Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CADTH Technology Report

December 2011

Physical Interventions to Interrupt or Reduce the Spread of Respiratory Viruses — Resource Use Implications: A Systematic Review

Supporting Informed Decisions

Cite as: Lee KM, Shukla VK, Clark M, Mierzwinski-Urban M, Pessoa-Silva CL, and Conly J. *Physical Interventions to Interrupt or Reduce the Spread of Respiratory Viruses — Resource Use Implications: A Systematic Review.* [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2011. Available from: http://www.cadth.ca/en/products/health-technology-assessment/publication/3140

Production of this report was made possible by the World Health Organization; the United States Agency for International Development, which provided financial support for the development and publication of this document; and by the Canadian Agency for Drugs and Technologies in Health (CADTH), which provided contributions in-kind in the planning and development of this document.

CADTH is funded by Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. CADTH takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

Legal Deposit — 2011
Library and Archives Canada
ISSN: 1922-611X (online)
M0024 — December 2011

Canadian Agency for Drugs and Technologies in Health

Physical Interventions to Interrupt or Reduce the Spread of Respiratory Viruses — Resource Use Implications: A Systematic Review

Karen M. Lee, MA[1]
Vijay K. Shukla, PhD[1]
Michelle Clark, BSc[1]
Monika Mierzwinski-Urban, MLIS[1]
Carmem L. Pessoa-Silva, MD, PhD[2]
John Conly, MD, FRCP, FACP[3]

December 2011

[1] Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa, Ontario, Canada
[2] Department of Global Alert and Response, Health Security and Environment, World Health Organization (WHO), Geneva, Switzerland
[3] Departments of Medicine, Microbiology, Immunology & Infectious Diseases, Pathology & Laboratory Medicine, Calvin, Phoebe and Joan Snyder Institute of Infection, Immunity and Inflammation, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada

Reviewers

The planning and processes for this systematic review and final document were peer reviewed by content experts, and the following individuals granted permission to be cited.

Peer Reviewers

Ian Shemilt
Senior Research Associate
University of Cambridge
Cambridge, United Kingdom

Fernando Otaiza-O'Ryan, MD, MSc
Epidemiology
Infection Control Program
Ministry of Health of Chile,
Santiago, Chile

Luke Vale, MA, MSc, PhD
Professor of Health Economics
Newcastle University
Newcastle upon Tyne, United Kingdom

Holger J. Schünemann MD, PhD
Chair and Professor
Department of Clinical Epidemiology and Biostatistics
McMaster University
Hamilton, Ontario, Canada

External Reviewers

Laurie O'Neil, RN, BN
Nurse Consultant
Nosocomial and Occupational Infections Section
Public Health Agency of Canada
Calgary, Alberta, Canada

Authorship

Karen M. Lee, research lead, coordinated the research project; selected studies; extracted, tabulated, and analyzed data; and wrote the report.
Vijay K. Shukla analyzed data and contributed to writing sections of the report.
Michelle Clark reviewed the results from the literature search, screened and selected articles, and extracted data.
Monika Mierzwinski-Urban designed and executed the literature search strategies.
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.

Acknowledgements

We would like to acknowledge the following:
Elaine MacPhail for coordinating the project, contributing to writing sections of the report, and providing editorial comments.
Krystle Griffin and Patricia Reynard for project management support.

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 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.

EXECUTIVE SUMMARY

The current guidelines, *Infection Prevention and Control of Epidemic- and Pandemic-Prone Acute Respiratory Diseases in Health Care,* were published in 2007, and since then, new evidence on some specific and controversial areas has emerged, necessitating an update of the guidelines. It has been demonstrated that implementing barriers to transmission, such as physical interventions (screening at ports of entry, isolation, quarantine, social distancing, barriers, personal protection [e.g., wearing masks, gloves, and gowns], hand hygiene) can be effective in containing respiratory virus epidemics or in health care settings such as hospital wards. Given that physical interventions can be instituted rapidly, are readily available, and may be independent of any specific type of infective agent, including novel viruses, they have the potential for widespread use. There is a growing interest in including economic considerations in practice guidelines to allow users and policy-makers to evaluate the use of resources and costs within their particular setting.

Objectives

This systematic review studies the resource use implications associated with physical interventions used for interrupting or reducing the spread of respiratory viruses, and serves to inform decision-makers when considering these interventions. It complements the updated Cochrane Review, *Physical interventions to interrupt or reduce the spread of respiratory viruses* (Jefferson 2011), which shows that physical interventions to interrupt or delay the spread of viruses are effective in protecting against viral transmission. The primary and secondary research questions for this work follow.

Primary Research Question

What are the resource use implications (e.g., number of units) associated with physical interventions (e.g., screening at ports of entry, isolation, quarantine, social distancing, barriers, personal protection [wearing masks, gloves, and gown], hand hygiene) used for the interruption of or reduction in the spread of respiratory viruses?

Secondary Research Question

What are the economic implications (e.g., total cost and cost-effectiveness ratios) associated with physical barriers used for interrupting or reducing the spread of respiratory viruses?

Methods

The authors used a peer-reviewed search strategy to search the following electronic bibliographic databases: PubMed, EMBASE, MEDLINE, CINAHL, and The Cochrane Library, including the National Health Service Economic Evaluation Database (NHS EED) and Health Economic Evaluations Database (HEED). The initial search was completed in November 2010, with regular alerts established in EMBASE, MEDLINE, and PubMed, and running until September 19, 2011. The publications identified were limited to economic studies published between 1995 and 2010. The search was not limited by language. Additional relevant information sources were identified through searches of the websites of health technology assessment and related agencies, professional associations, and other specialized databases; searches of Google, Google Scholar, and other Internet search engines; and review of bibliographies and abstracts of key papers and consultation with experts.

The authors used a novel approach for determining resource use and costing information that necessitated the adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Although the GRADE methodology has been increasingly used as a transparent and evidence-based approach for grading the quality of evidence and strength of recommendations, using it to assess resource use and costs is in the early stages. Nonetheless, it offers the same transparent and evidence-based approach for assessing economic studies.

Results and Conclusions

The literature search yielded 1,146 citations, which were screened against inclusion criteria based on abstracts. A total of 158 were deemed potentially relevant and retrieved for more detailed evaluation, of which 39 studies were subjected to full review. Seven studies met the inclusion criteria for the systematic review; i.e., they reported information on resource use of physical interventions or assessed the cost-effectiveness of physical interventions.
The seven studies were observational in nature, had issues regarding indirectness and, in some cases, imprecision due to small sample size. In some cases where studies were based on modelling exercises, the sensitivity of results to changes in key parameters limited the confidence in study results. All of the economic studies were designed to address specific study questions, resulting in single studies being available for the assessment of physical interventions for specific respiratory viruses. Furthermore, the studies were in settings subject to specific recommendations that varied by location. Given the differences in the economic studies, the results could not be directly compared, which complicates the assessment of consistency. Consequently, the quality of the evidence in the seven studies was found to be very low, based on the use of an adapted Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Based on the updated Cochrane Review, the use of physical interventions to interrupt or reduce the spread of respiratory viruses during epidemics and pandemics is effective. Studies show that the use of physical interventions increases during epidemics and pandemics. Given the general low cost of these interventions, the economic studies that were reviewed showed that use of personal protective equipment was economically attractive. These results are sensitive to assumptions about rate of transmission, facility infection rate, and compliance with interventions, with economic attractiveness increasing when transmission and fatality rates are high. Where guidelines for personal protective equipment use are not followed, cost-effectiveness could be reduced.

The generalizability of the results to different respiratory virus types and community settings requires further investigation. Additional studies are needed to inform the implications on resource use associated with physical interventions, including personal protective equipment, in interrupting or reducing the spread of various respiratory viruses.

