin's head in multiple treatment conditions including nebulizer administration of normal saline.[58] Experiments were conducted at 2 hospitals, 1 with a piston-compression nebulizer via face mask and the other with a breath-actuated nebulizer via mouthpiece. Particulate counts were measured at baseline and every 2 minutes for 12 minutes, of which the first 4 minutes were during nebulizer treatment. In 5 trials without the isolation chamber, peak particulate measurements of 59,627 particulate/cm3 for the piston compression nebulizer 2 at 1 minute, and 214,020 particulate/cm3 for the breath-actuated nebulizer at 5 minutes; measurements decreased to 4,193 (SD 2,260) and 4,903 (SD 326) at 9 minutes, and 927 (SD 2,225) and 1,030 (SD 131) at 13 minutes. Their isolation chamber system reduced >99% of nebulized particles in the surrounding environment. The fourth and fifth simulation publications by Hui and colleagues described experiments administering jet nebulization of sterile water using a human patient simulator that modeled variable lung damage (normal, mild, and severe injury) and used smoke particles to visualize exhaled air and aerosolized dispersion by laser light visualization.[20,21] In both publications with overlapping authors, they reported air particles measured at up to 0.45 meters for normal lung function and greater than 0.8 meters with simulated severe lung injury. The severe lung injury simulation had fewer high-concentration particles than healthier lung function models.

# RESULTS TABLES

**Table 2. Results of Cohort and Case-Control Studies**

| Study/ Country | Study Design/ Setting | Virus | Population Characteristics | Intervention/Exposure and Comparator | Outcomes | Strengths | Weaknesses |
|---|---|---|---|---|---|---|---|
| Heinzerling, 2020[49]<br><br>United States | Case-control<br><br>Hospital | SARS-CoV-2 | HCWs who had contact with index patient<br><br>N=121 | Unspecified nebulizer treatment type | 2/3 HCWs with COVID-19 had nebulizer exposure vs 3/34 without (p = 0.04). | • Standardized interviews of HCWs<br>• Lab confirmation of COVID-19<br>• Good effort to track down all HCWs tested | • No PPE or transmission precautions during exposure<br>• Not all exposed were tested<br>• 6 who were tested were not interviewed |
| Hall, 2014[48]<br><br>Saudi Arabia | Retrospective cohort<br><br>Multiple hospital settings | MERS | HCWs who had contact with index patient<br><br>N=48 | Unspecified nebulizer treatment type | 0/14 HCWs present during nebulizer treatment<br>0/34 HCWs not present during nebulizer treatment.<br><br>Outcome = EIA serum testing for MERS | • Adequate follow-up time<br>• Representative sample with exposed and non-exposed from the same population<br>• Antibody testing in all included HCWs | • Exposure not verified by medical records<br>• PPE use was variable and not described in relation to exposure |
| Raboud, 2010[24]<br><br>Canada | Retrospective cohort<br><br>Multiple Hospitals | SARS | HCWs<br><br>N=624<br>(9 exposed) | Exposed to nebulizer[a] vs not exposed (exposed = in room during treatment) | 0/26 cases (+SARS)<br>9/598 controls (-SARS)<br><br>Outcome = Positive Convalescent antibodies or SARS case definition criteria (SARS-CoV) | • Adequate follow up<br>• Risk from multiple clinical activities considered<br>• Standardized case definition with confirmatory lab testing<br>• Triangulated identification of eligible HCWs via multiple sources | • Variable use of PPE, training on use of PPE, and PPE removal behaviors<br>• PPE use not reported in relation to nebulizer exposure<br>• Multiple infected HCWs cared for multiple patients with SARS<br>• Likely recall bias at an unreported duration after exposure event |

| Study/ Country | Study Design/ Setting | Virus | Population Characteristics | Intervention/Exposure and Comparator | Outcomes | Strengths | Weaknesses |
|---|---|---|---|---|---|---|---|
| | | | | | | | • Generalizability limited to patients who were intubated |
| Loeb, 2004[23]<br><br>Canada | Retrospective cohort<br><br>Two intensive care units | SARS | Critical care nurses<br><br>N=43 (32 exposed) | Exposure to nebulizer treatment[a]<br>(type of nebulizer treatment not specified) | 3/5 exposed (+SARS)<br>5/27 not exposed(-SARS)<br>Relative risk = 3.24 (1.11, 9.42); p = 0.09<br><br>Outcome = Health Canada/WHO case definition | • Exposure reports validated by medical records<br>• Standardized case definition<br>• Convalescent antibody titers<br>• Likely adequate follow up | • Few exposures<br>• Variable PPE use<br>• No report of PPE specifically during exposure to nebulizer treatment |
| Yu, 2007[26]<br><br>China; Hong Kong | Case-control<br><br>Hospital wards with and without nosocomial super-spreader events of SARS | SARS | Inpatient wards<br><br>N=124 wards (26 hospitals) | Environmental factor = nebulizer[a] used at least once vs never<br><br>Host factor = use of nebulizer (yes/no) | Environmental: OR 1.37 (0.66, 2.85); p = 0.40<br>Host: OR 3.91 (1.42, 10.78); p = 0.006<br>Risk factors from multivariate analyses: distance between beds, staff working with symptoms, oxygen therapy, BiPAP. Nebulizer use not associated with super-spreading event.<br><br>Outcome = Super-spreader event[b] | • Adequate follow-up time<br>• Cases appear representative and were drawn from the same community as the controls<br>• case definition used was appropriate | • Data collection conducted 1-2 years after event<br>• Unclear if interviews were blinded<br>• Not reported how many distinct nebulizer events occurred |
| Wong, 2004[25]<br><br>Hong Kong | Retrospective cohort<br><br>Hospital ward | SARS[c] | Exposed medical students and assessors<br><br>N=66 students who visited ward | Index patient received QID 30 minute jet nebulizer treatment from 3/6/03 to 3/12/03 | No association between risk of infection and presence on ward when nebulizer was in use. 6/10 students (and 5/5 assessors) who visited ward before start of | • Adequate follow-up time<br>• Representative sample with exposed and non-exposed from the same population | PPE use not described |

