

# The risk of coronavirus to healthcare providers during aerosol-generating procedures: A systematic review and meta-analysis

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## Abstract:

**CONTEXT:** Several medical procedures are thought to increase the risk of transmission of infectious agents to health-care providers (HCPs) through an aerosol-generating mechanism.

**AIMS:** Given the significant influenza and coronavirus pandemics that have occurred in the 20<sup>th</sup> and 21<sup>st</sup> century, including the current severe acute respiratory syndrome coronavirus 2 global pandemic, the objective of this analysis is to assess the occurrence of disease transmission to HCPs from the performance aerosol-generating procedures (AGPs).

**SETTINGS AND DESIGN:** This was a systematic review and meta-analysis

**SUBJECTS AND METHODS:** We performed a systematic meta-analysis looking at the odds ratio (OR) of AGP, causing infection among HCPs. We searched the following databases: MEDLINE (PubMed), ProQuest, Cochrane databases, and the Gray literature (ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform). In addition, we conducted nondatabase search activities. The search terms used were "MERS-CoV," "COVID," and "SARS" combined with "provider" or "healthcare provider."

**STATISTICAL ANALYSIS USED:** RevMan meta-analysis was used for statistical analysis.

**RESULTS:** Following the search, we reviewed 880 studies, of which six studies were eligible. The estimated odd ratio utilizing a control group of HCPs who were exposed to AGP but did not develop the infection was 1.85 (95% confidence interval [CI]: 1.33, 2.57). The OR remained the same when we added another control group who, despite not being exposed to AGP, had developed the infection. The OR remained 1.85 (95% CI: 1.33, 2.55). However, there is an increase in the OR to 1.89 (95% CI: 1.38, 2.59) when we added HCPs who did not use adequate personal protective equipment (PPE) during the procedures to the total estimates.

**CONCLUSIONS:** The performance of AGP with inadequate PPE can result in an increased risk of disease transmission to HCWs.

## Keywords:

Coronavirus, health-care personnel, health-care-associated infections

Several medical procedures are thought to increase the risk of transmission of infection to health-care providers (HCPs), in particular those which are aerosol generating in nature,

for example, endotracheal intubation, respiratory suctioning, adjustment of oxygen masks, bag-valve-mask ventilation, and other forms of noninvasive ventilation, in addition to the performance of cardiopulmonary resuscitation (CPR).<sup>[1-4]</sup>

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Coronavirus is known to have three strains, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS coronavirus 2 (SARS-CoV-2). All share a similar mode of droplet transmission. As such, aerosol-generating procedures (AGPs) are thought to play a significant role in disease transmission among HCP.<sup>[5-7]</sup> Due to the widespread infections over the last two decades caused by novel viruses in the Coronaviridae family, the objective of this analysis is to assess the effects of AGP on the transmission of infectious agents among HCPs. Our review seeks to examine the risk of HCPs working during the current SARS-CoV-2 pandemic from the performance of AGPs.

## Subjects and Methods

### Methods

#### Search strategy

The eligibility criteria utilize a systematic search strategy for study selection to include observational studies of case-control and cohort studies that had “MERS-CoV,” “COVID,” and “SARS” combined with “provider” or “healthcare provider.” The following databases searched without date limitation: MEDLINE (PubMed), ProQuest, Cochrane databases, and Gray literature (ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform). Furthermore, we conducted a nondatabase search activity to include the related dissertations and reviews not identified by the initial database search strategies to ensure completeness. Data collection was started in March and completed in April 2020.

#### Selection criteria

The exclusion criteria were non-English articles that lack translation and studies that lack a control group. We defined the case as those who were exposed to AGP and developed the infection. The control group, defined by whom exposed to AGP but did not develop the infection, those who were not exposed and developed the infection and finally those despite their exposure is protected, with personal protective equipment (PPE) they nonetheless acquired the infection. We defined AGPs as the procedures of endotracheal intubation, tracheotomies, any form of oxygen administration, including noninvasive or manual ventilation, bronchoscopy, endotracheal aspiration, and CPR as reported in a previous systematic review.<sup>[1]</sup> Moreover, protected exposure entails wearing appropriate personal protective equipment (PPE) of gloves, gown, goggles, and an N95 mask. Furthermore, we defined HCPs as any health personnel who have a direct contact with patients who developed a test-positive infection of either SARS, MERS-CoV, or SARS-CoV-2 following interaction with a positive case during the epidemics. A definite case was

defined as a laboratory-confirmed case of either SARS, MERS-CoV, or SARS-CoV-2.