ACRONYMS AND ABBREVIATIONS

CADTH	Canadian Agency for Drugs and Technologies in Health
GRADE	Grading of Recommendations Assessment, Development and Evaluation
NI	nosocomial infection
PHAC	Public Health Agency of Canada
PPE	personal protective equipment
RSV	respiratory syncytial virus
SARS	severe acute respiratory syndrome
USD	United States dollars
VCH	Vancouver Coastal Health
WHO	World Health Organization

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1 INTRODUCTION

Viral epidemics or pandemics of acute respiratory infections like influenza or severe acute respiratory syndrome (SARS) have each posed global threats over the past decade.[1,2] The World Health Organization (WHO) interim guidelines document, *Infection Prevention and Control of Epidemic- and Pandemic-Prone Acute Respiratory Diseases in Health Care,* has provided infection control guidance to help prevent the transmission of acute respiratory diseases in health care, with an emphasis on acute respiratory diseases that have epidemic or pandemic potential or may constitute a public health emergency of potential concern.[3] The WHO current guidelines were published in 2007, and since then, new evidence on some specific and controversial areas has emerged, necessitating an update of the guidelines. Among the new data that will be used to update the WHO guidelines is a recently updated Cochrane Review that has found that implementation of physical interventions (screening at ports of entry, isolation, quarantine, social distancing, barriers, personal protection [e.g., wearing masks, gloves, and gowns], or hand hygiene) can be effective in containing respiratory virus epidemics or in hospital wards.[4] Given that physical interventions can be instituted rapidly, are readily available, and may be independent of any specific type of infective agent, including novel viruses, they have the potential for widespread use.

Over the last few years, there has been increasing interest in incorporating economic considerations into the development of evidence-based guidelines. The rationale is that including economic considerations allows users and policy-makers within organizations to evaluate the utility of the resources and costs with a perspective relevant to their particular setting. Resource use and economic implications are of interest to the WHO in order to gain an understanding of the amount of personal protective equipment (PPE), isolation, and other infection control measures that may be required during epidemics of acute respiratory infections. In addition, economic evaluations may be helpful for providing information on the benefits in terms of health care resources that are not used with lower rates of transmission.

As a result, this work was undertaken to determine the resource use implications associated with physical interventions to interrupt or reduce the spread of respiratory viruses.

The approach in this report for determining resource use and costing information was novel and necessitated the adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Although the GRADE methodology has been increasingly used as a transparent and evidence-based approach for grading the quality of evidence and strength of recommendations, using it to assess resource use and costs is in the early stages. Nonetheless, it offers the same transparent and evidence-based approach for assessing economic studies. The work related to this report has been divided into two parts:

- the update of the Cochrane Review[4] and the creation of evidence tables using the GRADE methodology[5]
- the review of literature for information on resource use associated with PPE and the development of GRADE to capture the resource use, costs, and clinical outcomes included in the studies. As there was limited published experience on the development of GRADE economic tables, an approach and methodology were established through collaboration with international experts.

The methodology and findings from the resource use work are detailed in this report.

Specifically, the research question, scope, and decisions regarding the presentation of the evidence in the GRADE tables were based on the need to inform the revision of the WHO interim guidelines and the need to assist in making recommendations on the use of PPE to reduce the transmission of respiratory viruses.

In some cases, the approach may limit the usability of the report and its results for other purposes. In addition, it should be emphasized that the transmission of various respiratory pathogens differs, which is then correspondingly reflected in the resourcing and costing of specific hygienic measures and PPE usage, which in turn may limit the generalizability of the findings beyond the context in which they are presented.

2 RESEARCH QUESTIONS

Primary

What are the resource use implications (e.g., number of units) associated with physical interventions (screening at ports of entry, isolation, quarantine, social distancing, barriers, personal protection [wearing masks, gloves, and gowns], hand hygiene) used for the interruption or reduction in the spread of respiratory viruses?

Secondary

What are the economic implications (e.g., total cost, cost-effectiveness ratios) associated with physical interventions used for the interruption or reduction in the spread of respiratory viruses?

3 STUDY OBJECTIVES

The following study objectives were developed:

- Review the economic literature related to resource implications associated with physical interventions used for interrupting or reducing spread of respiratory viruses
- Review the economic literature related to the cost and effectiveness of physical interventions used for interrupting or reducing spread of respiratory viruses
- Identify relevant studies associated with physical interventions used for interrupting or reducing spread of respiratory viruses
- Develop GRADE resource use tables for the identified studies.

4 METHODS

Literature Search

An information specialist performed the literature search using a peer-reviewed search strategy. To identify published literature a focused search (with main concepts appearing in title or major subject heading) was conducted using key health technology assessment resources, including: PubMed, EMBASE, MEDLINE, CINAHL (secondary search only), The Cochrane Library, and Health Economic Evaluations Database (HEED). The Cochrane Library search included the National Health Service Economic Evaluation Database (NHS EED). The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept for Search #1 was respiratory viruses; the main search concepts for the secondary search were respiratory viruses and physical intervention.

Methodological filters were applied to limit retrieval from both research questions to economic studies. In addition, for the primary search, utilization studies were considered. Retrieval was not limited by language, but was limited to articles published between 1995 and 2010 and humans. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on November 2, 2010. Regular alerts were established in EMBASE, MEDLINE, and PubMed, and were run until September 19, 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 Google Scholar and other Internet search engines were searched for additional information. These searches were supplemented by handsearching the bibliographies and abstracts of key papers and through contacts with the WHO and industry. See Appendix 2 for more information on the grey literature search strategy.

Two independent reviewers screened articles identified through the literature search, using predefined criteria. Where disagreements occurred, a third reviewer was available to provide an additional perspective to help resolve the disagreement.

The literature search focused on two categories of economic studies:

1. Economic studies (e.g., cost analyses, economic evaluations, or resource use studies) of physical interventions to control the spread of respiratory viruses
2. Burden-of-illness studies for respiratory viruses of any type, which include information on cost or resource use (utilization).

Scope

- *Physical interventions:* screening at ports of entry, isolation, quarantine, social distancing, barriers, personal protection (wearing masks, gloves, and gowns), hand hygiene
- *Setting:* community and hospital
- *Population:* general population (children and adults)
- *Respiratory viruses:* all respiratory viruses,* separating for influenza when possible (understanding that it may be unclear at time of admission what specific virus type a patient has)
- *Resource measures:* number of units of physical interventions used; rate of hospitalization; duration of hospitalization
- *Economic information:* costs, results of economic evaluations (e.g., cost-effectiveness ratios).

*Note that the list of respiratory viruses considered in the literature search strategy was reviewed by a content expert (JC) to ensure that a similar list similar to the Cochrane Review was considered. There were, however, a few specific viruses that were not included, but should be captured by the broad search terms.

See Appendix 2 for full details of literature search.

Selection Criteria

Eligible studies included economic evaluations, cost studies, utilization studies, and clinical trials (or studies examining effects). The study population included the community and hospital setting. The outcomes of interest were resource use of any of the physical interventions.

Article Selection

Two reviewers (KL and MC) independently applied the selection criteria and screened all citation titles and abstracts that were retrieved from the literature searches. The full texts of all citations and abstracts identified by the two reviewers were ordered. The reviewers then independently reviewed the full text and selected relevant studies for inclusion in this systematic review, based on a predetermined checklist of requirements. The included and excluded studies were compared and any differences were resolved by consensus. A third reviewer was available in cases where consensus could not be attained; thereafter, majority ruled. Full text articles were then reviewed.

Data Extraction

Data from each individual study were extracted by the first reviewer (MC) and reviewed by the second reviewer (KL), using a predesigned data extraction form. Any disagreements between the reviewers were resolved by consensus.

GRADE Tables

Making judgments about the quality of evidence required assessments of the validity of the results of individual studies for different outcomes. Explicit criteria were used in making these judgments. The GRADE working group has developed a standardized and transparent methodology for assessing the quality of evidence.[6] This approach has been adopted by a number of agencies and decision-making groups, including the WHO, which requested that studies in this review be presented in a GRADE format to assess the quality and reporting of the evidence.