| Study/ Country | Study Design/ Setting | Virus | Population Characteristics | Intervention/Exposure and Comparator | Outcomes | Strengths | Weaknesses |
|---|---|---|---|---|---|---|---|
| | | | | | nebulizer treatments contracted SARS vs 1/9 (and 3/5 assessors) who visited the day after nebulizer treatment started; note the 1 infected after visiting on 3/7 was present during the nebulizer administration time. | • Students without SARS at study outset, and exposure data were confirmed at least partially by school records | |
| Park, 2004[47]<br><br>United States | Retrospective Cohort<br><br>8 of 9 U.S. health care facilities that cared for known SARS patients in 2003 | SARS | HCW with exposure within 3 feet of a patient with laboratory-confirmed SARS-CoV<br><br>N = 110 | Exposure either protected by full PPE or unprotected<br><br>Full PPE defined as all recommended equipment including full-length gown, gloves, N95 or higher respirator, eye protection | 4 HCW reported exposure to aerosolized medication delivery (1 without a respirator, and 1 without gown, gloves, or eye protection); 0 of 103 patients tested positive for SARS (unknown if the 4 exposed to nebulizers were included in the 103 tested). | • 85% of estimated HCW with high risk exposure participated<br>• Convalescent antibodies tested for 103 interviewed HCWs<br>• Data collected across multiple facilities<br>• Not restricted to symptomatic HCWs | • One facility caring for the 8 SARS-positive patients in the United States in 2003 did not participate<br>• Risk of recall bias as exposure data collected by interview without medical record corroboration<br>• Few nebulizer exposure events, 4 of 110 HCWs<br>• Self-reported adherence to PPE recommendations<br>• No paired antibody samples |

[a] Type of nebulizer not specified.
[b] ≥3 cases within 2-10 days of admission of index patient +SARS or cluster 3+ cases in 8 days without known index.
[c] Case definition: fever + pneumonia on imaging.
Abbreviations: EIA= enzyme immunoassay; HCW=health care worker; PPE=personal protective equipment; QID=4 times daily; WHO= World Health Organization

**Table 3. Results of Case Series Studies**

| Study/ Country | Study Design Details | Virus | Setting | Population Characteristics | Exposure | Outcomes | Comments |
|---|---|---|---|---|---|---|---|
| Assiri, 2013[53]<br><br>Saudi Arabia | Case series | MERS | 4 hospitals: 3 general and 1 regional referral | 23 confirmed cases of MERS and 11 probable cases | 4 MERS patients in ICU of one hospital received unspecified type nebulizer treatments while also receiving continuous positive airway pressure | 2 additional cases were diagnosed among patients in ICU at the same time during which no special isolation procedures were noted. | • No further cases developed after implementation of infection control procedures.<br>• Genome sequencing employed |
| Hunter, 2016[54]<br><br>United Arab Emirates | Case series | MERS | 3 hospitals with health care associated MERS clusters | 30 cases of MERS transmitted in health care setting (n = 19 HCW) | Exposure to either inhaler or unspecified type of nebulizer treatment | 14 HCWs who developed MERS; 2 administered metered-dose inhaler or nebulizer treatment. | • 13 of 14 HCWs were exposed prior to diagnosis of index patient<br>• PPE use variable among 14 HCWs<br>• Genome sequencing employed |
| Nam, 2017[51]<br><br>South Korea | Case series | MERS | 2 Hospitals | 1 index patient admitted to both hospitals and 25 secondary cases of MERS | Lidocaine inhalation using jet nebulizer prior to bronchoscopy on second day of Hospital B | 25 total secondary cases (14 inpatients, 9 commercial/family caregivers, 2 hospital employees); 5 patients in same ward room in which nebulizer was used developed MERS Hospital B. | Hospital B had a higher case fatality rate vs Hospital A. Hospital B ward room had lower air ventilation and higher density of patients than Hospital A. No cases among bronchoscopy HCWs (all wore surgical masks, gloves, vinyl gowns) |
| Park, 2016[52]<br><br>South Korea | Case series | MERS | 2 Hospitals | 1 index patient admitted to both hospitals and 23 secondary cases and 3 tertiary cases | Lidocaine inhalation using jet nebulizer prior to bronchoscopy on second day of Hospital B | 13 secondary cases at Hospital A; 10 secondary cases at Hospital B (5 patients and 3 caregivers in same room infected). | Similar attack rates between hospitals (15.8% hospital A; 14.3% hospital B, p = 0.51); incidence rate higher in hospital B than A (7.7/100 vs 3.4/100 exposure days, IRR = 2.3, p <0.001).[c] No secondary cases among HCW |
| Lee, 2003[2]<br><br>Hong Kong | Case series[a] | SARS | Medical ward with isolation facilities | Secondary/Tertiary cases: | Jet nebulizer 6L/min; 4 times daily | 112 SARS patients with direct exposure to index patient (69 health | Nebulizer speculated as important in transmission |

