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Aerosol-Generating Procedures and Risk of Transmission of Acute Respiratory Infections : A Systematic Review

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Supporting Informed Decisions

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Aerosol-Generating Procedures and Risk of Transmission of Acute Respiratory Infections: A Systematic Review

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November 2011

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This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH) in partnership with the World Health Organization (WHO). The purpose of this report is to provide a review of available evidence on aerosol-generating procedures associated with increase in risk of infection transmission, for use in informing the revision and updating of the current WHO guidelines, *Infection Prevention and Control of Epidemic and Pandemic Prone Acute Respiratory Diseases in Health Care* (July 2007, http://www.who.int/csr/resources/publications/WHO_CD_EPR_2007_6/en/index.html). These guidelines and their revisions provide guidance and direction to the international community as well as Canada.

The report contains a comprehensive review of the existing public literature, studies, materials, and other information and documentation (collectively, the source documentation) available to CADTH at the time of report preparation, and was guided by expert input and advice throughout its preparation.

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Karen Cimon contributed to article selection, data extraction and tabulation, analysis of data, and writing of the report.

Melissa Severn was responsible for the design and execution of the literature search strategies, for the associated appendix, and for the bibliographies.

Carmem L. Pessoa-Silva assisted in the conception, question formulation, review of the literature search strategies, and review of data analysis, and participated in editing and revising the final draft.

John Conly assisted in all aspects of the project, including its conception, question formulation, design of the literature search strategies, article selection, and review of data analysis, and participated in editing and revisions of the final draft.

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Conflicts of Interest

John Conly has received honoraria from the Canadian Agency for Drugs and Technologies in Health for work as an expert reviewer and clinical expert, respectively, for projects on the role of rapid polymerase chain reaction (PCR) testing for methicillin-resistant *Staphylococcus aureus* in

hospitalized patients and the use of vancomycin or metronidazole for treatment of *Clostridium difficile* colitis. He has also received speaker's honoraria related to new antibacterial agents from Janssen-Ortho, Pfizer, and Astellas Pharma during the past five years.

Disclaimer

Carmem L. Pessoa-Silva is a staff member of the World Health Organization. The author alone is responsible for the views expressed in this publication and they do not necessarily represent the decisions or the stated policy of the World Health Organization.

ACRONYMS AND ABBREVIATIONS

ARI	acute respiratory infection
BiPAP	bi-level positive airway pressure
CI	confidence interval
CPAP	continuous positive airway pressure
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCW	health care worker
HTA	health technology assessment
OR	odds ratio
PCR	polymerase chain reaction
SARS	severe acute respiratory syndrome
SARS-CoV	SARS-coronavirus
WHO	World Health Organization

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TITLE: Aerosol-Generating Procedures and Risk of Transmission of Acute Respiratory Infections: A Systematic Review

DATE: November 2011

EXECUTIVE SUMMARY

Context and Policy Issues

It has been hypothesized that aerosol-generating procedures expose health care workers (HCWs) to respiratory pathogens, thereby increasing the risk of contracting the associated infectious diseases. However, the risk of transmission of acute respiratory infections from each aerosol-generating procedure has not been fully determined. WHO guidelines[1] have listed procedures that may be associated with increased risk of respiratory pathogen transmission.

Research Question

What is the clinical evidence for the risk of transmission of acute respiratory infections to health care workers caring for patients undergoing aerosol-generating clinical procedures, compared with the risk of transmission to health care workers caring for patients not undergoing aerosol-generating procedures?

Methods

A literature search was conducted on key health technology assessment resources, including PubMed, MEDLINE, Embase, CINAHL, The Cochrane Library (Issue 10, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, EuroScan, LILACS, Indian Medlars, Index Medicus for South-East Asia Region, international health technology agencies, and a focused Internet search. The search included all languages and was limited to articles published between Jan 1, 1990, and Oct 22, 2010. Regular alerts are current to January 15, 2011. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized controlled studies, and guidelines. Two independent reviewers screened abstracts from the literature search results, using predefined criteria. All studies selected by either reviewer, based on abstract screening, were obtained for full-text screening. The studies selected were health technology assessments (HTA), systematic reviews, meta-analyses, randomized controlled trials, and non-randomized controlled trials that evaluated the risk of disease transmission to HCWs exposed to aerosol-generating procedures.

Two reviewers independently screened full-text studies and selected relevant studies for inclusion. Disagreements regarding selection were resolved by consensus. An independent third reviewer was available to determine final study selection in instances where consensus could not be reached. However, no studies required consultation with a third reviewer to determine whether they met the inclusion criteria. Data were extracted by one reviewer and were verified by the second reviewer. The outcome of interest was risk of disease transmission. The quality of evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Summary of Findings

Ten relevant non-randomized studies were identified: five case-control and five retrospective cohort studies. All studies evaluated transmission of severe acute respiratory syndrome (SARS) to HCWs while caring for ill patients in hospital or intensive care unit settings during the 2002-2003 SARS outbreaks. Procedures that showed a statistically significant increased risk of SARS transmission to HCWs or were a statistically significant risk factor for SARS infection in HCWs included tracheal intubation (four cohort studies; pooled odds ratio [OR] 6.6; 95% confidence interval [CI] 2.3, 18.9, and four case control studies; pooled OR of 6.6 (95% CI 4.1, 10.6), non-invasive ventilation (two cohort studies; pooled OR 3.1; 95% CI 1.4, 6.8), tracheotomy (one case-control study; OR 4.2; 95% CI 1.5, 11.5),

and manual ventilation before intubation (one cohort study; OR 2.8; 95% CI 1.3, 6.4). The risk of transmission associated with suction before intubation (two cohort studies; pooled OR 3.5; 95% CI 0.5, 24.6), suction after intubation (two cohort studies; pooled OR 1.3; 95% CI 0.5, 3.4), manual ventilation after intubation (one cohort study; OR 1.3; 95% CI 0.5, 3.2), bronchoscopy (two cohort studies; pooled OR 1.9; 95% CI 0.2, 14.2), nebulizer treatment (two cohort studies; pooled OR 3.7; 95% CI 0.7, 19.5), manipulation of oxygen mask (two cohort studies; pooled OR 4.6; 95% CI 0.6, 32.5), manipulation of BiPAP mask (one cohort study; OR 4.2; 95% CI 0.64, 27.4), defibrillation (two cohort studies; pooled OR 2.5; 95% CI 0.1, 43.9), chest compressions (two cohort studies; pooled OR 1.4; 95% CI 0.2, 11.2), insertion of nasogastric tube (two cohort studies; pooled OR 1.2; 95% CI 0.4, 4.0), and collection of sputum sample (one cohort study; OR 2.7; 95% CI 0.9, 8.2) was not statistically significant. As well, high-frequency oscillatory ventilation (one cohort study; OR 0.7; 95% CI 0.1, 5.5), high-flow oxygen (one cohort study; OR 0.4; 95% CI 0.1, 1.7), endotracheal aspiration (one cohort study; OR 1.0; 95% CI 0.2, 5.2), suction of body fluid (one case-control study; OR 1.0; 95% CI 0.4, 2.8), administration of oxygen (one case-control study: OR 1.0; 95% CI 0.3, 2.8), chest physiotherapy (two cohort studies; pooled OR 0.8; 95% CI 0.2, 3.2), and mechanical ventilation (one cohort study; OR 0.9; 95% CI 0.4, 2.0) showed either no statistically significant difference in the risk of transmission or were a statistically significant risk factor for transmission. All studies were rated very low quality according to GRADE assessment of the evidence.

Conclusions and Implications for Decision- or Policy-Making

Our findings suggest that some procedures potentially capable of generating aerosols have been associated with increased risk of SARS transmission to HCWs or were a risk factor for transmission, with the most consistent association across multiple studies identified with tracheal intubation. Other associations included non-invasive ventilation from two studies, and manual ventilation before intubation and tracheotomy each from single studies. These findings must be interpreted in the context of the very low quality of the studies, which was assessed using well established GRADE methods. A significant research gap exists in this area, and studies of higher methodological quality are required to provide more precise information about the risk of aerosol generation and the risk of transmission of microbes causing specific acute respiratory infections , including influenza, to HCWs from patients undergoing aerosol-generating procedures.

1 CONTEXT AND POLICY ISSUES

Health care workers (HCWs) are at constant occupational risk for many infectious diseases transmitted from ill patients, despite existing safety protocols.[2] For instance, during the severe acute respiratory syndrome (SARS) outbreaks, many front-line HCWs had a greatly increased risk of contracting the SARS-coronavirus (SARS-CoV) that resulted in severe illness and death.[3] Although clinical guidelines and protective measures for the management of patients with acute respiratory infections (ARIs) exist, the magnitude of the risk of acquiring ARIs through some patient care procedures is not clearly understood.[4,5]

Procedures that are believed to generate aerosols and droplets as a source of respiratory pathogens include positive pressure ventilation (bi-level positive airway pressure [BiPAP] and continuous positive airway pressure [CPAP]), endotracheal intubation, airway suction, high-frequency oscillatory ventilation, tracheostomy, chest physiotherapy, nebulizer treatment, sputum induction, and bronchoscopy.[1,6,7] Although those procedures are known to stimulate coughing and to promote the generation of aerosols, the risk of transmission of ARIs is not well known. It is worth emphasizing that the scientific evidence for the creation of aerosols associated with these procedures, the burden of potential viable microbes within the created aerosols, and the mechanism of transmission to the host have not been well studied. It is unclear whether those procedures pose a higher risk of transmission and whether HCWs caring for patients undergoing the aerosol-generating procedures are at higher risk of contracting the diseases compared with HCWs caring for patients not undergoing the procedures.