<u>Rating the quality of clinical evidence in economic studies</u>

The clinical outcome measures in the economic studies were identified by the clinical reviewer (VS) in consultation with an economic reviewer (KL), and content experts (JC, CPS) conducted a check of the clinical information. The quality of the outcome measure was assessed using a standard GRADE approach as described by Guyatt et al.[6] The GRADE evidence tables for outcome measures used in the economic study were prepared using the GRADEPro program.[7]

As described in the GRADE methodology, evidence derived from randomized control trials starts as high-quality evidence and observational studies as low-quality evidence supporting an estimate of intervention effects (Table 1). Five factors could result in the downgrading of the evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias; however, three factors could result in upgrading the evidence: large effect, dose response, and all plausible confounders or biases would result in an underestimate of the effect size. Ultimately, the quality of evidence for each outcome falls into four categories: very low, low, moderate, and high.

Table 1: Quality Assessment Criteria Adapted from Guyatt[6]

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias –1 Serious –2 Very serious Inconsistency –1 Serious –2 Very serious Indirectness –1 Serious –2 Very serious Imprecision –1 Serious –2 Very serious Publication bias –1 Likely –2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Moderate		
Observational study →	Low		
	Very low		

Reprinted from *The Journal of Clinical Epidemiology*, 64(4), Guyatt G, Oxman AD, Akl, EA, Kunz R, Vist G, Brozek J, et al., GRADE guidelines: 1. Introduction — GRADE evidence profiles and summary of findings tables, 383-94, Copyright (2011), with permission from Elsevier.

Rating the quality of resource use evidence in economic studies

GRADE recommends that "the quality of evidence should be appraised explicitly for each important economic outcome using the same criteria as for health outcomes" (Brunetti M, et al. Unpublished data [GRADE Guidelines: 11. Special Challenges — quality of evidence for resource use. 2011]). It is suggested that as much as possible, the evaluation of the evidence be based on resource use estimates rather than costing information. Further, as with health outcomes, the assessment of quality should be based on the critical (or key) items of the economic study, and not on the assessment of parameters or assumptions that do not affect the results or conclusions of the study.

Reviewers (KL and VS) used their judgment for upgrading and downgrading the evidence and provided detailed reasons for doing so in the GRADE tables and the accompanying notes. The evidence was reviewed independently by the reviewers, the judgments discussed, and any conflicts resolved by consensus. Reviewers (JC and CPS) checked the information in the tables.

Study Limitations

Similar to clinical studies, non-random allocation or inadequate allocation concealment can lead to risk of bias in economic studies. Incomplete outcome data can also bias resource use estimates. If data are missing equally from treatment and control groups for similar reasons, the risk of bias may be low. Resource use should be captured over an "adequate follow-up period." Adherence to the intention-to-treat principle was considered important, to maintain the prognostic balance. Further, resource use information may be collected directly or indirectly from patients. Where information is collected directly, issues of recall bias may be an issue, depending on how frequently information was collected.

Consistency of Results

Consistency should be assessed regarding variation across identified studies in terms of both magnitude and direction of the differences. Where differences exist but authors failed to provide reasons, the quality of the evidence was downgraded.

Directness of Evidence

Directness assesses the applicability of the resource use information to the setting and population for which the guideline was being developed. Where costs were included, assessment of the unit costs and whether they can be applied to the targeted setting should be provided. Further, information obtained from older studies should be assessed to ensure that the information applies to current settings. Based on GRADE guidance, it was suggested that guidelines developers will likely choose to "focus on the evidence for resource use (and costs) that is most direct."

Imprecision

Variability in resource use between patients can be expected, but there should be sufficient power or number of events to detect differences in resources used.

Publication Bias

As with clinical studies, publication bias should be assessed for resource use studies and economic evaluations. Where only single studies are available, there is the potential for bias, as there are no other studies for comparison purposes.

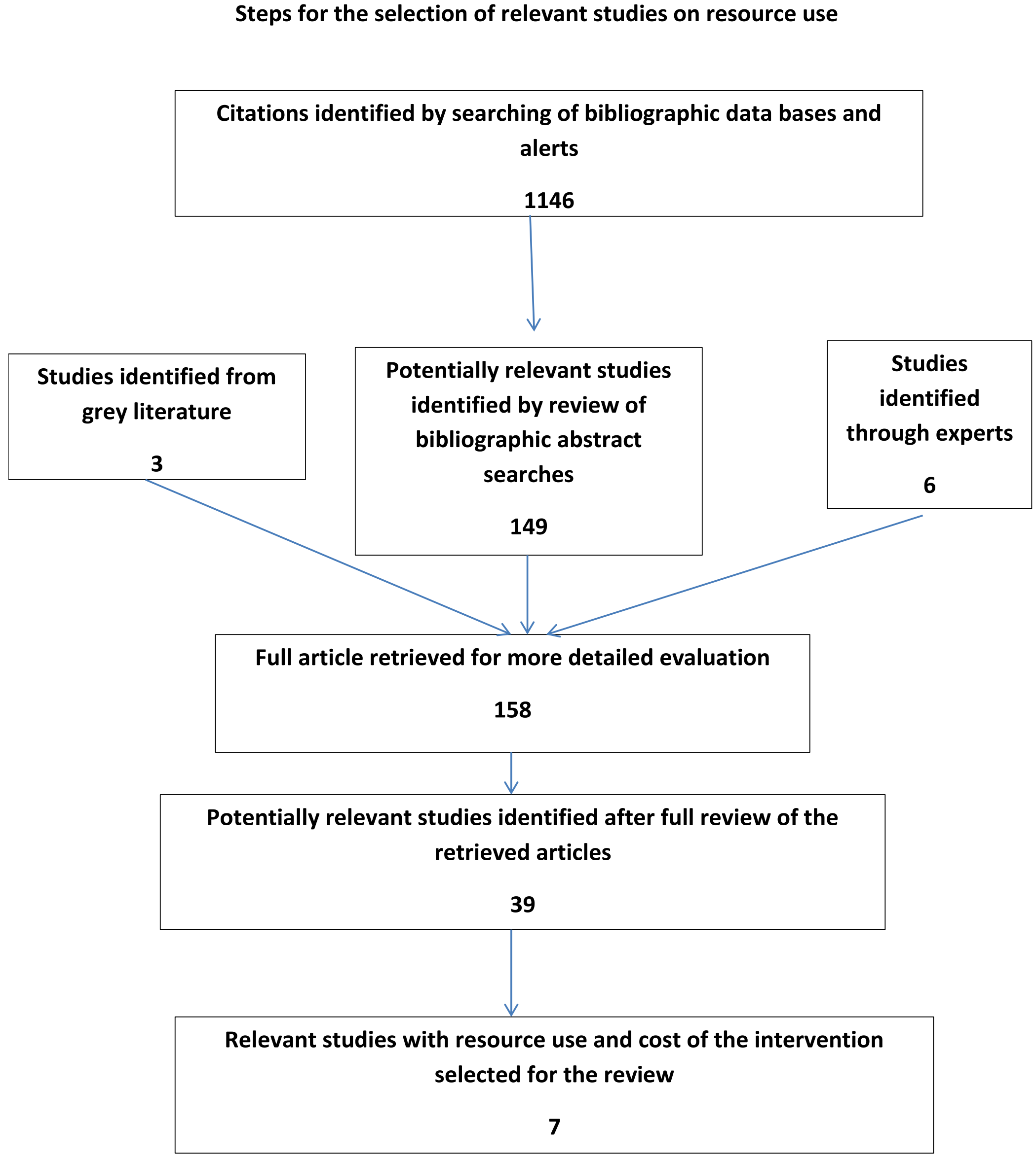
Based on the information provided in the two GRADE manuscripts on economic information and resource use[8] (Brunetti M, et al. Unpublished data [GRADE Guidelines: 11. Special Challenges — quality of evidence for resource use. 2011]), GRADE resource use tables were constructed. Feedback was obtained from a GRADE working group member (HS), given the ongoing advancements in this area of GRADE.

5 RESULTS

Literature Search

The literature search yielded 1,078 citations (Search # 1: 993; Search # 2: 71; Grey: 14) and 68 citations identified in the alerts that were conducted after the literature search had been run. Of those citations, 158 (149 from literature search, three from grey literature, one from experts, five from the Public Health Agency of Canada [PHAC]) were deemed potentially relevant. A total of 39 studies were selected and reviewed, of which seven reported information on resource use of physical interventions or assessed the cost-effectiveness of physical interventions, and 32 provided economic information on specific respiratory viruses (Figure 1).