| Study/ Country | Study Design Details | Virus | Setting | Population Characteristics | Exposure | Outcomes | Comments |
|---|---|---|---|---|---|---|---|
| | | | | Male 66, Female 72<br>Mean age 39.3 (SD 16.8)<br>N = 156 with SARS (138 secondary or tertiary cases) | administered to index patient | care worker, 16 medical students all with “unremarkable medical histories”). | |
| Varia, 2003[50]<br><br>Canada | Case series | SARS | Secondary-care community hospital in Toronto | N=128<br>Male N=51, Female N=77<br>Mean Age 44.8<br>HCWs N=47<br>household/ social Contacts N=38 | Index patient received nebulized[b] salbutamol while in the general observation area of the emergency department | 128 SARS patients that resulted from exposure to index patient, including two nearby patients from the ER (all cared for by the same nurse). | Highest transmission rate was observed in CCU nurses (60%) owing to prolonged exposure to severely ill patients. Unclear PPE use during the period of exposure. |
| Wong, 2004[3]<br><br>Hong Kong | Case report | SARS | General medical ward in a tertiary care hospital<br>Moved to negative pressure isolation room on day 8 of admission<br>N95 + disposable gloves used day 8 forward | SARS patient (N=1), limited information about patient | Jet nebulizer at 6LPM for bronchodilation used QID until day 8 | 100 SARS patients linked to index patient. | Setting not clear regarding poor PPE standards and lack of isolation before diagnosis |

[a] Case definition based on CDC, fever, lung consolidation on imaging and exposure to index or secondary case.
[b] Type of nebulizer not specified.
[c] Overlapping cases with Nam et al, 2017
Abbreviations: CCU= coronary care unit; HCW=health care worker; ICU= intensive care unit; IRR=incidence rate ratio; PPE=personal protective equipment; QID=4 times daily

**Table 4. Results of Experimental and Simulation Studies**

| Study/ Country | Study Design Details | Virus | Setting | Population Characteristics | Exposure | Outcomes | Comments |
|---|---|---|---|---|---|---|---|
| Simonds, 2010[55]<br><br>England | Non-randomized trial | NA among control patients; not specified for coryzal patients or those with acute infective exacerbation of chronic respiratory disease | Single inpatient room on a respiratory ward | N=11 Normal controls<br>N=11 Healthy patients with infective symptoms<br>N=21 Chronic lung disease with infective symptoms | All patients received: Oxygen therapy, Noninvasive ventilation, Modified NIV (add-on viral/ bacterial filter to NIV), Nebulized saline, Physiotherapy for patients with chronic respiratory illness.<br>A standard jet nebulizer with compressor was used to deliver 4ml of normal saline | Droplets were detected per intervention using an optical particle sizer. Droplet sampling was carried out over 30 seconds at 5-min intervals at baseline and during interventions. At 20cm from patient's mask and at 1 meter at 45 degrees lateral plane.<br><br>Nebulizer therapy: In all groups, there was a significant rise in droplets and aerosolization (ranges: 0.3-3.5 microns) at 20 cm and at 1 m. | Select patients did not undergo NIV due to claustrophobia |
| Hui, 2009[21]<br><br>Hong Kong | Human patient simulator experiment | NA | Negative pressure hospital isolation room | Adult high-fidelity human patient simulator: normal, mild and severe lung injury | Jet nebulizer<br>Air flow: 6L/min | Exhale air particles measured by laser light : Max distance ≤ 0.45 meters (normal lung) to >0.8 m (severe lung injury). | More distant leakage through nebulizer side vents with severe lung injury, but less high concentration smoke particles |
| Hui , 2014[20]<br><br>Hong Kong | Human patient simulator experiment | NA | Double-door negative pressure isolation room | Adult high-fidelity human patient simulator: normal, mild and severe lung injury | Jet nebulizer<br>Air flow: 6L/min | Exhale air particles measured by Laser light : Max distance ≤ 0.45 meters (normal lung) to >0.8 m (severe lung injury). | Possible companion paper; same methods, authors, and results as Hui 2009 report |
| Mueller, 2020[44a]<br><br>Germany | Non-randomized trial | NA | Sterile clean room; patient in seated position | Patients undergoing airway management procedure as part of routine clinical care | Portable home jet nebulizer plus oxygen mask | Droplets measured by high-speed (1000 frames/sec) camera with light against black background; No droplets visualized; Fine aerosols detected but not quantified due "to abundance." | N=8 patients were included. Unclear how many times each patient was evaluated (up to 5 times) |
| McGrath, 2019[57]<br><br>Ireland | Human patient simulator experiment | NA | Room with no external doors/windo ws, | Breathing simulator via absolute filter set to adult | Vibrating Mesh nebulizer with aerosol chamber (air flow 6L/min) and Jet | Aerosols measured by two aerodynamic particle sizers at 0.8m and 2.2m from simulated patient over 25 minutes. Vibrating Mesh nebulizer | Focus on potential exposure of medical aerosols that potentially contain |