#### Data extraction, quality assessment, and qualitative synthesis

Two independent researchers examined the studies' eligibility for inclusion and extracted the data. A third reviewer invited when there is a disagreement for study inclusion between the two researchers. We performed data extraction using a preset form. From each study, information were collected regarding study design, year, and country of the epidemic, the type of AGP studied, and infectious transmission outcome in addition to the number of cases and controls. We used the ROBINS-I tool<sup>[8]</sup> for assessing the risk of bias for observational studies to critically appraise the included studies, as shown in Tables 1 and 2. We noted a low risk of bias in the majority of the articles. The lack of information about bias in the selection of the reported data made its assessment not applicable. Moreover, we were unable to assess for confounding bias in three of the articles.

Data analysis performed using the Review Manager Web<sup>[9]</sup> using a random-effects model with an assumption held that those included studied are estimating different procedures with similar intervention effects. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in the report of this study.<sup>[10]</sup>

## Results

### Study selection

In total, the broad range of terms identified 880 articles. A flowchart illustrating the selection process of studies identified, included and excluded, and adapted from [www.prisma-statement.org](http://www.prisma-statement.org)<sup>[10]</sup> was illustrated in Figure 1. Out of the 84 studies screened, 78 articles were excluded based on the exclusion criteria. Six articles were included in our analysis after that.

### Study characteristics

The included studies in our analysis are conveyed in Table 3. Four countries were identified to have reported the rate of HCP infection associated with AGPs during the three epidemics; those include Saudi Arabia, China, Canada, and Singapore. The majority of the studies investigated this during the SARS epidemic, and only one article was conducted about the MERS-CoV epidemic. None of the studies included have investigated such an association during the COVID-19 pandemic. Four articles shared a similar control group.<sup>[11-14]</sup> The control group assigned in the investigation was those HCPs who were exposed to AGPs but did not develop the infection. One study<sup>[15]</sup> used the number of HCPs who were unexposed to AGPs and did develop the infection as a control group.

**Table 1: The risk of bias for observational studies considering only the main outcome of the studies**

|                            | Preintervention         |  | At intervention                         | Postintervention                                   |                          |                                 |  |
|----------------------------|-------------------------|--|---|--|--------------------------|---------------------------------|--|
|                            | Bias due to confounding | Bias in selection of participants into the study | Bias in classification of interventions | Bias due to deviations from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result |
| Alraddadi, B., 2016        | NI                      | M  | L                                       | L  | NI                       | S                               | NI                                       |
| Liu, W., et al., 2009      | M                       | S  | L                                       | L  | M                        | L                               | NI                                       |
| Loeb, M., et al., 2004     | NI                      | L  | L                                       | L  | L                        | L                               | NI                                       |
| Pei, LY., et al., 2006     | NI                      | L  | L                                       | L  | L                        | L                               | NI                                       |
| Raboud, J., et al., 2010   | L                       | L  | L                                       | L  | L                        | L                               | NI                                       |
| Teleman, MD., et al., 2004 | L                       | L  | L                                       | L  | L                        | L                               | NI                                       |

L=Low risk of bias, M=Moderate risk of bias, S=Serious risk of bias, C=Critical risk of bias, NI=No information

**Table 2: The risk of bias for observational studies for reaching an overall judgment for specific outcome**

| Domain   | Alraddadi, B., 2016  | Liu, W., et al., 2009   | Loeb, M., et al., 2004  |
|--|--|---|---|
| Bias due to confounding                            | Unclear no mentioned to confounder control   | Unclear no mentioned to confounder control (matching) adjusting)  |   |
| Bias in selection of participants into the study   | Yes<br>No justification for selecting HPC especially from neurology<br>Related to intervention and outcome | Yes<br>Cases selection is fine, but control selection is based on self-reporting of exposure to SARS. However, the interview based on pretested questionnaire unbalanced and unmatched case-control | Yes/low<br>Include only nurses but there is a detailed information how these nurses included    |
| Bias in classification of interventions            | Exposure variables are mentioned but not in clear way  | Low<br>Stated clearly   | Low<br>Stated clearly   |
| Bias due to deviations from intended interventions | No, all results related to the intervention  | Low<br>Stated clearly   | Low<br>Stated clearly   |
| Bias due to missing data                           | Nothing reported about missing data  | Yes   | Low   |
| Bias in measurement of outcomes                    | The statistical approach was not clear (e.g., combining between logistic and liner regression)             | Low   | Low   |
| Bias in selection of the reported result           | Need examination of a preregistered protocol or statistical analysis plan which we do not have             | Need examination of a preregistered protocol or statistical analysis plan which we do not have.   | Need examination of a preregistered protocol or statistical analysis plan which we do not have. |
| Domain   | Pei, LY., et al., 2006   | Raboud, J., et al., 2010  | Teleman, MD., et al., 2004  |
| Bias due to confounding                            | Unclear<br>It is not mentioned whether the confounder is controlled for                                    | There is a heterogeneity and potential confounding effect.  | There is an adjustment technique in this study analysis   |
| Bias in selection of participants into the study   | Low  | Low   | Low   |
| Bias in classification of interventions            | Low<br>Stated clearly  | Low<br>Stated clearly   | Low<br>Stated clearly   |
| Bias due to deviations from intended interventions | No. All the results are related to the intervention  | Low<br>Stated clearly   | Low<br>Stated clearly   |
| Bias due to missing data                           | Low<br>Nothing is reported about the missing data and the numbers are consistent                           | Low<br>Nothing is reported about the missing data and the numbers are consistent  | Low<br>Nothing is reported about the missing data and the numbers are consistent                |
| Bias in measurement of outcomes                    | Low  | Low   | Low   |
| Bias in selection of the reported result           | Needs an examination of a preregistered protocol or statistical analysis plan which is lacking             | Needs an examination of a preregistered protocol or statistical analysis plan which is lacking  | Needs an examination of a preregistered protocol or statistical analysis plan which is lacking  |