Figure 1: Selection of Studies



6 SUMMARY OF KEY STUDIES

Of the studies reviewed, seven studies met the inclusion criteria; i.e., reported the cost of physical interventions or resource use. Of these studies, three reported information on resource use, either from the collection of data (Murray; [9] Macartney[10]) or using simulation methods (Phin[11]). The other four studies considered the cost or cost-effectiveness of physical interventions using modelling exercises.[12-15] Given the distinct nature of the research questions in the studies and fundamental differences in the biology of the transmission of the individual pathogens, the individual studies were summarized.

Data collection studies

Murray (2010)[9]

The study was conducted to assess the impact of the use of facial protective equipment during a pandemic (H1N1) 2009 period at the Vancouver Coastal Health (VCH) services. The VCH services 1 million people and comprises three facilities: a tertiary care hospital (644 beds) and two community care hospitals (181 beds and 254 beds). Data were collected directly from the VCH central supply department on use of surgical masks, N95 respirators, and disposable eyewear by all patients admitted to the hospital with an influenza-like illness for the period from June 28, 2009 through December 19, 2009. The PHAC recommendations (2009) for use of facial protective equipment were used as the basis for PPE use.[16]

During the study period (24 weeks), 865 patients were admitted with suspected H1N1 influenza infection — 149 with laboratory-confirmed infection. Mean length of stay for laboratory-confirmed infection was 8.9 ± 12.1 days from date of specimen and a mean 9.2 ± 6.8 days in ICU. Patients with suspected infection had a mean 1.8 days in isolation, while those with confirmed infection had a mean 5.4 days in isolation — overall (confirmed and unconfirmed cases), the mean number of days in isolation was 2.4. When comparing resource use to the 2009 influenza season (weeks 1 to 14) and the same period in 2008 (weeks 27 to 51), resource use increased by 79% and 130%, respectively.
The authors noted a utilization ratio of 1:1 of masks to respirators per patient with laboratory-confirmed H1N1 infection during the study period. The resource use observed exceeded supply estimates from the WHO[3] by four-fold and the US by seven-fold.[17] However, WHO recommendations did differ from those of PHAC and the compliance with the recommendations is not known. When considering both confirmed and suspected cases, the authors estimated approximately 10 respirators and 10 masks per patient per day — or a mean of 200 respirators and 155 surgical masks per confirmed or suspected hospitalized case. Only 14 eyewear units per suspected or confirmed patient were observed, which was below the PHAC guidance and could in part be accounted for by use of reusable eyewear. Patient outcomes were found to be similar for the area covered by VCH, compared with other jurisdictions in Canada. While there was stockpiling of facial protective equipment based on Ministry of Health–dictated supplies (10-week supply), initial shortages of facial protective equipment were encountered, which could underestimate the use under sufficient supply conditions; however, this was not felt to significantly affect the estimates. Hospitals within the VCH group all have patients at high risk of contracting tuberculosis and resource use may thus be greater than in other facilities. There was significant variation in respirator use in the three hospitals. Costs and cost-effectiveness were not considered in this study.

Macartney (2000)[10]

The authors sought to evaluate the clinical and cost-effectiveness of infection control in the prevention of respiratory syncytial virus (RSV) nosocomial infection (NI) in a pediatric facility. The clinical benefits to the infection control program were evaluated for four seasons prior to the intervention (1989-1992) and four seasons after the intervention (1993-1996) in a 304-bed, pediatric hospital (Children's Hospital of Philadelphia). The control intervention included "contact precautions for all patients with symptoms of viral respiratory tract infection, consisting of hand washing before and after contact and the use of gloves and cotton cover gown by all staff for any physical interaction with a patient or the patient's

environment." Masks and protective eyewear were not used, and gown and glove use for visitors was not required. Resource use was determined by observing 10 isolated patients over a 24-hour period in various wards. The financial burden of RSV (beyond the cost of personal protective equipment) was estimated by comparing the hospital charges for 30 cases with 30 matched inpatients without RSV (controls). The authors estimated mean length of stay attributed to RSV NI to be 7.8 days (with sensitivity analyses ranging from 3.5 to 10.7 days). Resource use was estimated at 52 gloves per patient day and 15 gowns per patient day. Limitations with this study for the purpose of this review are as follows: the generalizability of RSV to pandemic respiratory viruses is limited; the resource use study was conducted in 10 patients; and the data were from 1996, which may no longer reflect current practice.
Costs were then calculated based on unit costs (USD 1996) by multiplying the number of predicted patient days and adjusting for compliance. The authors report that the mean cost of gloves per RSV season is $3,335 with a range of $2,223 to $4,446, based on sensitivity analysis. Similarly for gowns, the predicted mean cost per RSV season is $7,759, with a range of $5,173 to $10,345. The total cost, including personnel, materials, and RSV testing, was estimated to be $15,627, with a range of $9,418 to $24,577.

Simulation exercises

Phin (2009)[11]

A simulation exercise was conducted to look at the use of PPE for a 24-hour period on a typical general medical ward, during an influenza pandemic period in the UK. The purpose of the study was to "identify operational issues and to quantify PPE usage around the provision of cohorted care to influenza patients." Operational issues and PPE usage were in accordance with Department of Health, England and Health Protection Agency infection control guidance to the National Health Service (2007).[18] The ward in the study had 29 beds and a total complement of nursing staff (14 nurses, five health care assistants, four domestic staff). The simulated ward was assumed to be operating during the height of the influenza pandemic period to provide cohorted care (i.e., isolation) for patients with confirmed and suspected influenza. Staff were required to wear PPE consistent with the national guidance, and the amount of PPE use was recorded hourly. During the simulation period, the following units were used (rounded to the nearest 50): surgical masks (650), gloves (1,200 pairs), disposable aprons (750), gowns (13), FFP3 respirators (13), eye goggles (13), and visor (one), in addition to background use of PPE. A total of 167 visits were made by 115 different hospital personnel. Patients' visitors were not included in the exercise, and this could result in an underestimation of the use of PPE. Limitations are as follows: the exercise was run only for a 24-hour period; health care workers might be more proficient with PPE after continued use (i.e., it was observed that tasks and routine procedures took longer than usual) or if compliance decreases; and compliance with recommendations was not directly measured. The authors compared the results with expected use of PPEs based on the WHO guidance[3] and found that higher-level PPE (e.g., FFP3 respirators, visors, or goggles) use was less in the exercise, while basic PPE was greater. The authors stated that they felt this arose from the practicalities of dealing with a pandemic situation. Costs and cost-effectiveness estimates were not considered in this study.

Dan (2009)[12]

The authors sought to assess the cost-effectiveness of different levels of infection control in a hospital setting in response to an epidemic respiratory virus threat, such as H1N1, over a 30-day period. The different levels of infection control prevention were provided by Singapore's Ministry of Health,[19] which correlated roughly with the WHO Pandemic Response System.[20] Costs were obtained from actual financial charges for patients treated during the 2009 H1N1 pandemic obtained from Operations and Finance Departments of hospitals in Singapore. Clinical parameters (such as influenza virulence, rate of transmission, incubation period, and second attack rate) were obtained from various sources and tested extensively in sensitivity analyses. The authors considered SARS, H1N1, and Spanish influenza separately in their analyses. They reported the number of patients infected, number of deaths, and costs. Cost-effectiveness was reported as incremental cost per case prevented and incremental cost per death avoided. The authors found that isolation of infected patients and selective use of PPE was associated with an attractive cost-effectiveness ratio. Results were sensitive to choices of clinical input parameters, specifically exposure rate, secondary attack rate, case-fatality ratio, and risk of transmissions from atypical cases. The authors found that the incremental cost-effectiveness ratios increased with higher levels of infection control prevention for H1N1 and Spanish flu, while the incremental cost-effectiveness ratio varied for SARS, with higher levels of infection control precautions potentially as cost-effective options. The cost-effectiveness ratios could not be replicated based on the data reported. Results were not reported in a disaggregated manner at the level of resources used.