| Study/ Country | Study Design Details | Virus | Setting | Population Characteristics | Exposure | Outcomes | Comments |
|---|---|---|---|---|---|---|---|
| | | | mechanically ventilated | respiratory rate, tidal volume and inspiratory: expiratory ratio | nebulizer (8L/min); combined with both facemask and mouthpiece (filtered and unfiltered)<br><br>2.5ml albuterol sulfate nebulized | had fewer fugitive emissions than jet nebulizer. Unfiltered mouthpiece had fewer than facemask. No increase vs baseline in aerosol concentration with VMN/filtered mouthpiece. Size of fugitive emission aerosols ranged from 0.860 to 1.437 um across combinations. | viral particles rather than direct measure of infectious aerosols. |
| Blood, 2020[58]<br><br>United States | Proof-of-concept simulator experiment | NA | Negative pressure clinic procedure rooms without HEPA-filters | Manikin (type unspecified) | 4 minutes normal saline nebulizer via piston compression Nebulizer and Breath Actuated nebulizer; with and without addition of suction (120mmHg) and oxygen (10L/min)on | Control measurements at 3 inches above height of isolation chamber bag (appears to be 31 inches) from bed without isolation chamber found peak particular measurements of 59,627 particulate/cm3 for the Power Nebulizer 2 at 1 minute and 214,020 particulate/cm3 for the breath actuated nebulizer at 5 minutes; measurements decreased to 4193 (SD 2260) and 4903 (SD 326) at 9 minutes and 927 (SD 2225) and 1030 (SD 131) at 13 minutes respectively. | Manikins did not simulate human breathing. No information about size of manikins. |
| Tang, 2020[56]<br><br>Finland | Human patient simulator | Licensed live-attenuated influenza vaccine (LAIV) as surrogate virus tracer | Mock isolation room with mixed ventilation at 12 air exchanges per hour | Breath simulation produced by nebulizer with LAIV aerosols | Portable home jet nebulizer (air flow 6-8 L/min) nebulizing distilled water | Air-sampling for 10 minutes by 3 biosamplers into viral transport medium at 0.4m near head, 1.10m near abdomen, and 1.7m near the feet. Over 5 repetitions, average viral loads in viral transport medium were $7.34 \pm 0.28 \times 10^4$ copies/ml (head), $2.09 \pm 0.41 \times 10^4$ copies/ml (abdomen), and $1.41 \pm 0.23 \times 10^4$ copies/ml (feet). | 5 repetitions over 2 days. |

Abbreviations: NIV=noninvasive ventilation

[a] Preprint article

# DISCUSSION

This systematic review included 14 publications examining patients with SARS or MERS, 1 publication with SARS-CoV-2, and 7 publications of studies examining dispersion of droplets with sham nebulizer treatments in human simulators or patients without known coronavirus infections. Evidence that nebulizer treatments increase risk of coronaviruses similar to COVID-19 is inconclusive, and there is minimal direct evidence about risk for transmission of SARS-CoV-2. Specifically, across the 7 cohort/case-control studies, we found the risk of transmission due to nebulizer treatment exposure had a median odds ratio of 2.4, and ranged from 0.08 (95% CI 0.01 to 0.95) to 20.7 (1.4 to 300.9) based on very weak data among a small number of HCWs with variable use of PPE. In addition, there were no studies that compared the transmission risk between MDIs and nebulizers, nor did any of the studies address transmission risk in the outpatient setting or whether this risk was modified when HCWs used PPE. Moreover, only 1 of the case-control or cohort studies considered asymptomatic spread, and it was with SARS.

## KEY KNOWLEDGE GAPS OR RESEARCH QUESTIONS

We identified several gaps in the existing literature (Table 5 shows a modified gap framework[59]). Of particular relevance is a lack of direct comparison to other inhaled medication delivery mechanisms. In the current COVID-19 pandemic, many providers and health care systems are recommending use of MDIs, a practice that is leading to a shortage of MDIs.[60] In Wuhan, nebulizer treatments were used frequently in hospitalized patients with SARS-CoV-2,[61,62] but the relationship of these treatments to infection of hospital workers has not yet been reported. Studies could also explore more sophisticated and definitive methods to tie exposures to viral transmission such as molecular tracking.[53,54]