SARS=Severe acute respiratory syndrome, HPC=HCP: Healthcare provider

The last article<sup>[16]</sup> differentiated between the unprotected and protected exposures concerning the appropriate use of PPE as a case and control group, respectively.

The estimated odds ratio (OR) using a random effect for the first four studies<sup>[11-14]</sup> with a control of exposure to AGPs who did not develop the infection was



PRISMA 2009 Flow Diagram

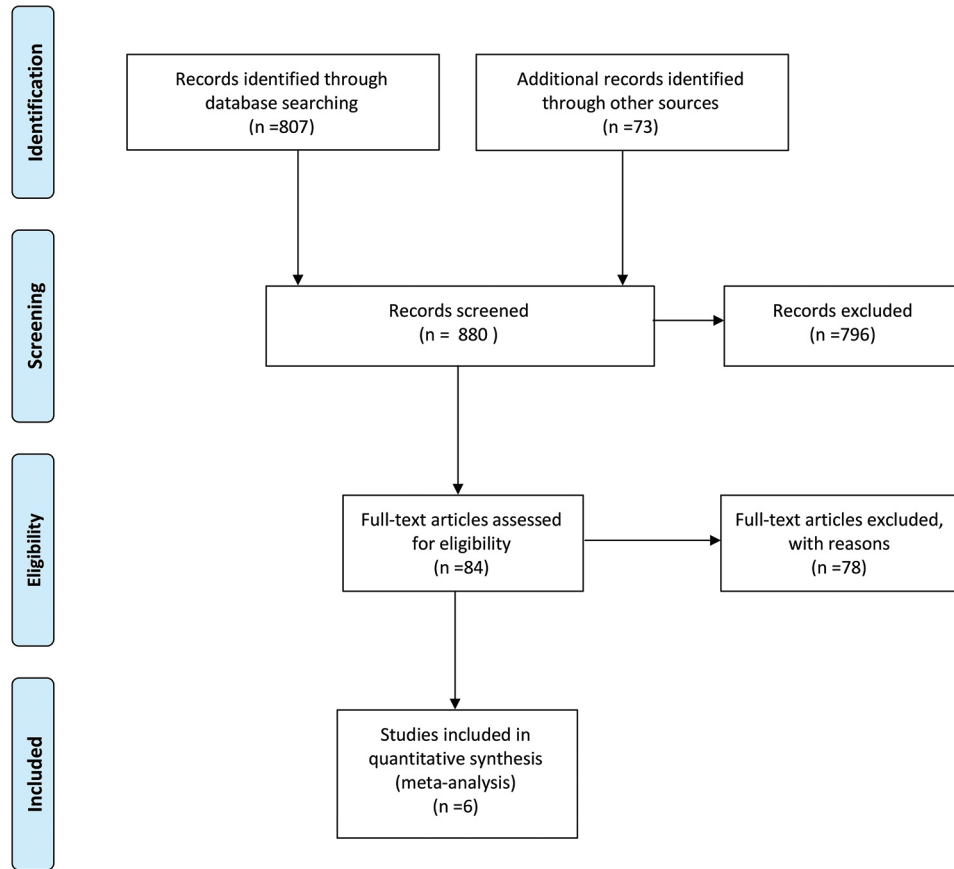


Figure 1: A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart illustrating the selection process of studies identified, included, and excluded