Perloth (2010)[13]
The authors developed a model to simulate the effects of three social-distancing strategies (social distancing, household quarantine, and school closure) and two antiviral medical strategies (antiviral treatment and prophylaxis), and multi-layering among the strategies to mitigate an influenza pandemic for a US community. The model focuses on the contacts between persons. The model considers the spread of influenza in a community of 10,000 people, centred on the school system. The authors state the results could be generalizable to a larger setting, assuming similar demographics, social networks, and contact rates. Information on influenza progression, resource use, costs of treatment, and health utilities was obtained from published literature. Information on medical costs was largely obtained from a published article by Molinari, [21] which evaluated the annual impact of seasonal influenza in the US based on health insurance claims. The cost per case averted was less than $35,000 (2009 USD) for the three social-distancing strategies: $5,600 for social distancing, $15,300 for quarantine, and $32,100 for school closure. However, when considering all possible multi-layering strategies, a combination of social distancing, school closure, and antiviral treatment and prophylaxis was found to be dominant (associated with greater clinical benefits and fewer costs). The results were sensitive to the rate of infection and the case-fatality rate. The authors identified the following limitations with their study: the results may be limited to suburban communities (rather than densely populated urban centres); results for social-distancing interventions are based on the assumption that communities are able to restrict social contact; and long-term outcomes were not considered. Results were not reported in a disaggregated manner at the level of resources used.

Gupta (2005)[14]
The objective of this study was to assess the economic impact of widespread quarantine in Toronto (Ontario, Canada) during the SARS outbreaks in 2003. Two public health scenarios were considered in a transmission model: no significant intervention (SARS is transmitted in population), and quarantine is implemented early (where quarantine was defined as "separation and/or restriction of movement of persons," and applies not only to people who are ill but those who have been exposed to the infection). The model was populated largely using data from "other researchers, the popular press, and interviews with those involved in the Toronto outbreaks in order to make educated estimates about the unknown or uncertain variables." Educated estimates applied to clinical as well as economic input parameters. The analysis was sensitive to rate of contact and transmission rates. The authors report that the total cost associated with SARS is $72 million ($48 million direct and $24 million indirect costs), while the total costs when widespread quarantine is implemented are $12.2 million ($12 million direct and $0.2 million indirect costs). Implementing quarantine during the outbreak of SARS resulted in a total cost savings of $59.8 million. Costs were reported in 2003 Canadian dollars. Results were not reported in a disaggregated manner at the level of resources used.

Putthasri (2009)[15]
The authors of this study sought to evaluate the resources and capacity of the health care system in Thailand to contain an influenza pandemic, by assessing the current level of resource available (through surveys to health care institutions and providers in various provinces) and estimating likely resources required, to provide information on gaps. The information for this study was obtained largely from survey

information that was used in simulation exercises using control scenarios developed by Thailand's Department of Disease Control (scenarios align with WHO Phase 4, human-to-human transmission from case-patients to caregivers, and WHO Phase 5, human-to-human transmission in localized clusters)[22] to derive the likely resources required to control an outbreak. The authors reported the total expected resource use for a pandemic influenza: disposable gowns = 1,377; N95 masks = 7,181; surgical masks = 16,440; plastic face shields = 567; goggles = 961; and surgical gloves = 66,201. The key limitations with this study were that the scenarios were based on individual experiences rather than defined standards of guidelines, and it did not provide the results for the specific scenarios. Costs and cost-effectiveness were not considered in this study.

GRADE Resource Use Tables

The GRADE resource use tables are found in Appendix 1. These tables include the resource use for the physical interventions employed to interrupt or reduce the spread of respiratory viruses.

GRADE guidance on the evaluation of economic and resource use information was used in creating the GRADE resource use tables[8] (Brunetti M, et al. Unpublished data [GRADE Guidelines: 11. Special Challenges — quality of evidence for resource use. 2011]). Given the limited number of studies specifically reporting resource use, individual GRADE tables were created for each of the seven studies that met the inclusion criteria for this work. As the studies evaluated different types of respiratory viruses, physical interventions, patient settings, and patient populations, the information was considered separately. The key studies for the purpose of resource use reporting were by Murray,[9] Phin,[11] and Macartney.[10]

In general, studies were subject to downgrading because of their observational nature (lack of control group). As a result, the quality of all seven studies was rated as "very low," given the potential for bias in the study design. Details in each of the GRADE tables provide context for interpreting the results of the studies. The following is a brief overview of each of the GRADE tables found in Appendix 1.

Murray (2010)[9]: In general, the study was well conducted, with no serious concerns for other quality assessment aspects. A limitation would be the observational design, which limits the comparison. In terms of generalizability, resource use was based on PHAC recommendations and utilization observed in three facilities comprising the Vancouver Coast Health region. Further, the resource use information was specific to a hospital setting and for the 2009 H1N1 pandemic period (Table 1A).

Macartney (2000)[10]: The authors considered the clinical effects, resource use, and costs associated with interventions for infection control, reporting the results in a disaggregated manner. Given the design of the clinical study, with data captured pre- and post-intervention, the study was downgraded to "low" quality. Resource use was based only on an assessment of 10 patients over 24 hours in a pediatric facility. Issues regarding indirectness and imprecision led to a further downgrading to "very low" for the resource use data. In addition, the generalizability of the information to pandemic respiratory viruses is uncertain (Table 1B).

Phin (2009)[11]: This study considered resource use in a simulated exercise during a 24-hour period. The observational nature of this study resulted in it being downgraded. Further, the exercise was conducted during a period that did not coincide with an influenza pandemic; this 24-hour period did not allow for participants to acclimate to the setting (potential inefficiencies with new protocols); the setting was a cohorted (or isolated) ward with 29 beds and subject to small numbers (potential for imprecision); and the Department of Health, England guidance was considered, which may not be generalizable to other jurisdictions (Table 1C).

The other four studies were based largely on modelling exercises with clinical and economic inputs obtained from a number of sources. The results of the studies were reported in terms of clinical benefits from physical interventions and total costs, and in two of the studies, cost-effectiveness ratios were calculated.[12,13] The study by Dan[12] was downgraded primarily because of the use of observational studies (clinical) and the limited information provided on the derivation of costs. There are inherent limitations with modelling exercises, such as the need for numerous data inputs often requiring assumptions that cannot be validated, and the need for extensive sensitivity analyses. The potential lack of generalizability of the study (based largely on data specific to Singapore) is noted (Table 1D, parts i-iii). The study by Perloth[13] was based on a number of published sources (observational in nature), for clinical, cost, and quality of life information (Table 1E). Gupta[14] used information from other researchers, the popular press, and interviews, in the absence of clinical trials or published economic evaluations. The quality of the evidence was downgraded because of the extensive use of interviews, which are prone to recollection bias (Table 1F). The basis for the Putthasri[15] study was survey data that were lower in quality in the hierarchy of observational studies and were downgraded accordingly. Further, a key limitation with the study was that the results were not reported in a disaggregated manner, by severity of pandemic level (Table 1G).

Given the differences in the research questions examined by the seven included economic evaluations, the fundamental differences in the biology of transmission of the pathogens studied, and the heterogeneity of the studies, the summary of the results of the systematic review in one GRADE evidence profile was not deemed to be appropriate for the purpose of this study. While summarizing studies in one table, is the standard approach when applying GRADE, the researchers felt that the individual GRADE profiles would better address specific respiratory viruses, interventions, and study designs to ensure clarity and best meet the needs of the readership.

7 DISCUSSION

The work described in this report represents the second component of a two-part project. The first part was the updating of a Cochrane Review[4] on the physical interventions to interrupt or reduce the spread of respiratory viruses. This second part focuses on the economic information and, more specifically, resource use. This was of interest as Cochrane Reviews do not consider economic information.

The detailed Cochrane Review on the efficacy of physical interventions to interrupt or reduce the spread of respiratory viruses was updated. Four authors of this review (CPS, JC, VS, KL) prepared GRADE evidence tables as part of the Cochrane Review. According to the analyses using GRADE methodology, the results suggest that physical interventions to interrupt or delay the spread of virus using personal protective equipment (such as masks, gowns, gloves, or eye protection) are effective in protecting against viral transmission. The quality of evidence was very low.