**Table 5. Evidence Gaps in the Risk of COVID-19 Transmission with Nebulizer Administration**

| Study Characteristic | Current Evidence | Evidence Gap |
|---|---|---|
| Population | • Symptomatic patients with primarily non-COVID illnesses<br>• Health care workers during SARS/ MERS epidemic and with variable personal protective equipment use | • More data from patients with COVID-19<br>• Asymptomatic patients<br>• Variability in health care workers following current personal protective equipment standards |
| Intervention | • Largely unspecified type of nebulizer | • Different types of nebulizer treatments with active therapeutic medications |
| Comparator | • No nebulizer exposure | • Metered dose inhaler with/without spacer (versus nebulizer) |
| Outcomes | • New cases of disease with probable or documented exposure to known case receiving nebulizer treatment | • Viable viral particles at different distances from patients with SARS-CoV-2 (or flu or other coronaviruses)<br>• Molecular tracking via DNA sequencing to definitively identify transmission from person to person |
| Setting | • Hospitalized patients | • Outpatient setting, emergency department |

| Study Characteristic | Current Evidence | Evidence Gap |
|---|---|---|
| Timing | • Retrospective transmission tracking | • Data collection ideally closer to time of exposure |
| Designs | • Retrospective cohort and case-control studies | • Prospective cohort studies |

## LIMITATIONS

Our review approach has limitations. Specifically, given the rapid production of literature specific to COVID-19, it is possible we missed relevant manuscripts despite searching various preprint servers. In view of the recent arrival of COVID-19, we also included data from other viral infections and simulation studies, which may not be directly applicable to patient care during this pandemic.

## CONCLUSIONS

The possibility that nebulizers increase viral transmission cannot be ruled out, and uncertainty is likely to remain during this pandemic. In the absence of definitive evidence, clinical management decisions could be driven by the most appropriate treatment choice for a given patient and the safest mode of therapy for HCWs and other potentially exposed caregivers. Specifically, MDIs may be preferable when available and suitable for an individual as they are thought to have lower risk for virus transmission,[18] and for some clinical situations are as effective as nebulized treatments.[63] In addition, some nebulizer types may pose less risk. For example, the study by McGrath et al found that aerosol emission was higher with jet nebulizers than with vibrating-mesh nebulizers and that the emission rate was attenuated by choice of patient applicators (*ie*, filtered mouthpiece vs facemask).[57] Finally, prolonged exposures during nebulizer treatments or otherwise are associated with increased risk and warrant minimization when possible.

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## COMPETING INTERESTS

The authors have no conflict of interest to declare.

# APPENDIX A. SEARCH STRATEGY

**Search date: 4/3/2020 (updated 7/17/2020)**
**Database: MEDLINE (via PubMed)**

| | | |
|---|---|---|
| #1 | “Coronavirus”[Mesh] OR "Coronavirus Infections"[Mesh] OR Coronavirus[tw] OR coronaviruses[tw] OR coronaviridae[tw] OR "Severe Acute Respiratory Syndrome"[Mesh] OR "SARS Virus"[Mesh] OR SARS[tw] OR SARS-CoV[tw] OR SARScov[tw] OR “severe acute respiratory”[tw] OR "Middle East Respiratory Syndrome Coronavirus"[Mesh] OR MERS[tw] OR MERS-CoV[tw] OR MERScov[tw] OR “Middle East respiratory”[tw] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "COVID-19"[tw] OR "COVID 19"[tw] OR COVID19[tw] OR 2019nCov[tw] OR "2019-nCoV"[tw] OR "2019 ncov"[tw] OR SARS-CoV-2[tw] | 27854 |
| #2 | "Nebulizers and Vaporizers"[Mesh] OR "Administration, Inhalation"[Mesh] OR nebul*[tw] OR inhaler*[tw] OR inhalation*[tw] | 141676 |
| #3 | #1 AND #2 | 172 |

**Search update: 12/1/2020**
**Database: MEDLINE (via PubMed)**

| | | |
|---|---|---|
| #1 | (("Coronavirus"[Mesh] OR "Coronavirus Infections"[Mesh] OR coronavirus[tw] OR coronaviruses[tw] OR coronaviridae[tw] OR "Severe Acute Respiratory Syndrome"[Mesh] OR "SARS Virus"[Mesh] OR SARS[tw] OR SARS-CoV[tw] OR SARScov[tw] OR "severe acute respiratory"[tw] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "COVID-19"[tw] OR "COVID 19"[tw] OR COVID19[tw] OR 2019nCov[tw] OR "2019-nCoV"[tw] OR "2019 ncov"[tw] OR SARS-CoV-2[tw]) AND ("Nebulizers and Vaporizers"[Mesh] OR "Administration, Inhalation"[Mesh] OR nebul*[tw] OR inhaler*[tw] OR inhalation*[tw])) | 124 |

**Search date: 4/4/20 (updated 4/16/20)**
**Database: MEDLINE (via PubMed)**

| | | |
|---|---|---|
| #1 | "Influenza, Human"[Mesh] OR "Influenzavirus A"[Mesh] OR "Influenzavirus B"[Mesh] OR "Influenzavirus C"[Mesh] OR influenza[tw] OR influenzavirus[tw] OR flu[tw] | 112048 |
| #2 | "Nebulizers and Vaporizers"[Mesh] OR "Administration, Inhalation"[Mesh] OR nebul*[tw] OR inhaler*[tw] OR inhalation*[tw] | 141692 |
| #3 | “Risk”[Mesh] OR “Risk Assessment”[Mesh] OR risk[tw] OR risks[tw] OR “Cross-Infection”[Mesh] OR cross-infection*[tw] OR “cross infection”[tw] OR “cross infections”[tw] OR nosocomial[tw] OR healthcare-acquired[tw] OR “healthcare acquired”[tw] OR hospital-acquired[tw] OR “hospital acquired”[tw] OR "Disease Transmission, Infectious"[Mesh] OR transmi*[tw] OR "Health Personnel"[Mesh] OR worker[tw] OR workers[tw] OR staff[tw] OR personnel[tw] OR clinician*[tw] OR provider*[tw] OR physician*[tw] OR doctor*[tw] OR nurse*[tw] OR nursing[tw] OR residen*[tw] OR intern[tw] OR interns[tw] OR “allied health”[tw] OR therapist*[tw] OR | 5354003 |