Prolonged exposure and poor infection control compliance, such as poor handwashing, may be associated with risk of occupational acquired infection.[8,9] Inadequate spacing and ineffectiveness of personal protective equipment may also contribute to nosocomial transmission.[5] There is some evidence that training programs and adequate personal protection equipment are associated with a decreased risk of transmission of SARS.[10] For instance, with proper control measures in three key areas (including staff personal protection, categorization of patients to stratify risk of SARS transmission, and reorganization of the operating room), high-risk aerosol-generating procedures (surgical tracheostomy) performed on SARS patients appeared to be low risk to HCWs who were in direct contact with the patients in the operating room.[11]

While there appears to be a lack of high-quality evidence regarding the risk of transmission of ARIs from aerosol-generating procedures, the current evidence-based guidelines[1,6,7,12-17] recommend that additional precautionary measures be taken for specified aerosol-generating procedures performed on patients with suspected respiratory infection. These precautionary measures include performing aerosol-generating procedures in a single room with a minimal number of personnel present; using the most qualified personnel to perform the aerosol-generating procedures; and requiring the use of personal protective equipment, specifically an N95 mask or equivalent, full waterproof gown, face shield or goggles, and gloves. Many of these guidelines do, however, draw recommendations based on little understanding of the risk of transmission of the aerosol-generating procedures.

This report systematically reviewed the risk of transmission of ARIs to HCWs exposed to patients undergoing aerosol-generating procedures, as specified in the existing literature.[1,6,7] It does not address the generation of aerosols from specific procedures and does not address the presence of viable microbes responsible for ARIs within aerosols that may have been created by specific procedures and does not address the risk of transmission of airborne pathogens such as *Mycobacterium tuberculosis*.

2 RESEARCH QUESTION

What is the clinical evidence for the risk of transmission of acute respiratory infections to HCWs caring for patients undergoing aerosol-generating clinical procedures, compared with the risk of transmission to HCWs caring for patients not undergoing aerosol-generating procedures?

2.1 Key Findings

Very low-quality evidence suggests that some procedures potentially capable of generating aerosols have been associated with increased risk of SARS transmission of SARS-CoV from infected patients to HCWs, with the most consistent association across several studies being with tracheal intubation.

3 METHODS

3.1 Literature Search

Peer-reviewed literature searches were conducted to obtain published literature for this review. All search strategies were developed by the information specialist with input from the CADTH project team. Search terms were also reviewed by project team members from WHO and revised accordingly.

3.2 Technology Overview

The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Embase, and CINAHL. Parallel searches were run in PubMed, The Cochrane Library (Issue 10, 2010), LILACS, Indian Medlars, and Index Medicus for South-East Asia Region. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Methodological filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines. See Appendix 1 for the detailed search strategies.

The search included all languages and was limited to articles published between Jan 1, 1990, and Oct 22, 2010. Conference abstracts were excluded from the search results. Regular alerts were established on Embase, MEDLINE, CINAHL, and PubMed, and information retrieved via alerts was current to Jan 15, 2011.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional information. These searches were supplemented by handsearching the bibliographies and abstracts of key papers, and through contacts with appropriate experts and agencies.

3.3 Selection Criteria

Eligible studies included HTAs, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. The study population involved HCWs caring for patients with ARIs. The intervention was the provision of care to patients undergoing aerosol-generating procedures (exposed to the procedures). The comparator was the provision of care to patients not undergoing aerosol-generating procedures (unexposed to the procedures). The outcome of interest was the risk of transmission of ARIs from patients to HCWs. Procedures that might promote the generation of droplets or aerosols (non-exhaustive list) included non-invasive ventilation (CPAP, BiPAP), endotracheal intubation, airway suctioning, high-frequency oscillatory ventilation, bag-valve mask ventilation, chest physiotherapy, nebulizer therapies, aerosol humidification, bronchoscopy or other upper airway endoscopy, tracheotomy, and open thoracotomy.

3.4 Article Selection

Two reviewers (KT and KC) independently applied the selection criteria and screened all

citation titles and abstracts that were retrieved from the literature search. The full texts of articles selected by either reviewer were obtained. The reviewers then independently reviewed the full text articles and selected studies for inclusion. The included and excluded studies were compared and any differences between reviewers were resolved by consensus. An independent third reviewer was available to determine final study selection in instances where consensus could not be reached. However, no studies required consultation with a third reviewer to determine whether they fit the inclusion criteria.

3.5 Data Extraction and Analysis

Relevant data from each of the individual studies were extracted by one reviewer (KT) and verified by a second reviewer (KC) using the pre-designed data extraction form to capture the study characteristics and the outcome of interest. The study characteristics included information about the origin of the study, the period of evaluation, the population, types of laboratory tests to confirm the diseases, and assessment of training and protection equipment use. The outcome of interest was the risk of disease transmission from patients to HCWs. Any disagreements between reviewers were resolved by consensus. An independent third reviewer was available to determine final data extraction in instances where consensus could not be reached. However, there were no data elements extracted that required consultation with a third reviewer to determine accuracy. Where appropriate, study results were pooled in a meta-analysis. The appropriateness of pooling of data was determined based upon the degree of clinical and statistical heterogeneity between trials. Where statistical heterogeneity was found ($I^2 > 25\%$), it was planned that sensitivity analyses on the summary treatment effect would be conducted. Pooling was also conducted separately for different types of design such as cohort and case-control studies. Data analysis was to be performed with Review Manager Software using a random effects model.[18] Effect sizes were reported as odds ratios (OR) along with 95% confidence intervals (CI). A GRADE evaluation of the quality of evidence was performed, in which four keys elements (study design, study quality, consistency and directness) were considered.[19]

3.6 Peer Review

This report was peer reviewed by clinical experts from WHO and the Public Health Agency of Canada and internally by independent experts within CADTH . Feedback from these reviews was incorporated into the final report.

4 SUMMARY OF FINDINGS

The literature search identified a total of 1,862 publications. Of those citations, 1,776 were excluded after screening of titles and abstracts, and 86 were retrieved for full-text screening. Ten publications were included in this report, and the remaining 76 articles were excluded (Appendix 2). The lists of included studies and excluded studies are shown in Appendices 3 and 4, respectively.

Ten non-randomized studies were included, consisting of five case-control studies[20-24] and five retrospective cohort studies.[25-29] One study[22] was published in Chinese language and was translated by a CADTH researcher. No relevant systematic reviews, meta-analyses, or randomized controlled trials were identified.

4.1 Non-randomized Studies

The study characteristics and outcomes (risks of disease transmission) are shown in Appendices 5 and 6, respectively. All 10 studies investigated the protective measures or the risk factors of transmission of SARS-CoV from patients to HCWs in hospital or intensive care unit settings during the 2002-2003 SARS outbreaks. Four studies were carried out in Canada,[25-27,29] one in Singapore,[23] and five in China.[20-22,24,28] Six studies[20-22,24-26] included more than 100 HCWs (ranging from 122 to 758), and four studies[23,27-29] included fewer than 100 HCWs (ranging from 43 to 86). Doctors, nurses, residents, therapists, technologists, housekeepers, and others were

among HCWs in eight studies,[20-26,29] while one study included only nurses[27] and the other included only medical students.[28] Most studies assessed whether HCWs had proper infection control training or wore personal protective equipment while caring for patients with SARS. The SARS cases were confirmed by various laboratory tests for the presence of antibodies against SARS-CoV.

The results of GRADE evaluation categorized all 10 studies[20-29] as providing very low-quality evidence (Appendix 7).

Table 1 and Appendix 6 show the risks of SARS transmission to HCWs exposed to specific aerosol-generating procedures that have been identified in these studies, compared with the risks of SARS transmission to HCWs not exposed to aerosol-generating procedures. Table 1 and Appendix 6 also show performance or participation in an aerosol-generating procedure as a risk factor for SARS transmission to HCWs, depending on the type of study.

Four cohort studies[25-27,29] showed that HCWs performing or being exposed to a tracheal intubation procedure had a higher risk of disease transmission compared with unexposed HCWs (Table 1). A summary estimate (using a random effects model) for the cohort studies yielded an OR of 6.6 (95% CI 2.3, 18.9) with moderate statistical heterogeneity (I^2 = 39.6%) (Figure 1). Four case-control studies[20,21,23,24] identified that tracheal intubation was a significant risk factor for transmission of SARS to HCWs (Table 1). A summary estimate (using a random effects model) for the case-control studies yielded an OR of 6.6 (95% CI 4.1, 10.6) with high statistical heterogeneity (I^2 = 61.4%) (Figure 2). Exclusion of an outlier study (Teleman[23]) from the summary estimate yielded an OR of 8.8 (95% CI 5.3, 14.4) with no statistical heterogeneity (I^2 = 0%). In three of the case control studies,[20,21,24] the authors reported tracheal intubation as an independent risk factor for acquisition of SARS based on results obtained using multivariate analysis.

One case-control study[22] reported that there was a significant risk with four procedures evaluated in combination (intubation, tracheotomy, airway care, and cardiac resuscitation) with an OR of 6.2 (95% CI 2.2, 18.1) estimated from multivariate analysis. This combined analysis was derived from the same data set as that of Liu et al., 2009,[24] but was based on a clinical diagnosis of SARS. Other aerosol-generating procedures either reported as a risk factor or with an increased risk of transmission for SARS among HCWs included tracheotomy in one case-control study,[20] non-invasiveventilation,[25,26] from two cohort studies and manual ventilation before intubation[25] from one cohort study.

Two cohort studies[25,27] reported some risks associated with nebulizer treatment exposure, while another cohort study[28] showed otherwise. The latter study by Wong et al. (2004)[28] showed that medical students performing bedside clinical assessment had an increased risk of SARS infection even before nebulizer therapy was used. This study did not assess the training for infection control measures among medical students, which may be a source of bias and thus the study may yield a different result compared to the cohort studies by Loeb et al.(2004)[27] and Raboud et al. (2010).[25] A summary estimate of those three studies yielded an OR of 0.9 (95% CI 0.1, 13.6) with high statistical heterogeneity (I2=73.1%). In a sensitivity analysis, exclusion of the data of Wong et al. (2004)[28] from meta-analysis yielded an OR of 3.7 (95% CI 0.7, 19.5) with no statistical heterogeneity (I^2 = 0%).