The information presented in this report focuses on resource use associated with the use of physical interventions, with the inclusion of economic implications (such as costs and cost-effectiveness estimates) to supplement the findings. Three studies provide information on resource use alone,[9,11,15] which is difficult to interpret without the context of the clinical benefits, and based on the compliance with recommendations on PPE use provided by public health agencies. In general, the use of PPE increases during pandemic, and epidemic, periods. According to the Cochrane Review, simple, low-cost interventions — such as frequent hand hygiene and, when indicated, wearing masks, gloves, and gowns — and the use of these interventions in combination reduce the risk of spread of some respiratory viruses by approximately 70% to 90%, depending upon the intervention and combination of these interventions (odds ratio for infection: 0.09 to 0.45). The studies included in the review evaluated interventions for different respiratory infections (largely SARS) with different modes of transmission, different settings, and different epidemiological situations. Due to these variations, the effect size of intervention may vary depending upon the circumstances. However, given the overall (large) range of effect size, it is likely that if this data were included in an economic evaluation, these low-cost interventions would result in an attractive cost-effectiveness ratio. This was beyond the scope of the current project but represents an area of possible future research.

Of note, the pathogens considered in the Cochrane Review, as well as in the published economic evaluations, may be associated with different rates and modes of transmission. As a result, individual PPE items may differ in terms of the level of importance, depending on the pathogen. This has not been fully explored in the scope of this report.

The three economic studies that reported cost-effectiveness[10,12,13] found that the use of physical interventions was in general economically attractive, with cost-effectiveness improving with higher risk pandemics or epidemics (i.e., higher rates of transmission). Dan[12] found that when comparing Green level PPE protection to Green 0 level[a] in hospital, the incremental cost per death prevented was less than US$25,000. The movement to higher levels of precautions (Yellow, enforced protection in high-risk areas, and Orange, protection throughout hospital)[b] was found to be less cost effective, with the incremental cost-effectiveness ratio increasing as high as $827,000 when comparing Yellow with Green levels, and above $2 million when comparing Orange with Yellow, for H1N1. When considering the incremental cost per case averted, the cost-effectiveness ratios were generally less than $10,000. Given the use of antivirals in levels above Green 0, the exclusion of harms associated with antivirals may underestimate the costs, which would lead to greater cost-effectiveness estimates. Perloth[13] considered the use of various mitigation strategies in the community and found that results were dependent on the fatality rate, transmission rate, and compliance with the strategies. Of specific interest was the consideration of quarantine, social distancing, and school closure, which were found to have an incremental cost per case averted of $15,300, $5,600, and $32,100, respectively, when compared with "doing nothing." The authors found that a multi-layered approach of social distancing, school closure, and antiviral therapy (treatment and prophylaxis) was the dominant strategy in their analysis. Macartney[10] reported that a hospital program to reduce the spread of RSV (targeted control program including laboratory testing, cohorting, and glove and gown use) resulted in a cost-effectiveness ratio of $1,563 per case averted. When considering the cost in terms of lost wages for caregivers, this may represent a reasonable cost from a societal perspective.

A finding from the studies by Murray[9] and Dan[12] is that PPEs may be overused and inappropriately used when faced with a new pandemic. While appropriate use of PPEs is largely seen as cost effective, where recommended use is not adhered to and overuse occurs, this could lead to PPEs not being cost effective.

Using the GRADE methodology, the economic evaluations were graded as "very low" quality. The components within each economic study were evaluated (clinical data, cost and/or resource use information, and quality of life information). The clinical data used in these studies tended to be observational in nature and were downgraded because of indirectness. Similarly, resource use and cost studies were observational in nature, had issues regarding indirectness, and in some cases, limitations in imprecision as a result of small sample sizes. Where studies were based on modelling exercises, the results were subject to the same limitations as the inputs, but in some cases, the sensitivity of the results to changes in key parameters affected the confidence that could be placed on the study results (imprecision). In all cases, the economic studies sought to answer specific questions, and as a result, there were only single studies available for the assessment of physical interventions for use in specific respiratory viruses, which could result in a risk of publication bias.

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[a] Green level PPE was defined as full PPE for suspected cases and all suspected cases to be isolated, tracing contacts and antiviral treatment for confirmed cases. Green 0 level (or no additional measures) was defined as triage and isolation of patients, and use of PPE as appropriate at health care institutions.
[b] Yellow level was defined as for PPE for health care workers in high-risk contact tracing for confirmed cases, visitor restriction, restricted movement of patients and health care workers. Orange level was defined as full personal protective equipment for health care workers in high-risk contact (including N95 masks, gloves, gowns, and eye protection), visitor restriction, no inter-hospital movement of patients or health care workers, and prophylaxis for contacts.

This review is subject to a number of limitations. While numerous economic evaluations in the area of respiratory viruses have been published, the purpose of many has been to evaluate the use of antivirals in treatment or prevention. Only a few economic studies evaluating physical interventions are available, and this might largely be due to the lack of sponsorship for these studies. Of the studies published, a small number have specifically reported resource use in their publications. Where studies have considered the use of antivirals in the assessment of PPEs, the failure to consider harms (which is an emerging area of understanding) could significantly underestimate the cost-effectiveness.

Given the limited information on resource use associated with physical interventions in the interruption or reduction of the spread of respiratory viruses, information about the use of various physical interventions for specific respiratory viruses (SARS, H1N1, Spanish influenza, and influenza) is sparse. Whether results can be generalized among respiratory virus type needs to be evaluated. Similarly, because the majority of the evidence pertains to hospital populations rather than communities, assessment on how these results might be applied to the community setting requires further investigation. This review suggests that further studies on resource use and economic implications associated with PPE are needed for various respiratory viruses.

Studies measuring resource use (Murray,[9] Macartney[10]) were based on local recommendations or guidelines, which could affect the generalizability of the results. The results of the studies are difficult to apply to other jurisdictions, as they tended to be based on specific recommendations (PHAC; Department of Health, England) and in some cases were applied in a manner specific to the interests of the jurisdiction or facility.

The economic studies evaluated different specific research questions, which may not directly inform this review. Given the differences in these studies, in most cases the results could not be directly compared. This complicates the assessment of consistency, given the uniqueness of the studies.

This study on resource use was conducted alongside the update of a Cochrane Review assessing the clinical evidence for physical interventions to interrupt or reduce the spread of respiratory viruses. The combination of the clinical findings from the Cochrane Review and the economic information gleaned from this systematic review could be considered for future work. This review found that economic evaluations exist to evaluate some physical interventions, but they are limited by the availability of clinical information to populate the input parameters (transmission rates, case fatality, and compliance). Resource use and economic implications are important considerations in understanding the potential financial burden of recommending the use of personal protective equipment, both in terms of the resources required and health care resource use that may be avoided through the reduction of infected cases and complications.

8 CONCLUSIONS

Based on the published economic evaluations and clinical studies, it appears that use of physical interventions to interrupt or reduce the spread of respiratory viruses increases during epidemics and pandemics. This is likely in part because local or WHO guidelines on the use of personal protective equipment and isolation were followed. Based on the updated Cochrane Review, it appears that these measures are effective at reducing the spread of viruses. Given the general low cost of these interventions, based on the economic studies reviewed, PPEs appear to be an economically attractive option for reducing the burden of respiratory viruses. These results are sensitive to assumptions regarding the rate of transmission, facility infection rate, and compliance with the interventions, with the economic attractiveness increasing when transmission is high and fatality rate is high. Where guidelines for PPE use are not followed, and inappropriate use of PPEs occurs (i.e., increased use resulting from fear of a new pandemic), this could increase the cost-effectiveness estimates.