Table 3: The studies included in investigating the exposure to aerosol-generating procedures and the health-care providers' risk of infection

| Study                      | Country      | Epidemic | Study design         | Year | Case  | Control                                   |
|----------------------------|--------------|----------|----------------------|------|---|---|
| Teleman, MD., et al., 2004 | Singapore    | SARS     | Case-control         | 2003 | Exposed to AGP, infection (+)               | Exposed to AGP, infection (-)             |
| Raboud, J., et al., 2010   | Canada       | SARS     | Retrospective Cohort | 2003 |   |   |
| Pei, LY., et al., 2006     | China        | SARS     | Case-control         | 2004 |   |   |
| Liu, W., et al., 2009      | China        | SARS     | Case-control         | 2003 |   |   |
| Loeb, M., et al., 2004     | Canada       | SARS     | Case-control         | 2003 |   | Unexposed to AGP, infection (+)           |
| Alraddadi, B., 2016        | Saudi Arabia | MERS-CoV | Case-control         | 2012 | Unprotected* exposure to AGP, infection (+) | Protected exposure* to AGP, infection (+) |

\*Unprotected versus protected exposure: protected exposure entails wearing appropriate PPE of gloves, gown, goggles, and N95 mask. PPE=Personal protective equipment, AGP=Aerosol-generating procedure, SARS=Severe acute respiratory syndrome

1.85 (95% confidence interval [CI]: 1.33, 2.57) with no heterogeneity among the studies ( $I^2 = 0\%$ ), as illustrated in Figure 2.

Furthermore, Figure 3 illustrates the estimated OR when we added another control group who, despite not being exposed to AGP, developed the infection. The OR was 1.85 (95% CI: 1.33, 2.55) with no heterogeneity among the studies ( $I^2 = 0\%$ ).

Finally, the estimated OR using a random effect when we added the study that differentiated between protected and unprotected exposure to AGPs was 1.89 (95% CI: 1.38, 2.59), no heterogeneity among the studies ( $I^2 = 0\%$ ), as seen in Figure 4.

The two models illustrated the pooled estimates of the OR. A random-effects model is illustrated in Figure 4, while a fixed model in Figure 5.

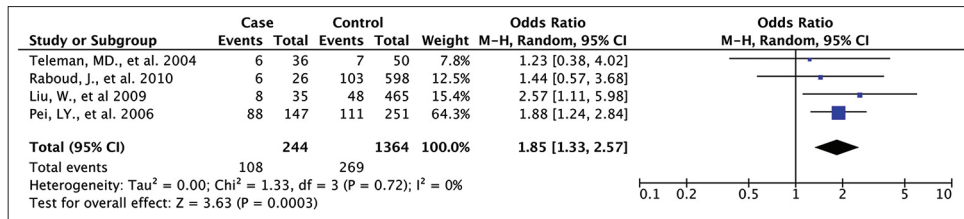


Figure 2: Forrest blot of the risk of aerosol-generating procedure to health-care providers with control of exposed to aerosol-generating procedures which did not develop the infection

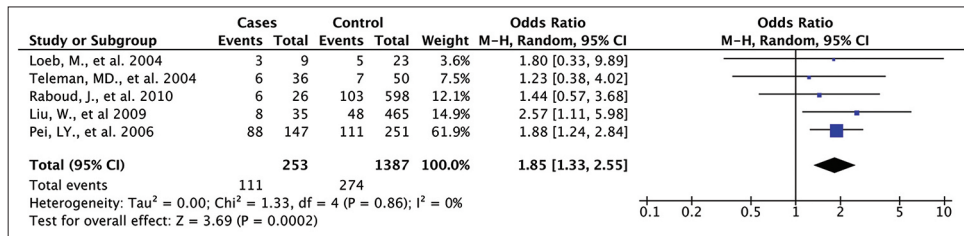


Figure 3: Forrest blot of the risk of aerosol-generating procedures to health-care providers, with control of unexposed but developed the infection

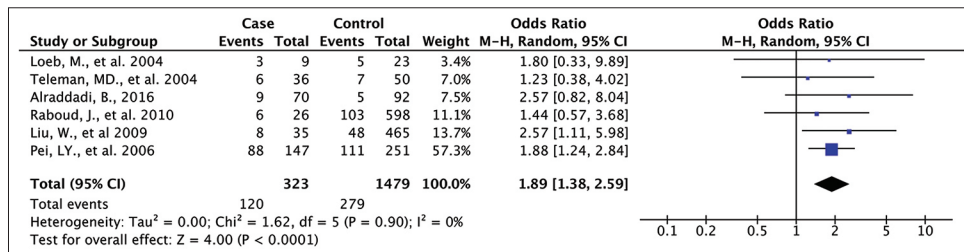


Figure 4: Forrest blot of the total estimates of the risk of aerosol-generating procedure to health-care providers irrespective of the control group using a random-effects model

Tau<sup>2</sup> is 0, indicating no detectable heterogeneity among studies.