Pooled estimates suggest that activities such as chest compressions (cardiopulmonary resuscitation),[25,27] suction before intubation,[25,27] suction after intubation,[25,27] manipulation of oxygen mask,[25,27] bronchoscopy,[25,27] insertion of nasogastric tube,[25,27] and defibrillation[25,27] might be associated with an increased risk of transmission, but the odds ratios were not statistically significant. Chest compressions from one case control study [24] were found to be a risk factor for transmission but this finding was in contradistinction to the findings from the pooled estimate from two cohort studies, which did not find a significantly increased risk of transmission.[25,27] For procedures such as manipulation of BiPAP mask,[27] endotracheal aspiration,[27] suction of body fluids,[23] mechanical

ventilation,[25] manual ventilation,[27] manual ventilation after intubation,[25] high-frequency oscillatory ventilation,[26] administration of oxygen,[23] high-flow oxygen,[25] chest physiotherapy,[25,27] and collection of sputum sample,[25] the point estimates showed no significant difference.

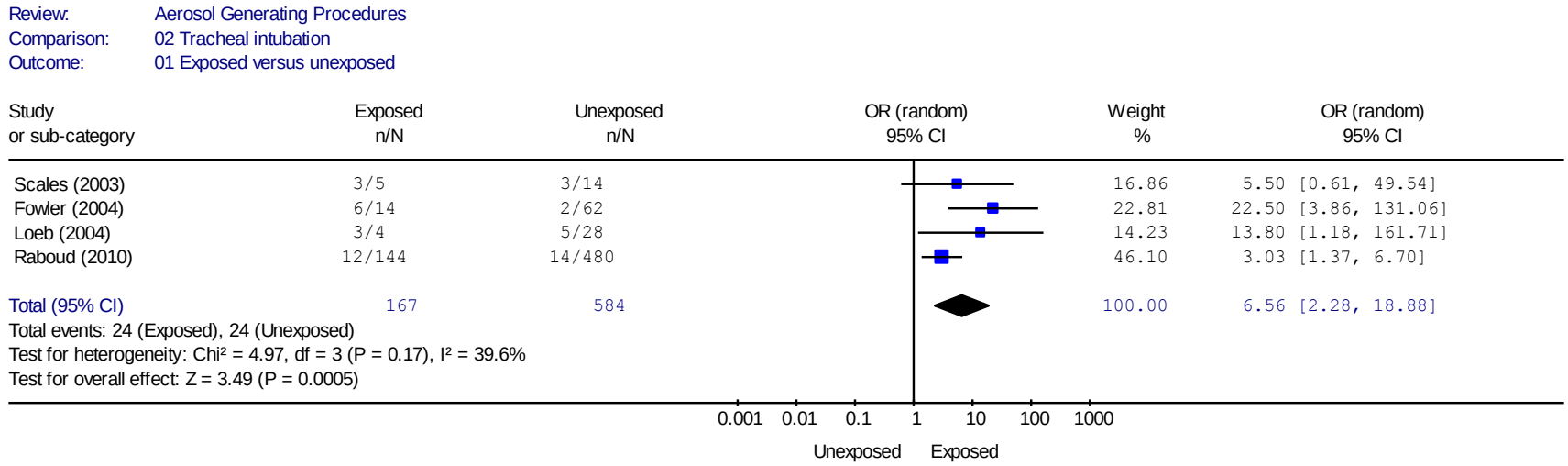
Table 1: Risk of SARS Transmission to HCWs Exposed and Not Exposed to Aerosol-Generating Procedures, and Aerosol-Generating Procedures as Risk Factors for SARS Transmission

Aerosol-Generating Procedures	OR (95% CI)
Tracheal intubation (4 cohort studies)	3.0 (1.4, 6.7)[25]
	22.8 (3.9, 131.1)[26]
	13.8 (1.2, 161.7)[27]
	5.5 (0.6, 49.5)[29]
Pooled estimate (I^2 = 39.6%)	6.6 (2.3, 18.9)
Tracheal intubation (4 case-control studies)	0.7 (0.1, 3.9)[23]
	9.2 (4.2, 20.2)[21]
	8.0 (3.9, 16.6)[20]
	9.3 (2.9, 30.2)[24]
Pooled estimate (I^2 = 61.4%)	6.6 (4.1, 10.6)
Suction before intubation (2 cohort studies)	13.8 (1.2, 161.7)[27]
	1.7 (0.7, 4.2)[25]
Pooled estimate (I^2 = 59.2%)	3.5 (0.5, 24.6)
Suction after intubation (2 cohort studies)	0.6 (0.1, 3.0)[27]
	1.8 (0.8, 4.0)[25]
Pooled estimate (I^2 = 28.8%)	1.3 (0.5, 3.4)
Nebulizer treatment (3 cohort studies)	6.6 (0.9, 50.5)[27]
	0.1 (0.0*, 1.0)[28]
	1.2 (0.1, 20.7)[25]
Pooled estimate (I^2 = 73.1%)	0.9 (0.1, 13.6)
Manipulation of oxygen mask (2 cohort studies)	17.0 (1.8, 165.0)[27]
	2.2 (0.9, 4.9)[25]
Pooled estimate (I^2 = 64.8%)	4.6 (0.6, 32.5)
Bronchoscopy (2 cohort studies)	3.3 (0.2, 59.6)[27]
	1.1 (0.1, 18.5)[25]

Table 1: Risk of SARS Transmission to HCWs Exposed and Not Exposed to Aerosol-Generating Procedures, and Aerosol-Generating Procedures as Risk Factors for SARS Transmission	
Aerosol-Generating Procedures	**OR (95% CI)**
Pooled estimate (I^2 = 0%)	1.9 (0.2, 14.2)
Non-invasive ventilation (2 cohort studies)	2.6 (0.2, 34.5)[26]
	3.2 (1.4, 7.2)[25]
Pooled estimate (I^2 = 0%)	3.1 (1.4, 6.8)
Insertion of nasogastric tube (2 cohort studies)	1.7 (0.2, 11.5)[27]
	1.0 (0.2, 4.5)[25]
Pooled estimate (I^2 = 0%)	1.2 (0.4, 4.0)
Chest compressions (1 case-control study)	4.5 (1.5, 13.8)[24]
Chest compressions (2 cohort studies)	3.0 (0.4, 24.5)[25]
	0.4 (0.0**, 7.8)[27]
Pooled estimate (I^2 = 27.3%	1.4 (0.2, 11.2)
Defibrillation (2 cohort studies)	0.5 (0.0**, 12.2)[27]
	7.9 (0.8, 79.0)[25]
Pooled estimate (I^2 = 55.3%)	2.5 (0.1, 43.9)
Chest physiotherapy (2 cohort studies)	1.3 (0.2, 8.3)[27]
	0.5 (0.1, 3.5)[25]
Pooled estimate (I^2 = 0%)	0.8 (0.2, 3.2)
High-frequency oscillatory ventilation (1 cohort study)	0.7 (0.1, 5.5)[26]
High-flow oxygen (1 cohort study)	0.4 (0.1, 1.7)[25]
Tracheotomy (1 case-control study)	4.2 (1.5, 11.5)[20]
Intubation, tracheotomy, airway care, and cardiac resuscitation (1 case-control study)	6.2 (2.2, 18.1)[22]
Manipulation of BiPAP mask (1 cohort study)	4.2 (0.6, 27.4)[27]
Endotracheal aspiration (1 cohort study)	1.0 (0.2, 5.2)[27]
Suction of body fluid (1 case-control study)	1.0 (0.4, 2.8)[23]
Administration of oxygen (1 case-control study)	1.0 (0.3, 2.8)[23]
Mechanical ventilation (1 cohort study)	0.9 (0.4, 2.0)[25]
Manual ventilation before intubation (1 cohort study)	2.8 (1.3, 6.4)[25]
Manual ventilation after intubation (1 cohort study)	1.3 (0.5, 3.2)[25]
Manual ventilation (1 cohort study)	1.3 (0.2, 8.3)[27]
Collection of sputum sample (1 cohort study)	2.7 (0.9, 8.2)[25]

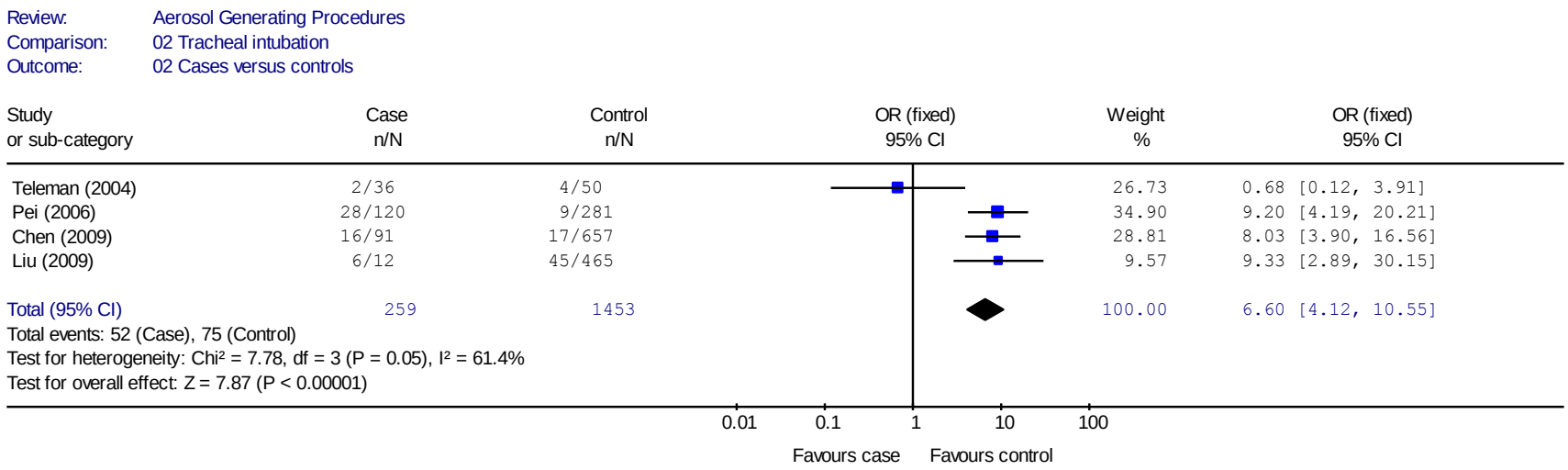
BiPAP = bi-level positive airway pressure; CI = confidence interval; HCWs = health care workers; OR = odds ratio; SARS = severe acute respiratory syndrome.
* actual value is 0.01; ** actual value is 0.02.