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APPENDIX 1: GRADE RESOURCE USE TABLES

Author(s): Karen Lee, MA; Vijay Shukla, PhD; **Reviewer(s)**: John Conly, MD; Carmem Pessoa-Silva, MD, PhD
Date: 2011-03-24
Question: What is the impact of H1N1 on the use of facial masks and eyewear equipment use?
Settings: Hospital setting
Bibliography: Murray et al. Facial protective equipment, personnel, and pandemic: impact of the pandemic (H1N1) 2009 virus on personnel and use of facial protective equipment. Infect Control Hosp Epidemiol 2010; 31(10):1011-1016

TABLE 1A

	Quality Assessment						**Use of Physical Interventions In Pandemic Year (2009)**			
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mean resource use per case[2,3,4]**	**Mean resource use per case per isolation day[5]**	**Quality**	**Comment**
Impact and use of personal facial protective equipment (follow-up mean 6 months[1]; assessed with: Resources)										
Resources used	Observational studies	Very serious[2]	No serious inconsistency	Very serious[6]	No serious imprecision	None	Surgical masks 155 N95 200 Eyewear 14	Surgical masks 64 N95 82 Eyewear 6	⊕OOO **VERY LOW**	• In adherence with 2009 PHAC recommendations to use surgical masks and protective eyewear within 2 m of patients with influenza-like illness and the use of N95 respirator during any aerosol-generating medical procedure • Setting: VCH (serving 1 million; 3 facilities: 1,079 beds); 865 suspected and confirmed cases over 2009 pandemic period • Estimates of resource use obtained from VCH central supply department

PHAC = Public Health Agency of Canada; VCH = Vancouver Coastal Health.

[1] Patients in hospital followed during the pandemic period from June 28 through Dec 19, 2009 (weeks 27 to 51).
[2] Longitudinal real-world follow-up study with no control group.
[3] Resources have been calculated and reported as the mean unit per hospitalized case, confirmed or suspected (n=865), as requested by WHO.
[4] Mean length of stay for patients during this time period was 8.9 days for confirmed cases, and 1.8 days of isolation for suspected cases (5.4 days for confirmed cases).
[5] Resources have been reported as the mean unit per day of isolation of confirmed or suspected cases (n= 2,101) of 1.8 days.
[6] Resource use based on Public Health Agency of Canada recommendations, which are specific to Canada and may not be generalizable to other jurisdictions, although the authors feel the results are in line with other jurisdictions for this time period. The authors note that actual resource use differs from recommendations (i.e., higher than expected), but have provided details for why this might have occurred.

Author(s): Karen Lee, MA; Vijay Shukla, PhD; **Reviewer(s)**: John Conly, MD; Carmem Pessoa-Silva, MD, PhD
Date: 2011-04-19
Question: Should Infection control interventions be used for spread of respiratory syncytial virus (RSV) nosocomial infection (NI)?
Settings: Hospital
Bibliography: Macartney et al. Nosocomial respiratory syncytial virus infections: The cost-effectiveness and cost-benefit of infect control. Pediatrics 2000; 106(3):520-526.

TABLE 1B

	Quality Assessment						No. of Patients or Units		Effect	Quality	Comment
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Infection control interventions**	**Control**			
Nosocomial RSV infections (follow-up mean 8 seasons[1]; measured with: infection per 1,000 days at risk; Better indicated by lower values)											
No. infected	Observational studies	Serious[2]	No serious inconsistency	No serious indirectness[3]	No serious imprecision	• Reporting bias[4] • Strong association[5] • Dose response gradient[6]	2065[7]	1604[8]	10 infected cases per season[9] 40 cases	⊕⊕OO **LOW**	
Resource use	Observational study	Small sample (N = 10) over 24 hours	Single study	Serious[10,11]	Serious[12]	None	Gloves 52/pt day	-	NA	⊕OOO **VERY LOW**	• Gloves mean cost per RSV season $3,335 (sensitivity analyses: $2,223 to $4,446)[13] • Gowns mean cost per RSV season $7,759 (sensitivity analyses: $5,173 to $10,345) • TOTAL (includes personnel, materials, RSV tests): $15,627 (sensitivity analyses: $9,418 to $24,577) • PPE recommendations included gloves and gown when caring for patients
							Gowns 15/pt day	-	NA		
							Length of stay 25.8-31.9 days	20.2-22.5	NA		

	Quality Assessment						No. of Patients or Units		Effect	Quality	Comment
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Infection control interventions**	**Control**			
Nosocomial RSV infections (follow-up mean 8 seasons[1]; measured with: infection per 1,000 days at risk; Better indicated by lower values)											
Cost per infection prevented	Calculation[13,14]	Prone to same limitations as inputs	Prone to same limitations as inputs	Prone to same limitations as inputs	Prone to same limitations as inputs	None	-	-	$1,563 per infection prevented ($942 to $2,458)	-	

NA = not applicable; pt = patient; RSV = respiratory syncytial virus.

[1] Four seasons before interventions and four seasons after interventions.
[2] Before-after study subject to time bias.
[3] Study was not downgraded for indirectness due to its naturalistic design. Results cannot be applied to other viral infections and epidemic setting.
[4] Single study.
[5] Consistently lower infection rate observed post intervention.
[6] Study has demonstrated relationship between infection rate and RSV exposure strata.
[7] Number of patients hospitalized due to RSV NI post-intervention phase (860 infected per 82,196 patient days at risk).
[8] Number of patients hospitalized due to RSV NI pre-intervention phase (88 infected per 90,174 patient days at risk).
[9] Cases per 1,000 hospital-day exposure.
[10] Resource use associated with RSV may not be directly generalizable to pandemic respiratory viruses.
[11] Study was conducted specifically for a pediatric population.
[12] Resource use was based on 10 patients for a 24-hour period in 1996.
[13] Costs reported as 1996 USD. US $1 (1996) = US$1.35 (2011).
[14] Costs estimated resource use and hospital charges for financial burden of RSV.

Author(s): Karen Lee, MA; Vijay Shukla, PhD; **Reviewer(s)**: John Conly, MD; Carmem Pessoa-Silva, MD, PhD
Date: 2011-03-24
Question: Personal protective equipment used in 24 hours for influenza pandemic
Settings: Hospital
Bibliography: Phin et al. Personal protective equipment in an influenza pandemic: a UK simulation exercise. J Hos Infect 2009; 71(1):15-21

TABLE 1C

	Quality Assessment						Use of Physical Interventions[1]	Quality	Comment
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mean resource use per case[2,3]**		
PPE in an influenza pandemic (follow-up 24 hours; assessed with: PPE use)									
Resources used	Observational studies[4]	Very serious[5]	No serious inconsistency	Very serious[6,7]	Serious imprecision[8]	None	Surgical masks 22 Gloves 41 pairs Disposable apron 26 Gown 0.45 Eye goggles 0.45 FFP3 respirator 0.45 Visor 0.03	⊕OOO **VERY LOW**	• Methodology included a simple before and after comparison • Simulation ran over only 24 hours • Personal protective equipment based on Dept of Health (England) guidance for routine care in cohorted or isolated area (within 1 m), including surgical mask, gloves, and eye protection and gown if risk of splashes; use of gown, gloves, particulate respirator, and eye protection during aerosol generation procedure • Study did not take place during a pandemic period when RU will be ubiquitous and staff awareness heightened; this might alter compliance and consumption of PPE. • Based on a 29-bed acute medical ward used to provide cohorted care to influenza patients in a pandemic • Ward complement includes 14 nurses, 5 health case assistants, 4 domestic staff.

PPE = Personal protective equipment; RU = resource use.

[1] Resources have been reported as the mean unit per day per number of beds in the facilities (N = 29).
[2] Simulation exercise with no control group.
[3] Resources have been reported as the mean unit per isolated case (N = 29).
[4] A UK simulation exercise for 24 hours by all staff on an acute general medicine ward, who wore PPE and adopted the procedure described in UK pandemic influenza guidance.
[5] Simulation exercise without control group, subject to biases of observational studies.
[4] Simulation exercise in UK. Not clear whether the results will be valid in other jurisdictions, as this study represents a case for high-level respiratory precautions.
[6] Resource use based on Department of Health guidelines, which are specific to England and may not be generalizable to other jurisdictions.
[7] Sample size is very small. Data were obtained from 29 patients during a 24-hour period.