## Discussion

There is concern that AGPs are risk factors for the transmission of SARS-CoV-2 to HCPs. We demonstrated that the odds of infection among HCPs with exposure to AGPs is 1.85 times greater than the odds of exposure among controls. Of note, the risk of AGPs mentioned is inter-related with the risk attributed to unprotected exposure. It should be noted that the effect of unprotected exposure was allowed to confound this estimate. The reason is that in one of the studies,<sup>[11]</sup> the reported unprotected exposure in those who acquire the infection was 50%, although due to a lack of clarity, an exact estimate could not be calculated. Such confounders may be present in four articles.<sup>[11,13-15]</sup> Adding the number of unprotected exposure to the total estimates explained the small increase of the OR from 1.85–1.89. Nonetheless, the risk attributed to unprotected exposure during an AGP is justifiable, yet the incidence of infection despite PPE raises a concern for whether PPE was ineffective or insufficient. There are three explanations for such findings. First, HCPs may acquire the infection during donning and doffing through self-contamination. In

concordance with the literature, donning and doffing played a significant role in infection acquisition, whether due to lack of knowledge of the correct sequence of steps for donning and doffing.<sup>[17,18]</sup> Another explanation lies in the urgency to help a patient in need, as such urgency sometimes precludes wearing proper PPE.<sup>[19,20]</sup> Finally, psychological stress, fatigue, and exhaustion can also preclude adherence to infection control measures, mainly PPEs.<sup>[21]</sup> Further studies are warranted to investigate the association between fatigue and infection control measures. There are limitations for such analysis; those include the possibility of publication bias associated with observational studies in general and the possibilities of bias that would result from the weight driven by a single study done by Pei, LY *et al.* 2006. Although the analysis was driven mostly from the SARS-CoV data, we plead to extrapolate the findings into the ongoing COVID-19 pandemic. The reason lies in the similarities between the two viruses in their genome,<sup>[22]</sup> reproduction number (R0),<sup>[23-25]</sup> and nosocomial infection rate.<sup>[26,27]</sup> Furthermore, it is justifiable to incorporate MERS-CoV data about the protected/unprotected exposure to AGPs since the virus exhibits a higher reproduction number within the hospital settings<sup>[28]</sup> that are attributed predominantly to the aerosol-generating mechanism. Overall, the homogeneity of this analysis, despite

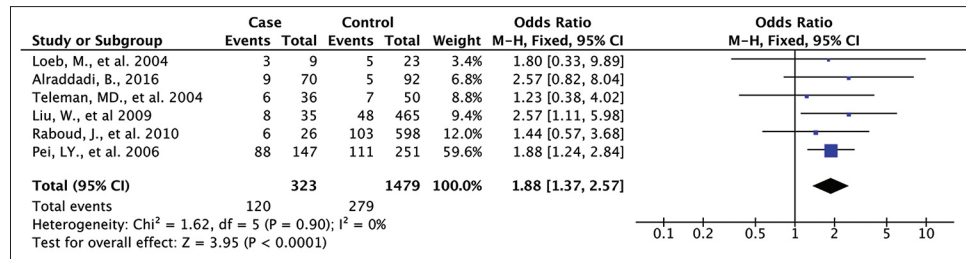


Figure 5: Forrest blot of the total estimates of the risk of aerosol-generating procedure to health-care providers irrespective of the control group using a fixed model

different contexts, times, and populations, supports the generalizability of the findings to any infectious disease epidemics with similar virulence and transmissibility.

## Conclusions

Our analysis suggests that AGPs can increase the risk of infectious agent transmission to HCPs. From a policy perspective, such unmitigated nosocomial risk requires identifying its magnitude and developing an action plan to lessen such exposure to create a safer environment for HCPs. Given the transmissibility and virulence of the SARS-CoV-2 virus seen in the current pandemic, the health-care system should reform modifiable risk factors to decrease the chance of viral transmission among HCPs. This review illustrates the need for implementation of policies regarding AGPs and PPE, with specific protocols designed according to the workplace environment. Training programs and infection control policies should also foster. Such measures should have a continuous and rigorous review.

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## Conflicts of interest

There are no conflicts of interest.

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