Figure 1: Risk of SARS Transmission to HCWs Exposed to Tracheal Intubation



CI = confidence interval; HCWs = health care workers; n = number of events; N = sample size; OR = odds ratio; SARS = severe acute respiratory syndrome.

Figure 2: Tracheal Intubation as Risk Factor of SARS Transmission



CI = confidence interval; HCWs = health care workers; n = number of events; N = sample size; OR = odds ratio; SARS = severe acute respiratory syndrome

4.2 Limitations

The included studies in this report have a number of limitations. The evidence (all 10 included studies) was of very low quality, according to assessments made using a GRADE approach. Details of limitations of individual studies are presented in the summary table of GRADE evidence profiles (Appendix 7). In general, limitations in design and imprecision are main issues in all studies that lead to the very low rating according to GRADE. Further, all of the included studies evaluated the risk of transmission of SARS and may not be generalizable to other acute respiratory pathogens, specifically the influenza virus. The extent of multivariate adjustments varied across studies, and thus the effects of residual confounding may vary from study to study. Also, with the exception of tracheal intubation, a limited number of studies was identified (one to three) for each procedure.

Seven out of 10 studies conducted the investigation at only one hospital, which could limit the generalizability of the results. Four studies included fewer than 100 patients. The number of HCWs included in the studies who were exposed to the aerosol-generating procedures was small, ranging from two to 120. The sample size of the studies could limit statistical power, and results from analyses based on studies of small sample size may be less reliable than those based on a larger sample size. Related to this, the number of events was small in a number of studies. As noted in the results, for a number of potentially aerosol-generating procedures (bronchoscopy,[27] non-invasive positive pressure ventilation,[26] manipulation of BiPAP mask,[27] and insertion of nasogastric tube[27]), point estimates suggested an increased risk, but confidence intervals were wide and were not statistically significant. Not all HCWs caring for SARS patients were included in the studies, since there were some HCWs who refused to participate in the interview. HCWs' recalls might be imperfect, thus generating recall bias if some were more complete or more accurate than others. Since the source of transmission (i.e., primary, secondary, or tertiary cases) was sometimes unclear, it is difficult to accurately determine whether HCWs were infected directly or indirectly from the index patients.

The estimated risk of transmission of infection through aerosol-generating procedures or of a certain procedure being a risk factor for infection transmission in the included studies could have been confounded by the medical characteristics of the patients, the level of infection control training, and compliance with the use of effective personal protection methods among HCWs. Among the included studies, five[20-22,24,25] showed that infection control training and personal protective measures were effective against the nosocomial spread of SARS. These factors might also influence the spread of the diseases, in addition to the aerosol-generating procedures themselves.

5 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

Any conclusions drawn from this systematic review must be interpreted with caution, given the number, quality, and design of the studies. The evidence included in this review, considered to be of very low quality based on GRADE, suggests that some procedures potentially capable of generating aerosols have been associated with an increased risk of SARS transmission from SARS-CoV–infected patients to HCWs. Of the procedures that were assessed, performing or being exposed to a tracheal intubation appeared to be most consistently associated with transmission of SARS or was the most consistently found risk factor for SARS transmission. Tracheal intubation may require HCWs to be in close proximity to a patient's airway for prolonged periods of time. While other procedures, including tracheotomy, non-invasive ventilation, and manual ventilation before intubation, were either found to be a risk factor or associated with an increased risk for SARS infection, these findings were identified from a very limited number of studies and data

were insufficient to establish the risk with any certainty. No other procedures were found to be significantly associated with a risk of SARS transmission.

Despite the comprehensive nature of the search, the limitations of the included studies serve to emphasize the lack of high-quality studies that have examined the risk of transmission of microbes responsible for acute respiratory infections to HCWs caring for patients undergoing aerosol-generating procedures. In addition, it serves to highlight the lack of precision in the definition of aerosol-generating procedures. Further, the results of this report could not be generalized to all acute respiratory infections because the evidence available is strictly limited to SARS. A significant research gap exists in the epidemiology of the risk of transmission of acute respiratory infections to HCWs from patients undergoing aerosol-generating procedures. Given the importance to policy-makers with respect to guidelines and barrier precautions for the protection of HCWs who are providing care for patients undergoing aerosol-generating procedures, funding agencies, health care organizations, and governments should establish a priority to foster high-quality research in this area.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase <1980 to 2010 Week 41> Ovid MEDLINE <1950 to October Week 3 2010> Ovid MEDLINE In-Process & Other Non-Indexed Citations <October 22, 2010> **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 22, 2010
Alerts:	Monthly search updates began October 23, 2010, and ran until Jan 15, 2011
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; controlled clinical trials; cohort studies; cross-over studies; case control studies; observational studies; practice guidelines; non randomized studies.
Limits:	Publication years 1990 – 2010

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
emez	EMBASE 1980 to Present
prmz	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present
.pt	Publication type

Multi-database Strategy	
#	**Searches**
1	exp Positive-Pressure Respiration/ use prmz
2	positive end expiratory pressure/ use emez
3	exp High-Frequency Ventilation/ use prmz
4	exp ventilators, mechanical/ use prmz
5	high frequency ventilation/ use emez
6	intermittent positive pressure ventilation/ use emez
7	Ventilation/ use prmz
8	exp Intubation, Intratracheal/ use prmz
9	endotracheal intubation/ use emez
10	suction/
11	Tracheostomy/
12	tracheobronchial toilet/ use emez
13	Bronchoscopy/ use prmz
14	exp bronchoscopy/ use emez
15	Thoracostomy/ use prmz
16	thorax drainage/ use emez
17	exp "Nebulizers and Vaporizers"/ use prmz
18	nebulization/ use emez
19	exp nebulizer/ use emez
20	Sputum/
21	sputum analysis/ use emez
22	sputum examination/ use emez
23	Oxygen Inhalation Therapy/ use prmz
24	oxygen therapy/ use emez
25	Autopsy/
26	exp Respiratory Function Tests/ use prmz
27	exp Spirometry/ use prmz
28	exp lung function test/ use emez
29	exp cardiopulmonary resuscitation/ use prmz
30	respiration, artificial/ use prmz
31	resuscitation/ use emez
32	artificial ventilation/ use emez
33	breathing exercise/ use emez
34	Breathing exercises/ use prmz
35	or/1-34

36	Physical Therapy Modalities/ use prmz
37	thorax/ use prmz
38	36 and 37
39	35 or 38
40	(ventilation or ventilator or ventilating or ventilatory).ti,ab.
41	(respirator or respirators or respirat* support or respirat* care).ti,ab.
42	(intubation or intubated or extubation or extubated).ti,ab.
43	((respiratory or airway or air way or open) adj3 suction*).ti,ab.
44	(nebulize* or nebulise* or aerosolize* or aerosolise*).ti,ab.
45	heat moisture exchange*.ti,ab.
46	(bronchoscopy or tracheostomy or thoracostomy).ti,ab.
47	(chest adj3 physiotherapy).ti,ab.
48	(sputum adj3 (induction or inducing)).ti,ab.
49	oxygen therap*.ti,ab.
50	(lung function test* or pulmonary function test*).ti,ab.
51	((continuous or bilevel) adj2 (positive airway or positive pressure)).ti,ab.
52	(cardiopulmonary resuscitation or artificial resuscitation or artificial respiration).ti,ab.
53	(autopsy adj3 lung tissue*).ti,ab.
54	or/40-53
55	39 or 54
56	exp Health personnel/ use prmz
57	exp health care personnel/ use emez
58	(health care worker* or healthcare worker* or health care provider* or healthcare provider* or physiotherapist* or dentist* or nurse* or doctor* or physician* or health personnel or medical personnel or hospital personnel or hospital worker* or staff or healthcare professional* or health care professional* or care giver* or caregiver* or paramedic* or therapist*).ti,ab.
59	or/56-58
60	Infectious Disease Transmission, Patient-to-Professional/ use prmz
61	occupational exposure/
62	air microbiology/ use prmz
63	infectious disease transmission/ use prmz
64	airborne infection/ use emez
65	infection control/
66	infection control, dental/ use prmz
67	exp cross infection/
68	hospital infection/ use emez
69	virus transmission/ use emez
70	bacterial transmission/ use emez