| | | |
|---|---|---|
| | dentist*[tw] OR “Masks”[MeSH] OR mask*[tw] OR “Filtration”[MeSH] OR respirator[tw] OR respirators[tw] | |
| #4 | #1 AND #2 AND #3 | 330 |

**Search date: 4/7/2020**
**Database: China National Knowledge Infrastructure (CNKI) database**

| | | |
|---|---|---|
| #1 | “SU=('新型冠状病毒'+'COVID-19'+'SARs-CoV-2'+'非典型肺炎'+'SARS'+'严重急性呼吸综合征'+'中东呼吸综合征冠状病毒'+'MERS')*('雾化'+'吸入') | 373 |

**Search update: 9/1/2020**
**Database: China National Knowledge Infrastructure (CNKI) database**

| | | |
|---|---|---|
| #1 | SU=('新型冠状病毒'+'COVID-19'+'SARs-CoV-2')*('雾化'+'吸入') | 9 |

**Search date: 4/7/2020**
**Database: Wanfang database**

| | | |
|---|---|---|
| #1 | ((题名或关键词=( "新型冠状病毒" OR "COVID-19" OR "SARs-CoV-2" OR "非典型肺炎" OR "SARS" OR "严重急性呼吸综合征" OR "中东呼吸综合征冠状病毒" OR "MERS") ) AND ( 题名或关键词=("雾化" OR "吸入" ))） OR （(摘要=( "新型冠状病毒" OR "COVID-19" OR "SARs-CoV-2" OR "非典型肺炎" OR "SARS" OR "严重急性呼吸综合征" OR "中东呼吸综合征冠状病毒" OR "MERS") ) AND (摘要=("雾化" OR "吸入" ))） | 48 |

**Search update 9/1/2020**
**Database: Wanfang database**

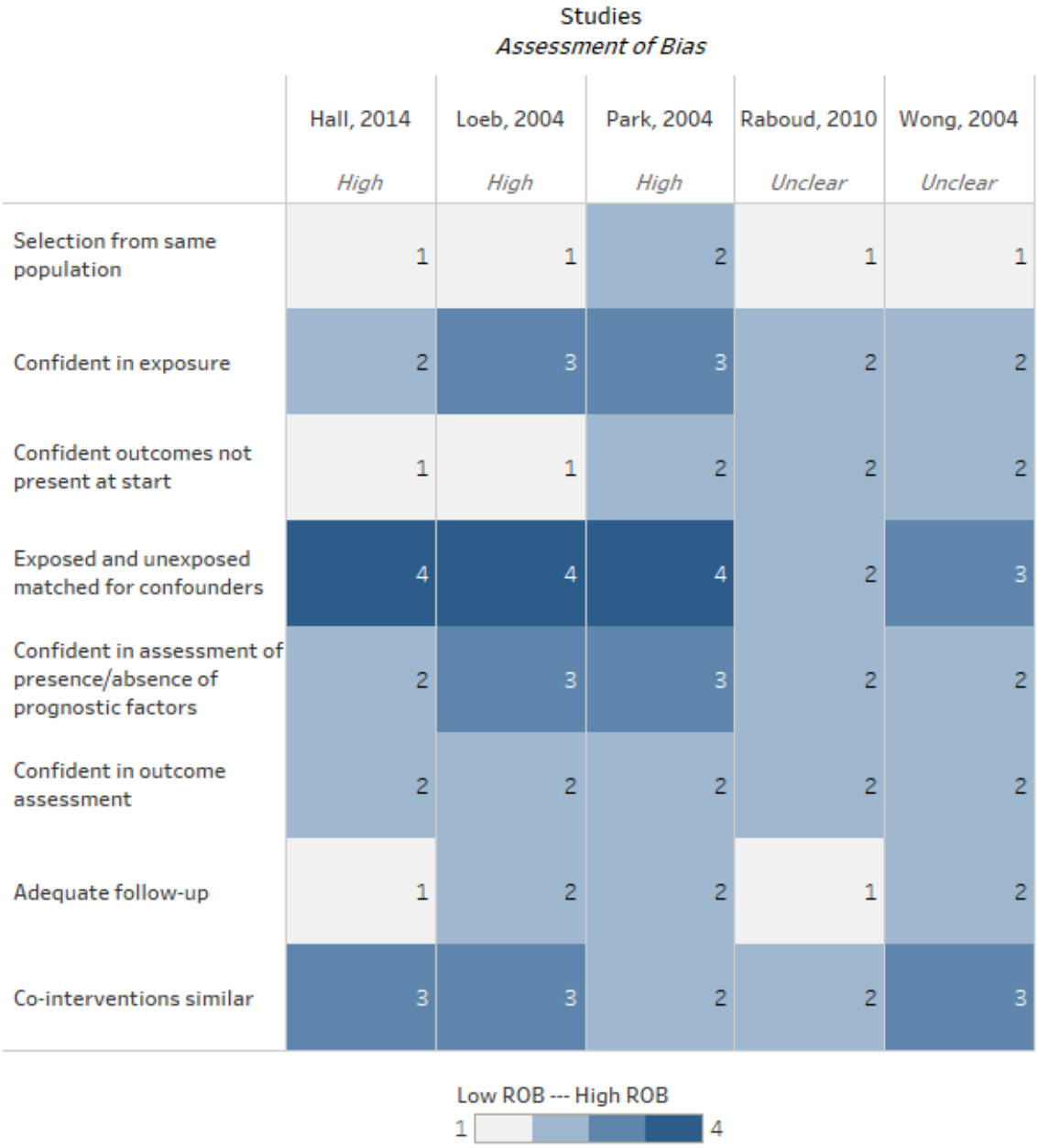
| | | |
|---|---|---|
| #1 | ((（题名或关键词=( "新型冠状病毒" OR "COVID-19" OR "SARs-CoV-2") ) AND ( 题名或关键词=("雾化" OR "吸入" ))） OR （(摘要=( "新型冠状病毒" OR "COVID-19" OR "SARs-CoV-2") ) AND (摘要=("雾化" OR "吸入" ))） | 64 |