71	Disease Outbreaks/ use prmz
72	disease transmission/ use emez
73	Aerosols/ use prmz
74	aerosol/ use emez
75	((aerosol* or cough* or droplet* or infection* or infectious or disease*) adj3 (generat* or induc* or stimulat* or produc*or creat* or respirable range* or dispers* or transmission or transmitted or transmit or spread* or disseminat* or count* or precaution* or control* or inhibit* or prevent* or reduc*)).ti,ab.
76	cross infection.ti,ab.
77	or/61-76
78	55 and 60
79	55 and 59 and 77
80	78 or 79
81	(aerosol* adj2 generat* adj2 procedure*).ti,ab.
82	80 or 81
83	exp *Health personnel/ use prmz
84	exp *health care personnel/ use emez
85	(health care worker* or healthcare worker* or health care provider* or healthcare provider* or physiotherapist* or dentist* or nurse* or doctor* or physician* or hospital personnel or health personnel or medical personnel or hospital worker* or staff or healthcare professional* or health care professional* or care giver* or caregiver* or paramedic* or therapist*).ti.
86	or/83-85
87	Infectious Disease Transmission, Patient-to-Professional/ use prmz
88	occupational exposure/
89	air microbiology/ use prmz
90	infectious disease transmission/ use prmz
91	airborne infection/ use emez
92	infection control/
93	infection control, dental/ use prmz
94	exp cross infection/
95	hospital infection/ use emez
96	virus transmission/ use emez
97	bacterial transmission/ use emez
98	Disease Outbreaks/ use prmz
99	disease transmission/ use emez
100	Aerosols/ use prmz
101	aerosol/ use emez
102	((aerosol* or cough* or droplet* or infection* or infectious or disease*) adj3 (generat* or induc* or stimulat* or produc*or creat* or respirable range* or dispers* or transmission or transmitted or transmit or spread* or disseminat* or count* or precaution* or control* or

	inhibit* or prevent* or reduc*)).ti,ab.
103	cross infection.ti,ab.
104	or/87-103
105	human influenza/ use prmz
106	exp Influenza A virus/ use prmz
107	SARS virus/ use prmz
108	Severe Acute Respiratory Syndrome/ use prmz
109	exp coronavirus infection/ use emez
110	exp influenza virus/ use emez
111	exp influenza/ use emez
112	Parainfluenza virus infection/ use emez
113	exp tuberculosis/ use prmz
114	tuberculosis/ use emez
115	lung tuberculosis/ use emez
116	drug resistant tuberculosis/ use emez
117	exp pneumonia/ use prmz
118	streptococcus pneumoniae/ use emez
119	pneumonia/ use emez
120	Respiratory syncytial pneumovirus/ use emez
121	or/105-120
122	(influenza* or H1N1 or tuberculosis or pneumonia or pneumococcus or severe acute respiratory syndrome or SARS or acute respiratory infection*).ti,ab.
123	121 or 122
124	86 and 104 and 123
125	82 or 124
126	meta-analysis.pt.
127	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
128	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
129	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
130	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
131	(data synthes* or data extraction* or data abstraction*).ti,ab.
132	(handsearch* or hand search*).ti,ab.
133	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
134	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.

135	(meta regression* or metaregression* or mega regression*).ti,ab.
136	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
137	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
138	(cochrane or health technology assessment or evidence report).jw.
139	(meta-analysis or systematic review).md.
140	or/126-139
141	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
142	Randomized Controlled Trial/
143	Randomized Controlled Trials as Topic/
144	Controlled Clinical Trial/
145	Controlled Clinical Trials as Topic/
146	Randomization/
147	Random Allocation/
148	Double-Blind Method/
149	Double Blind Procedure/
150	Double-Blind Studies/
151	Single-Blind Method/
152	Single Blind Procedure/
153	Single-Blind Studies/
154	Placebos/
155	Placebo/
156	Control Groups/
157	Control Group/
158	(random* or sham or placebo*).ti,ab,hw.
159	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
160	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
161	(control* adj3 (study or studies or trial*)).ti,ab.
162	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
163	(allocated adj1 to).ti,ab,hw.
164	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
165	or/141-164
166	epidemiologic methods.sh.
167	epidemiologic studies.sh.
168	cohort studies/
169	cohort analysis/
170	longitudinal studies/

171	longitudinal study/
172	prospective studies/
173	prospective study/
174	follow-up studies/
175	follow up/
176	followup studies/
177	retrospective studies/
178	retrospective study/
179	case-control studies/
180	exp case control study/
181	cross-sectional study/
182	observational study/
183	quasi experimental methods/
184	quasi experimental study/
185	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab.
186	(cohort adj7 (study or studies or design or analysis or analyses)).ti,ab.
187	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab.
188	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab.
189	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab.
190	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab.
191	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab.
192	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab.
193	(population adj3 (study or studies or analysis or analyses)).ti,ab.
194	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab.
195	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab.
196	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab.
197	((natural adj experiment) or (natural adj experiments)).ti,ab.
198	(quasi adj (experiment or experiments or experimental)).ti,ab.
199	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab.
200	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab.
201	case series.ti,ab.
202	case reports.pt.
203	case report/
204	case study/

205	(case adj3 (report or reports or study or studies or histories)).ti,ab.
206	organizational case studies.sh.
207	or/166-206
208	exp clinical pathway/
209	exp clinical protocol/
210	exp consensus/
211	exp consensus development conference/
212	exp consensus development conferences as topic/
213	critical pathways/
214	exp guideline/
215	guidelines as topic/
216	exp practice guideline/
217	practice guidelines as topic/
218	health planning guidelines/
219	exp treatment guidelines/
220	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
221	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab.
222	(standards or guideline or guidelines).ti.
223	((practice or treatment*) adj guideline*).ab.
224	(CPG or CPGs).ti.
225	consensus*.ti.
226	consensus*.ab. /freq=2
227	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab.
228	recommendat*.ti.
229	(care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab.
230	(algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab.
231	(algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab.
232	or/208-231
233	140 or 165 or 207 or 232
234	125 and 233
235	limit 234 to yr="1990 -Current"
236	conference abstract.pt.
237	235 not 236
238	remove duplicates from 237

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 10, 2010	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Cochrane Library databases.
CINAHL (EBSCO interface)	Same keywords, and date limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for EBSCO platform.
LILACS	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Indian Medlars	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Index Medicus for South-East Asia Region	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

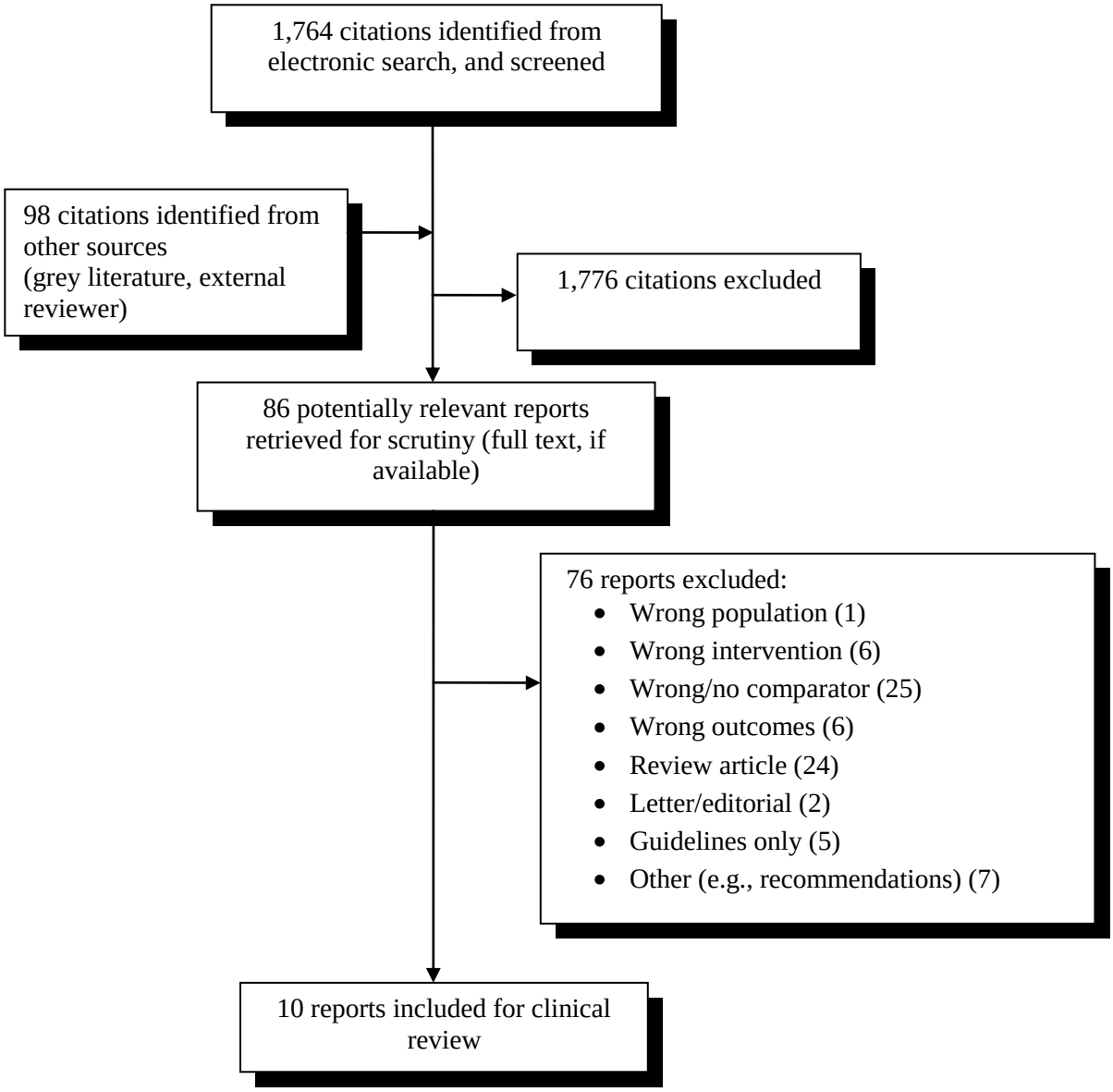
Grey Literature

Dates for Search:	October 2010
Keywords:	Included terms for aerosol-generating procedures, airborne droplets, H1N1, pandemic influenza, SARS, tuberculosis, pneumonia, infection control, transmission, terms for health care workers.
Limits:	Publication years 1990 – present

The following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/grey-matters), were searched:

- Health Technology Assessment Agencies
- Clinical Practice Guidelines
- Databases (free)
- Advisories and Warnings
- Internet Search

APPENDIX 2: SELECTION OF PUBLICATIONS



APPENDIX 3: LIST OF INCLUDED STUDIES

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APPENDIX 4: LIST OF EXCLUDED STUDIES

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APPENDIX 5: CHARACTERISTICS OF INCLUDED STUDIES

Study; Country	Design/ Setting	Period of Evaluation	Population	Assessment of Training and Protection Equipment?	Laboratory Tests
Raboud et al., 2010[25] Canada	Retrospective cohort study Multiple hospitals	2003 SARS outbreak in Toronto	624 HCWs (physicians, residents, nurses, therapists, technologists, housekeepers, others)	Yes	Culture and PCR for SARS-CoV
Chen et al., 2009[20] China	Case-control study Hospital	2003 SARS outbreak in Guangzhou	758 HCWs (doctors, nurses, health attendants, technicians, others)	Yes	ELISA for antibody against SARS-CoV
Liu et al., 2009[24] China	Case-control study Hospital	2003 SARS outbreak in Beijing	477 HCWs (medical staff, nursing staff, others)	Yes	ELISA for antibody against SARS-CoV
Pei et al., 2006[21] China	Case-control study Three hospitals	2002-2003 SARS outbreak in Beijing and Tianjin	443 HCWs (doctors, nurses, technicians, administrators, others)	Yes	Not mentioned re. methods to detect antibodies against SARS-CoV
Fowler et al., 2004[26] Canada	Retrospective cohort study Intensive care unit	2003 SARS outbreak in Toronto	122 critical-care staff (physicians, nurses, nursing assistants, respiratory therapists, others)	No, on training All HCWs wore gloves, gowns, N-95/PCM 2000 masks, and hairnets. Eye and face shields were variably employed	PCR or serology for SARS-CoV
Loeb et al., 2004[27] Canada	Retrospective cohort study Intensive care unit Coronary care unit	2003 SARS outbreak in Toronto	43 nurses	Yes	Serology, immunofluorescence
Ma et al., 2004[22]	Case-control study	2003 SARS outbreak in	HCWs (nurse assistants,	Yes	Diagnostic criteria for SARS from Chinese

Study; Country	Design/ Setting	Period of Evaluation	Population	Assessment of Training and Protection Equipment?	Laboratory Tests
China	Five hospitals	Beijing	janitors, and others) (N = 473)		Minister of Health
Teleman et al., 2004[23] Singapore	Case-control study Hospital	2003 SARS outbreak in Singapore	86 HCWs (doctors, nurses, others)	Not mentioned	Symptoms, chest X-ray and serology
Wong et al., 2004[28] China	Retrospective cohort study Hospital	2003 SARS outbreak in Hong Kong	66 medical students	Yes, on personal protection equipment No, on training	Indirect immunofluorescent to detect antibodies against SARS-CoV
Scales et al., 2003[29] Canada	Retrospective cohort study Intensive care unit	2003 SARS outbreak in Toronto	69 intensive-care staff	Unclear	Radiographic lung infiltrates

CoV = coronavirus; HCWs = health care workers; PCR = polymerase chain reaction; SARS = severe acute respiratory syndrome.

APPENDIX 6: ASSOCIATION OF RESPIRATORY PRACTICES WITH RISK OF TRANSMISSION OF ARI TO HEALTH CARE WORKERS OR RESPIRATORY PRACTICES AS A RISK FACTOR FOR TRANSMISSION OF ARI

Study	Aerosol-Generating Procedures	Measure of Association (95% CI)	GRADE Evaluation	Conclusion
Raboud et al., 2010[25]	Non-invasive ventilation	OR: 3.2 (1.4, 7.2)	⊕OOO VERY LOW	Close contact with severely ill patients and failure of infection control practices were associated with risk of transmission of SARS-CoV.
	High-flow oxygen	OR: 0.4 (0.1, 1.7)		
	Mechanical ventilation	OR: 0.9 (0.4, 2.0)		
	Tracheal intubation	OR: 3.0 (1.4, 6.7)		
	Suction before intubation	OR: 1.7 (0.7, 4.2)		
	Suction after intubation	OR: 1.8 (0.8, 4.0)		
	Manual ventilation before intubation	OR: 2.8 (1.3, 6.4)		
	Manual ventilation after intubation	OR: 1.3 (0.5, 3.2)		
	Cardiac compression*	OR: 3.0 (0.4, 24.5)		
	Broscoscopy	OR: 1.1 (0.1, 18.5)		
	Chest physiotherapy	OR: 0.5 (0.1, 3.5)		
	Defibrillation	OR: 7.9 (0.8, 79.0)		
	Collection of sputum sample	OR: 2.7 (0.9, 8.2)		
	Nebulizer treatment	OR: 1.2 (0.1, 20.7)		
	Manipulation of oxygen mask	OR: 2.2 (0.9, 4.9)		
	Insertion of nasogastric tube	OR: 1.0 (0.2, 4.5)		
Chen et al., 2009[20]	Tracheotomy	OR: 4.2 (1.5, 11.5)	⊕OOO VERY LOW	Tracheal intubation for SARS patients was positively associated with risk of transmission among HCWs.
	Tracheal intubation	OR: 8.0 (3.9, 16.6)		

Study	Aerosol-Generating Procedures	Measure of Association (95% CI)	GRADE Evaluation	Conclusion
Liu et al., 2009[24]	Tracheal intubation	OR: 9.3 (2.9, 30.2)	⊕OOO VERY LOW	Tracheal intubation and chest compression were highly associated with risk for SARS infection during close contact with SARS patients
	Chest compression*	OR: 4.5 (1.5, 13.8)		
Pei et al., 2006[21]	Tracheal intubation	OR: 9.2 (4.2, 20.2)	⊕OOO VERY LOW	Tracheal intubation was a significant risk factor for transmission of the disease to HCWs.
Fowler et al., 2004[26]	Tracheal intubation	OR: 22.5 (3.9, 131.1)	⊕OOO VERY LOW	HCWs performing tracheal intubation had an increased risk of developing SARS. Nurses caring for patients receiving non-invasive positive-pressure ventilation may be at an increased risk.
	Non-invasive ventilation	OR: 2.6 (0.2, 34.5)		
	High-frequency oscillatory ventilation	OR: 0.7 (0.1, 5.5)		
Loeb et al., 2004[27]	Tracheal intubation	OR: 13.8 (1.2, 161.7)	⊕OOO VERY LOW	Tracheal intubation, suction before intubation, nebulizer treatment, and manipulation of oxygen mask were high-risk procedures of transmission of SARS-CoV to HCWs. Other activities may be associated with an increased risk.
	Suction before intubation	OR: 13.8 (1.2, 161.7)		
	Suction after intubation	OR: 0.6 (0.1, 3.0)		
	Nebulizer treatment	OR: 6.6 (0.9, 50.5)		
	Manipulation of oxygen mask	OR: 17.0 (1.8, 165.0)		
	Insertion of a nasogastric tube	OR: 1.7 (0.2, 11.5)		
	Manipulation of BiPAP mask	OR: 4.2 (0.6, 27.4)		
	Endotracheal aspiration	OR: 1.0 (0.2, 5.2)		
	Bronchoscopy	OR: 3.3 (0.2, 59.6)		
	Manual ventilation	OR: 1.3 (0.2, 8.3)		
	Defibrillation	OR: 0.5 (0.0, 12.2)		
	Cardiopulmonary resuscitation*	OR: 0.4 (0.0, 7.8)		
	Chest physiotherapy	OR: 1.3 (0.2, 3.2)		

Study	Aerosol-Generating Procedures	Measure of Association (95% CI)	GRADE Evaluation	Conclusion
Ma et al., 2004[22]	Intubation, tracheotomy, airway care, and cardiac resuscitation combined	OR: 6.2 (2.2, 18.1)	⊕OOO VERY LOW	Health care workers need proper protection during process of clinical diagnosis and treatment of SARS patients.
Teleman et al., 2004[23]	Intubation	OR: 0.7 (0.1, 3.9)	⊕OOO VERY LOW	There was no significant difference in the distribution of suctioning, intubation, and oxygen administration between cases and controls.
	Suction of body fluid	OR: 1.0 (0.4, 2.8)		
	Administered oxygen	OR: 1.0 (0.3, 2.8)		
Wong et al., 2004[28]	Nebulizer treatment	Before nebulizer therapy: 6/10 infected During nebulizer therapy: 1/9 infected OR: 0.1 (0.0, 1.0)	⊕OOO VERY LOW	Medical students performing bedside clinical assessment had high risk of SARS infection even before nebulizer therapy was used.
Scales et al., 2003[29]	Tracheal intubation	Performed: 3/5 (60%) infected Not performed: 3/14 (21%) infected OR: 5.5 (0.6, 49.5)	⊕OOO VERY LOW	Tracheal intubation may be associated with an increased risk of transmission.

BiPAP = bi-level positive airway pressure; CI = confidence interval; CoV = coronavirus; HCWs = health care workers; OR = odds ratio; RR = relative risk; SARS = severe acute respiratory syndrome.

* Cardiopulmonary resuscitation, cardiac compressions, and chest compressions considered as similar for purposes for analysis.