# APPENDIX B. GUIDELINES

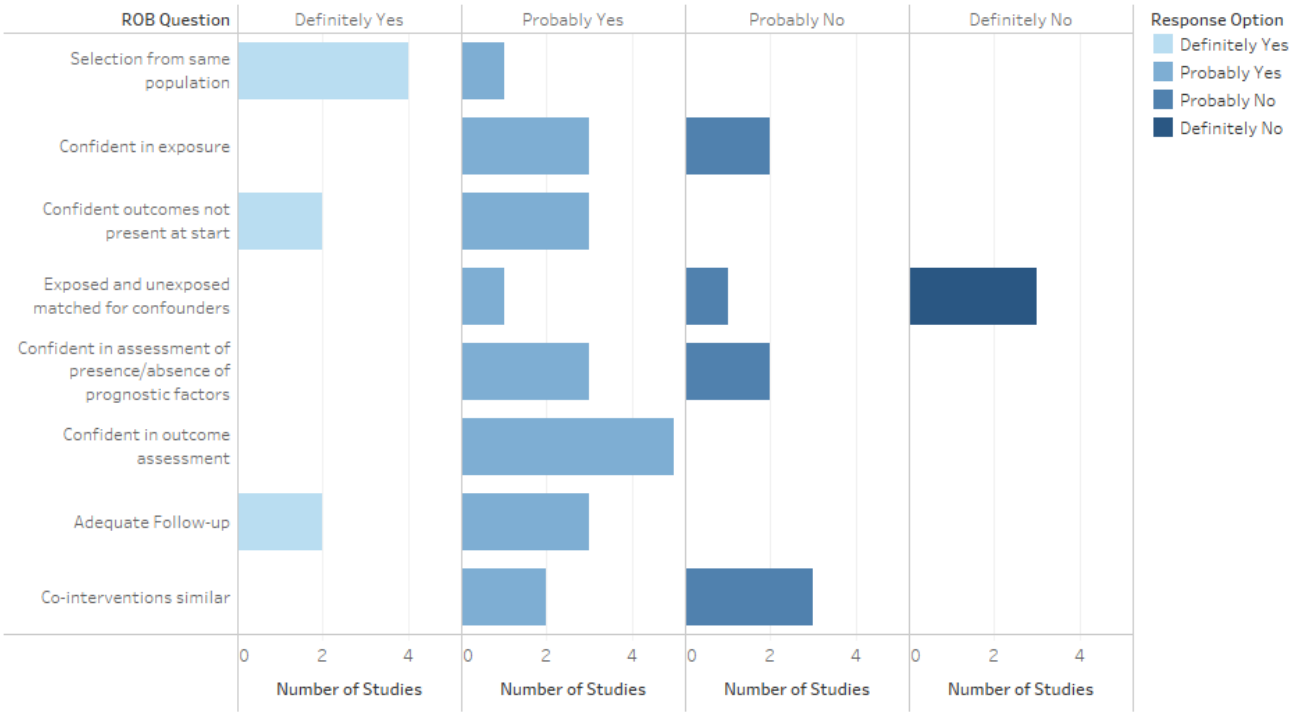
| Source | Recommendation | Date Published | Date Accessed |
|---|---|---|---|
| World Health Organization<br><br>"Clinical management of severe acute respiratory infection when COVID-19 disease is suspected." | Aerosol transmission discussed in context of aerosol-generating procedures and the imperative use of appropriate PPE, such as gloves, long-sleeved gowns, eye protection and fit-tested particulate respirators (N95, N95-equivalent, or higher level of protection). Such procedures include open suctioning of respiratory tract, intubation, bronchoscopy and CPR. When able, all aerosol-generating procedures should be performed in a negative pressure-room in the ICU with a minimum of 12 air changes per hour. | 03-19-2010 | 04-05-2020 |
| Centers for Disease Control and Prevention<br><br>"Interim US guidance for risk assessment and public health management of healthcare personnel with potential exposure in a healthcare setting to patients with COVID-19" | Nebulizer therapy is considered an aerosol-generating procedure. If no PPE is used during prolonged exposure to a patient undergoing nebulizer therapy, the healthcare provider is a *high-risk* exposure. *Medium risk* exposure include those that wear appropriate PPE during prolonged close contact / aerosol generating procedure. *Low-risk* exposure include brief interactions with COVID-19 patients while wearing appropriate PPE. | 03-07-2020 | 04-05-2020 |
| Society of Critical Care Medicine<br><br>"Surviving Sepsis Campaign: guidelines on the management of critically ill adults with COVID-19" | Nebulizer therapy is considered an aerosol-generating procedure and healthcare workers should wear N95 or N95-equivalent fitted respirator masks. Nebulizer therapy on ICU patients with COVID-19 should be performed in a negative pressure | 03-20-2020 | 04-06-2020 |