APPENDIX 7: GRADE EVIDENCE PROFILES OF INDIVIDUAL STUDIES

Retrospective Observational Studies

Quality Assessment						No. of Patients		Effect			
Design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Health Care Workers Exposed to Aerosol-Generating Procedures**	**Health Care Workers Unexposed to Aerosol-Generating Procedures**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Rabood (2010) Infection with SARS through tracheal intubation (follow-up 3 months; assessed with: culture and PCR for SARS-CoV); multiple hospitals											
observational study; retrospective	very serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association (OR: 3.0 [1.4, 6.7], P = 0.004) increased effect for RR ~1[b]	12/144 (8.3%)	14/480 (2.9%) 1.7%	OR 3.0 (1.4, 6.7)	54 more per 1,000 (from 11 more to 138 more) 32 more per 1000 (from 7 more to 87 more)	⊕OOO VERY LOW	CRITICAL[c]
Fowler (2004) Infection with SARS through tracheal intubation (follow-up 23 days; assessed with: PCR or serology for SARS-CoV); 1 intensive care unit											
observational study; retrospective	very serious[j]	no serious inconsistency	no serious indirectness	very serious (very wide confidence interval)	very strong association (OR: 22.5 [3.9, 131.1], P = 0.003) increased effect for RR ~1[i]	6/14 (42.9%)	2/62 (3.2%) 3.2%	OR 22.5 (3.9, 131.1)	396 more per 1,000 (from 82 more to 781 more) 395 more per 1,000 (from 81 more to 780 more)	⊕OOO VERY LOW	CRITICAL[c]
Fowler (2004) Infection with SARS through non-invasive positive-pressure ventilation (follow-up 23 days; assessed with: PCR or serology for SARS-CoV); 1 intensive care unit											
observational study; retrospective	very serious[j]	no serious inconsistency	no serious indirectness	very serious (very wide confidence interval)	Strong association (OR [95% CI]: 2.6 [0.2, 34.5], P = 0.5) increased effect for RR ~1[i]	1/6 (16.7%)	2/28 (7.1%) 7.1%	OR 2.6 (0.2, 34.5)	95 more per 1,000 (from 56 fewer to 655 more) 95 more per 1,000 (from 56	⊕OOO VERY LOW	CRITICAL[c]

Quality Assessment						No. of Patients		Effect			
Design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Health Care Workers Exposed to Aerosol-Generating Procedures**	**Health Care Workers Unexposed to Aerosol-Generating Procedures**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
									fewer to 654 more)		
Fowler (2004) Infection with SARS through high-frequency oscillatory ventilation (follow-up 23 days; assessed with: PCR or serology for SARS-CoV); 1 intensive care unit											
observational study; retrospective	very serious[j]	no serious inconsistency	no serious indirectness	very serious (very wide confidence interval)	reduced effect for RR >> 1 or RR << 1[j]	2/38 (5.3%)	2/28 (7.1%)	OR 0.7 (0.1, 5.5)	19 fewer per 1,000 (from 64 fewer to 225 more)	⊕OOO VERY LOW	CRITICAL[c]
							7.1%		19 fewer per 1,000 (from 63 fewer to 224 more)		
Loeb (2004) Infection with SARS through tracheal intubation (follow-up 14 days, March 8 to March 21, 2003; assessed with: serology, immunofluorescence); intensive care unit and coronary care unit											
observational study; retrospective	very serious[k]	no serious inconsistency	no serious indirectness	serious (wide confidence interval)	strong association (OR [95% CI]: 13.8 [1.2, 161.7], P = 0.04) increased effect for RR ~1[l]	3/4 (75%)	5/28 (17.9%)	OR 13.8 (1.2, 161.7)	571 more per 1,000 (from 26 more to 794 more)	⊕OOO VERY LOW	CRITICAL[c]
							17.9%		572 more per 1,000 (from 26 more to 793 more)		
Loeb (2004) Infection with SARS through suction before intubation (follow-up 14 days, March 8 to March 21, 2003; assessed with: serology, immunofluorescence); intensive care unit and coronary care unit											
observational study; retrospective	very serious[k]	no serious inconsistency	no serious indirectness	serious (wide confidence interval)	strong association (OR [95% CI]: 13.8 [1.2, 161.7], P = 0.04) increased effect for RR ~1	3/4 (75%)	5/28 (17.9%)	OR 13.8 (1.2, 161.7)	571 more per 1,000 (from 26 more to 794 more)	⊕OOO VERY LOW	CRITICAL[c]
							17.9%		572 more per 1,000 (from 26 more to 793 more)		

Quality Assessment						No. of Patients		Effect			
Design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Health Care Workers Exposed to Aerosol-Generating Procedures**	**Health Care Workers Unexposed to Aerosol-Generating Procedures**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Loeb (2004) Infection with SARS through suction after intubation (follow-up 14 days, March 8 to March 21, 2003; assessed with: serology, immunofluorescence); intensive care unit and coronary care unit											
observational study; retrospective	very serious[k]	no serious inconsistency	no serious indirectness	serious (wide confidence interval)	reduced effect for RR >> 1 or RR << 1	4/19 (21.1%)	4/13 (30.8%)	OR 0.6 (0.1, 3.0)	98 fewer per 1,000 (from 257 fewer to 265 more)	⊕OOO VERY LOW	CRITICAL[c]
							30.8%		97 fewer per 1,000 (from 257 fewer to 265 more)		
Loeb (2004) Infection with SARS through nebulizer treatment (follow-up 14 days, March 8 to March 21, 2003; assessed with: serology, immunofluorescence); intensive care unit and coronary care unit											
observational study; retrospective	very serious[k]	no serious inconsistency	no serious indirectness	serious (wide confidence interval)	strong association (OR [95% CI]: 6.6 [0.9, 50.5], P = 0.09) increased effect for RR ~1[l]	3/5 (60%)	5/27 (18.5%)	OR 6.6 (0.9, 50.5)	415 more per 1,000 (from 22 fewer to 735 more)	⊕OOO VERY LOW	CRITICAL[c]
							18.5%		415 more per 1,000 (from 22 fewer to 735 more)		
Loeb (2004) Infection with SARS through manipulation of oxygen mask (follow-up 14 days, March 8 to March 21, 2003; assessed with: serology, immunofluorescence); intensive care unit and coronary care unit											
observational study; retrospective	very serious[k]	no serious inconsistency	no serious indirectness	serious (wide confidence interval)	very strong association (OR [95% CI]: 17.0 [1.8, 165.0], P = 0.01) increased effect for RR ~1[m]	7/14 (50%)	1/18 (5.6%)	OR 17.0 (1.8, 165.0)	444 more per 1,000 (from 38 more to 851 more)	⊕OOO VERY LOW	CRITICAL[c]
							5.6%		446 more per 1,000 (from 38 more to 851 more)		

Quality Assessment						No. of Patients		Effect			
Design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Health Care Workers Exposed to Aerosol-Generating Procedures**	**Health Care Workers Unexposed to Aerosol-Generating Procedures**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Loeb (2004) Infection with SARS through insertion of a nasogastric tube (assessed with: serology, immunofluorescence); intensive care unit and coronary care unit											
observational study; retrospective	very serious[k]	no serious inconsistency	no serious indirectness	very serious (small sample size; total number of exposed nurses was very small; reporting bias)	increased effect for RR ~1[m]	2/6 (33.3%)	6/26 (23.1%)	OR 1.7 (0.2, 11.5)	103 more per 1,000 (from 164 fewer to 544 more)	⊕OOO VERY LOW	CRITICAL[c]
							23.1%		103 more per 1,000 (from 164 fewer to 544 more)		
Loeb (2004) Infection with SARS through manipulation of BiPAP mask (follow-up 14 days, March 8 to March 21, 2003; assessed with: serology, immunofluorescence); intensive care unit and coronary care unit											
observational study; retrospective	very serious[k]	no serious inconsistency	no serious indirectness	serious (wide confidence interval)	strong association (OR [95% CI]: 4.2 [0.6, 27.4], P = 0.15) increased effect for RR ~1[l]	3/6 (50%)	5/26 (19.2%)	OR 4.2 (0.6, 27.4)	308 more per 1,000 (from 60 fewer to 675 more)	⊕OOO VERY LOW	CRITICAL[c]
							19.2%		308 more per 1,000 (from 60 fewer to 675 more)		
Loeb (2004) Infection with SARS through endotracheal aspiration (assessed with: serology, immunofluorescence); intensive care unit and coronary care unit											
observational study; retrospective	very serious[k]	no serious inconsistency	no serious indirectness	very serious (Small sample size; reporting bias)	reduced effect for RR >> 1 or RR << 1[n]	3/12 (25%)	5/20 (25%)	OR 1.0 (0.2, 5.2)	0 fewer per 1,000 (from 190 fewer to 385 more)	⊕OOO VERY LOW	CRITICAL[c]
							25%		0 fewer per 1,000 (from 190 fewer to 385 more)		

Quality Assessment						No. of Patients		Effect			
Design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Health Care Workers Exposed to Aerosol-Generating Procedures**	**Health Care Workers Unexposed to Aerosol-Generating Procedures**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Loeb (2004) Infection with SARS through bronchoscopy (follow-up 14 days; assessed with: serology, immunofluorescence); intensive care unit and coronary care unit											
observational study; retrospective	very serious[k]	no serious inconsistency	no serious indirectness	serious (wide confidence interval)	strong association (OR [95% CI]: 3.3 [0.2, 59.6], P = 0.44) increased effect for RR ~1[l]	1/2 (50%)[6]	7/30 (23.3%)	OR 3.3 (0.2, 59.6)	267 more per 1,000 (from 181 fewer to 714 more)	⊕OOO VERY LOW	CRITICAL[c]
							23.3%		267 more per 1,000 (from 181 fewer to 715 more)		
Wong (2004) Infection with SARS through nebulizer treatment (follow-up 7 days; assessed with: indirect immunofluorescent to detect antibodies against SARS-CoV); hospital											
observational study; retrospective, cohort of medical students visiting the index patient's ward	very serious[r]	very serious[s]	serious[s]	serious (wide confidence interval)	strong association (OR [95% CI]: 0.1 [0.0, 1.0], P = 0.08) increased effect for RR ~1[r]	1/9 (11.1%)	6/10 (60%)	OR 0.1 (0.0, 1.0)	493 fewer per 1,000 (from 12 fewer to 585 more)	⊕OOO VERY LOW	CRITICAL[c]
							0%		-		
							60%		493 fewer per 1,000 (from 12 fewer to 585 more)		
Scales (2003) Infection with SARS through tracheal intubation (assessed with: radiographic lung infiltrates); intensive care unit											
observational study; retrospective	very serious[t]	no serious inconsistency	no serious indirectness	very serious (wide confidence interval)	strong association (OR [95% CI]: 5.5 [0.6, 49.5], P = 0.10) increased effect for RR ~1[l]	3/5 (60%)	3/14 (21.4%)	OR 5.5 (0.6, 49.5)	386 more per 1,000 (from 72 fewer to 717 more)	⊕OOO VERY LOW	CRITICAL[c]
							21.4%		386 more per 1,000 (from 72 fewer to 717 more)		