# APPENDIX C. RISK OF BIAS ASSESSMENT

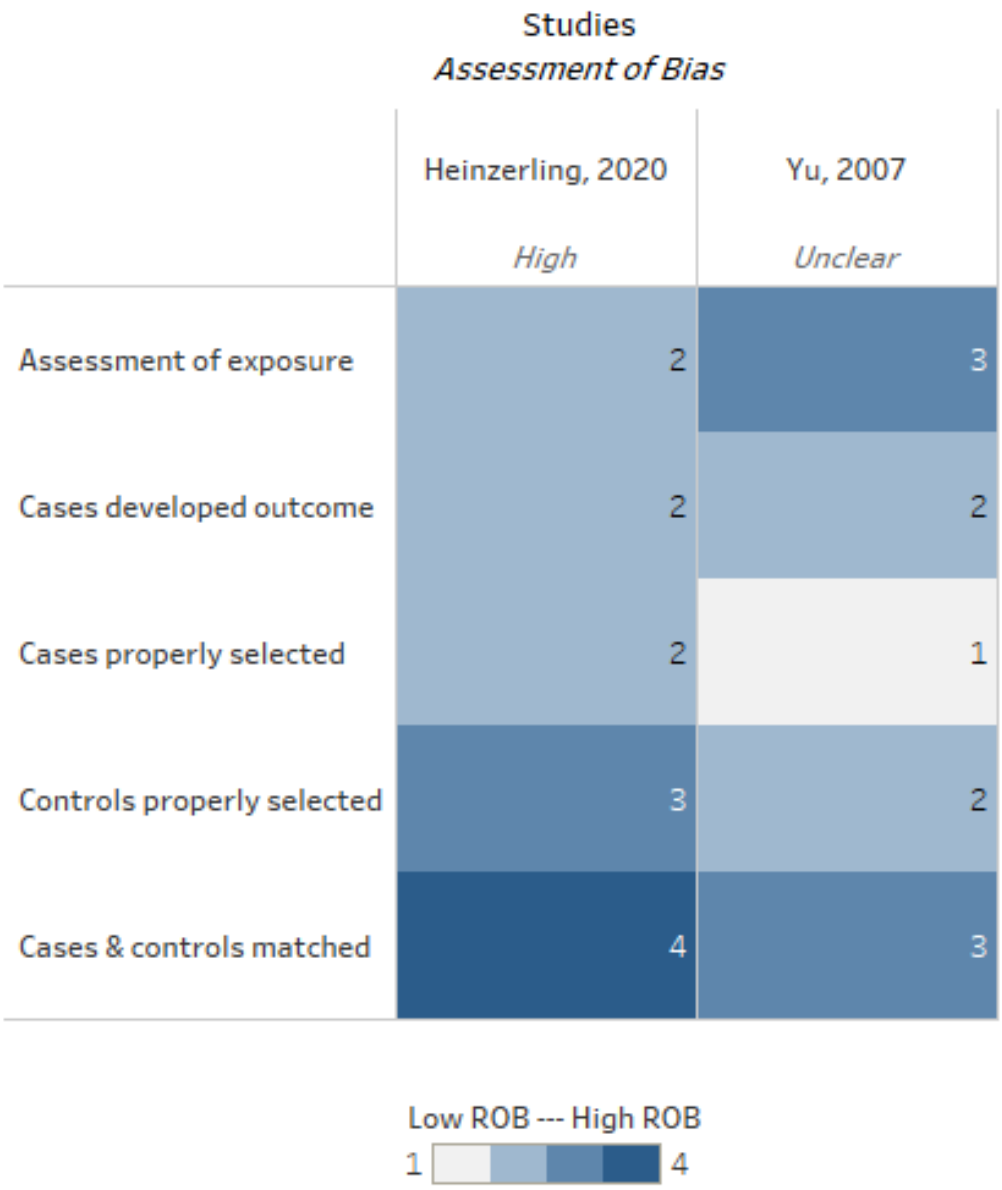
## Risk of Bias Assessment for Cohort Studies



## Risk of Bias Summary for Cohort Studies



**Risk of Bias Assessment for Case-Control Studies**



## Risk of Bias Summary for Case-Control Studies