BiPAP = bi-level positive airway pressure; CI = confidence interval; CoV = coronavirus; HCWs = health care workers; OR = odds ratio; RR = relative risk; SARS = severe acute respiratory syndrome.

a Recall experience may not be accurate (recall bias); source of transmission was unclear; infection control training varied among health care workers, and use of personal protection equipment not standardized.

b The number of health care workers caring for index patients undergoing tracheal intubation might be low compared with the number of health care workers caring for all SARS patients.

c Aerosol-generating procedure.

d Retrospective; limited to 2 hospitals; ventilation not assessed; tree structure (primary, secondary, tertiary class cases) could not be traced; reporting bias (questionnaire).

e Small number of health care workers caring for patients undergoing tracheal intubation.

f Nov 2002 to Jun 2003.

g Methods not mentioned.

h Reporting bias (filled out questionnaire); non-standardized personal protection equipment; varied in education and level of training; heterogeneousness of health care worker population; severity of the disease was not known at the beginning of the outbreak.

i Total number of exposed group was small.

j Potential of reporting bias; small sample size (N = 122 from ICU); heterogeneous population; education and level of training for infection control varied among health care workers; duration of exposure to index patients varied.

k Small population (43 nurses); non-standardized personal protection equipment; some nurses were unaware that their patients had SARS; retrospective (recall bias).

l Small sample size; total number of exposed nurses was very small; reporting bias.

m Small sample size; reporting bias.

n Patients might become less contagious; reporting bias.

o Retrospective interview (potential recall bias); small population, non-standardized personal protection equipment; inequality in the level of infection control training among health care workers.

p Evaluation of 4 procedures in combination.

q Retrospective telephone interviews; potential recall bias; incomplete data on time and duration of exposure; viral load measurements not available; non-standardized infectious control training and the use of personal protection equipment; small population.

r Very small number of medical students (N = 19); reporting bias; infection control training among students not assessed; unsure if the students were infected by the index patients; unclear about personal protection equipment.

s Indirect information; i.e., based on the numbers of students who contracted SARS before and after nebulizer treatment was used.

t Retrospective (reporting bias); small population; lack of knowledge of SARS transmissibility during the initial phase of the outbreak; non-standardized personal protection equipment; health care workers might not be properly protected.

Case-Control Studies

Quality Assessment						No. of Patients		Effect			
Design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Health Care Workers Who Developed SARS**	**Cohort Control Group of Health Care Workers Who Did Not Develop SARS**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Chen (2009) Infection with SARS through tracheal intubation (timing of exposure mean 4 months; assessed with: ELISA for SARS-CoV); 2 hospitals											
observational study; retrospective, case-control	very serious[d]	no serious inconsistency	no serious indirectness	serious (wide confidence intervals)	strong association (OR: 8.0 [3.9, 16.6], P < 0.001) increased effect for RR ~1[e]	91 cases	657 controls 2.7%	OR 8.0 (3.9, 16.6)	- 155 more per 1,000 (from 71 more to 288 more)	⊕OOO VERY LOW	CRITICAL[c]
Chen (2009) Infection with SARS through tracheotomy (timing of exposure mean 4 months; assessed with: ELISA for SARS-CoV); 2 hospitals											
observational study; retrospective, case-control	very serious[d]	no serious inconsistency	no serious indirectness	serious (wide confidence intervals)	strong association (OR [95% CI]: 4.2 [1.5, 11.5], P < 0.01) increased effect for RR ~1	91 cases	657 controls 1.7%	OR 4.2 (1.5, 11.5)	- 50 more per 1,000 (from 8 more to 149 more)	⊕OOO VERY LOW	CRITICAL[c]
Liu (2009) Infection with SARS from tracheal intubation (timing of exposure 2 months; assessed with: serologically using ELISA method)											
observational study; retrospective, case-control	very serious[h]	no serious inconsistency	no serious indirectness	very serious[u]	strong association[v] increased effect for RR ~1	51 cases	426 controls 9.7%	OR 9.3 (2.9, 30.2)	- 404 more per 1,000 (from 140 more to 667 more)	□□□□ VERY LOW	CRITICAL[c]
Liu (2009) Infection with SARS through chest compression (timing of exposure 2 months; assessed with: serologically using ELISA method)											
observational study; retrospective, case-control	very serious[h]	no serious inconsistency	no serious indirectness	serious[u]	strong association[v] increased effect for RR ~1	51 cases	426 controls 10%	OR 4.5 (1.5, 13.8)	- 234 more per 1,000 (from 41 more to 505 more)	□□□□ VERY LOW	CRITICAL[c]

Quality Assessment						No. of Patients		Effect			
Design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Health Care Workers Who Developed SARS**	**Cohort Control Group of Health Care Workers Who Did Not Develop SARS**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Pei (2006) Infection with SARS through tracheal intubation (timing of exposure 7 months[f]; assessed with: detect antibodies against SARS-CoV [g]); 3 hospitals											
observational study; retrospective (health care workers filled out pre-designed questionnaire), case-control	very serious[h]	no serious inconsistency	no serious indirectness	serious (wide confidence intervals)	strong association (OR [95% CI]: 9.2 [4.2, 20.2], P = 0.000) increased effect for RR ~1[i]	120 cases	281 controls	OR 9.2 (4.2, 20.2)	- 201 more per 1,000 (from 90 more to 369 more)	⊕OOO VERY LOW	CRITICAL[c]
							3.2%				
							0%		-		
Ma (2004) Infection with SARS through intubation, tracheotomy, airway care, and cardiac resuscitation (assessed with: diagnostic criteria for SARS from Chinese Minister of Health); hospital											
observational study; retrospective, case-control	very serious[o]	no serious inconsistency	no serious indirectness	serious (wide confidence interval)	strong association (OR [95% CI]: 6.22 [2.2, 18.1]) increased effect for RR ~1[p]	47 cases	426 controls	OR 6.2 (2.2, 18.1); from multivariate logistic regression	-	⊕OOO VERY LOW	CRITICAL[c]
							0% (control risk not reported)		-		
Teleman (2004) Infection with SARS through intubation (timing of exposure 31 days, March 1-31, 2003; assessed with: symptoms, chest X-ray, and serology); hospital											
observational study; retrospective, case-control	very serious[q]	no serious inconsistency	no serious indirectness	serious (wide confidence interval)	none	36 cases	50 controls	OR 0.7 (0.1, 3.9)	- 24 fewer per 1,000 (from 70 fewer to 174 more)	⊕OOO VERY LOW	CRITICAL[c]
							8%				
Teleman (2004) Infection with SARS through suction of body fluids (timing of exposure 31 days, March 1-31, 2003; assessed with: symptoms, chest X-ray, and serology); hospital											
observational study; retrospective, case-control	very serious[q]	no serious inconsistency	no serious indirectness	serious (wide confidence interval)	none	36 cases	50 controls	OR 1.0 (0.4, 2.8)	- 2 more per 1,000 (from 129 fewer to 226 more)	⊕OOO VERY LOW	CRITICAL[c]
							22.2%				

Quality Assessment						No. of Patients		Effect			
Design	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Health Care Workers Who Developed SARS**	**Cohort Control Group of Health Care Workers Who Did Not Develop SARS**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Teleman (2004) Infection with SARS through administration of oxygen (timing of exposure 31 days, March 1-31, 2003; assessed with: symptoms, chest X-ray, and serology); hospital											
observational study; retrospective, case-control	very serious[q]	no serious inconsistency	no serious indirectness	serious (wide confidence interval)	none	36 cases	50 controls 20.0%	OR 1.0 (0.3, 2.8)	- 5 fewer per 1,000 (from 124 fewer to 215 more)	⊕OOO VERY LOW	CRITICAL[c]

CI = confidence interval; CoV = coronavirus; HCWs = health care workers; OR = odds ratio; RR = relative risk; SARS = severe acute respiratory syndrome.

a Recall experience may not be accurate (recall bias); source of transmission was unclear; infection control training varied among health care workers, and use of personal protection equipment not standardized.

b The number of health care workers caring for index patients undergoing tracheal intubation might be low compared with the number of health care workers caring for all SARS patients.

c Aerosol-generating procedure.

d Retrospective; limited to 2 hospitals; ventilation not assessed; tree structure (primary, secondary, tertiary class cases) could not be traced; reporting bias (questionnaire).

e Small number of health care workers caring for patients undergoing tracheal intubation.

f Nov 2002 to Jun 2003.

g Methods not mentioned.

h Reporting bias (filled out questionnaire); non-standardized personal protection equipment; varied in education and level of training; heterogeneousness of health care worker population; severity of the disease was not known at the beginning of the outbreak.

i Total number of exposed group was small.

j Potential of reporting bias; small sample size (N = 122 from ICU); heterogeneous population; education and level of training for infection control varied among health care workers; duration of exposure to index patients varied.

k Small population (43 nurses); non-standardized personal protection equipment; some nurses were unaware that their patients had SARS; retrospective (recall bias).

l Small sample size; total number of exposed nurses was very small; reporting bias.

m Small sample size; reporting bias.

n Patients might become less contagious; reporting bias.

o Retrospective interview (potential recall bias); small population, non-standardized personal protection equipment; inequality in the level of infection control training among health care workers.

p Evaluation of 4 procedures in combination.

q Retrospective telephone interviews; potential recall bias; incomplete data on time and duration of exposure; viral load measurements not available; non-standardized infectious control training and the use of personal protection equipment; small population.

r Very small number of medical students (N = 19); reporting bias; infection control training among students not assessed; unsure whether the students were infected by the index patients; unclear about personal protection equipment.

s Indirect information; i.e., based on the numbers of students who contracted SARS before and after nebulizer treatment was used.

t Retrospective (reporting bias); small population; lack of knowledge of SARS transmissibility during the initial phase of the outbreak; non-standardized personal protection equipment; health care workers might not be properly protected.

u Wide confidence intervals.

v Small population of case group.