Author(s): Karen Lee, MA; Vijay Shukla, PhD; **Reviewer(s)**: John Conly, MD; Carmem Pessoa-Silva, MD, PhD
Date: 2011-03-24
Question: Cost-effectiveness Green 1 strategy versus Green 0 strategy for pandemics? [1]
Settings: hospital setting
Bibliography: Dan et al. Cost effectiveness analysis of hospital infection control response to an epidemic respiratory virus threat. Emerg Infect Dis 2009;15(2):1909-1916

TABLE 1D-i

	Quality Assessment						Outcome (No. of Patients or Cost)				
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Health care resources (Green)[1]**	**Control (Green 0; no additional measures)**	**Difference**	**Quality**	**Comment**
CEA of hospital infection control response to an epidemic respiratory virus threat (assessed with: Incremental cost per death averted by following Green strategy)											
No. infected	Observational studies[2]	Very serious[3]	No serious inconsistency	Very serious[3]	No serious imprecision	Very strong association[4]	H1N1: 316	2,580	(2,264)	⊕OOO **VERY LOW**	
							Spanish flu: 624	3,210	(2,586)		
							SARS: 105	825	(720)		
Deaths	Modelling exercise	Inherent limitations with modelling	Not considered; single study	Based on case-fatality data from Singapore	No ranges reported	None	H1N1: 1	10	(9)	⊕OOO **VERY LOW**	• Simulation exercise
							Spanish flu: 31	161	(130)		
							SARS: 11	83	(72)		
Cost[5]	Derived from operational costs	Details on costs inputs based alert policy not provided	Jurisdiction specific	Obtained from Singapore sources[6,7]	No ranges reported	None[8]	H1N1: $326,430	$25,200	$301,230	⊕OOO **VERY LOW**	• Costs reported in USD
							Spanish flu: $468,000	$80,000	$388,000		
							SARS: $220,500	$99,200	$121,300		
Cost per case prevented	Calculation	Prone to same limitations as inputs	Prone to same limitations as inputs	Prone to same limitations as inputs	Serious[9]	Minimal details were provided with respect to sensitivity analyses			H1N1: $133	-	• Results sensitive to rate of exposure, transmissibility, fatality rate, transmission from
									Spanish flu: $150		
									SARS: $168		

	Quality Assessment						Outcome (No. of Patients or Cost)		Difference	Quality	Comment
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Health care resources (Green)**[1]	**Control (Green 0; no additional measures)**			
CEA of hospital infection control response to an epidemic respiratory virus threat (assessed with: Incremental cost per death averted by following Green strategy)											
Cost per death avoided	Calculation	Prone to same limitations as inputs	Prone to same limitations as inputs	Prone to same limitations as inputs	Serious[9]	Minimal details were provided with respect to sensitivity analyses			H1N1: $33,470	-	atypical cases • Reported cost-effectiveness estimates could not be replicated. Values present recalculated estimates.
									Spanish flu: $2,985		
									SARS: $1,685		

CEA = cost-effectiveness analysis; SARS = severe acute respiratory syndrome; USD = US dollars.

[1] Singapore Ministry of Health evaluated the impact of different alert levels. Based on hospital measures, the levels are defined as follows: Green 0 (or no additional measures) = triage and isolation of patient, use of personal protective equipment as appropriate (WHO alert level 1); Green 1 = full PPE for suspected cases, tracing contacts for confirmed cases, and antiviral treatment for confirmed cases (WHO alert level 2-3).
[2] Impact of an outbreak from a single index case that was not detected by hospital surveillance and was found in general ward was modelled.
[3] Clinical data were generated by modelling of undetected single index case.
[4] A patient with undiagnosed infection at base case with no protection measure will result in 2580 infected patients at 30 days in this model.
[5] Costs reported in 2009 USD. US$1 (2009) = US$1.02 (2011)
[6] Resource use based on Disease Outbreak Response System and may not be generalizable to other jurisdictions.
[7] Costs were obtained from Operations and Finance Departments from hospitals; might not be reflective of other facilities. Limited information provided on methodology; information from direct charges and assumptions around indirect costs.
[8] Harms and attendant costs of antivirals were not included, nor was the use of antiviral prophylaxis.
[9] Analyses sensitive to case-fatality rate, exposure rate, and secondary attack rate.

Author(s): Karen Lee, MA; Vijay Shukla, PhD; **Reviewer(s)**: John Conly, MD; Carmem Pessoa-Silva, MD, PhD
Date: 2011-03-24
Question: Cost-effectiveness of Yellow strategy versus Green 1 strategy (no additional measures) for pandemics?
Settings: Hospital setting
Bibliography: Dan et al. Cost effectiveness analysis of hospital infection control response to an epidemic respiratory virus threat. Emerg Infect Dis 2009;15(12):1909-1916

TABLE 1D-ii

	Quality Assessment						**Outcome (No. of Patients or Cost)**				
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Health care resources (Yellow)**[1]	**Control (Green 1)**	**Difference**	**Quality**	**Comment**
CEA of hospital infection control response to an epidemic respiratory virus threat (assessed with: Incremental cost per death averted by following Yellow strategy)											
No. infected	Observational studies[2]	Very serious[3]	No serious inconsistency	Very serious[4]	No serious imprecision	Very strong association[7]	H1N1: 59	316	(257)	⊕OOO **VERY LOW**	
							Spanish flu: 120	624	(504)		
							SARS: 43	105	(62)		
Death	Modelling exercise	Inherent limitations with modelling	Not considered; single study	Based on case-fatality data from Singapore	No ranges reported	None	H1N1: 0.2	1	(0.8)	⊕OOO **VERY LOW**	• Simulation exercise
							Spanish flu: 6	31	(25)		
							SARS: 4	11	(7)		
Cost[5]	Derived from operational costs	Details on cost inputs-based alert policy not provided	Jurisdiction specific	Obtained from Singapore sources[6,7]	No ranges reported	None[8]	H1N1: $1,485,500	$326,430	$1,159,070	⊕OOO **VERY LOW**	• Costs reported in USD
							Spanish flu: $2,212,000	$468,000	$2,468,000		
							SARS: $1,188,000	220,500	$967,500		
Cost per case prevented	Calculation	Prone to same limitations as inputs	Prone to same limitations as inputs	Prone to same limitations as inputs	Serious[9]	Minimal details were provided with respect to sensitivity analyses			H1N1: $3,221	-	• Results sensitive to rate of exposure, transmissibility, fatality rate, transmission from atypical cases
									Spanish flu: $2,472		
									SARS: $11,146		

	Quality Assessment						Outcome (No. of Patients or Cost)				
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Health care resources (Yellow)[1]**	**Control (Green 1)**	**Difference**	**Quality**	**Comment**
CEA of hospital infection control response to an epidemic respiratory virus threat (assessed with: Incremental cost per death averted by following Yellow strategy)											
Cost per death avoided	Calculation	Prone to same limitations as inputs	Prone to same limitations as inputs	Prone to same limitations as inputs	Serious[9]	Minimal details were provided with respect to sensitivity analyses			H1N1: $827,907	-	• Reported cost-effectiveness estimates could not be replicated. Values present recalculated estimates.
									Spanish flu: $49,829		
									SARS: $121,241		

CEA = cost-effectiveness analysis; PPE = personal protective equipment; SARS = severe acute respiratory syndrome.

[1] Singapore Ministry of Health evaluated the impact of different alert levels. Based on hospital measures, the levels are defined as follows: Green 1 = full PPE for suspected cases, tracing contacts for confirmed cases, and antiviral treatment for confirmed cases (WHO alert level 2-3); Yellow = PPE for health care workers: for middle-risk PPE, included N95 mask, gown, and gloves (eye protection if risk of splashes); PPE including N95 mask in all patient areas, and gown and gloves, and eye protection if risk of splashes; if high-risk activity (high probability of close contact to aerosol-generating procedures), then PPE included N95 mask in all patient areas, and gown and gloves, and eye protection if contact tracing for confirmed cases, visitor restriction, restricted movement of patients and health care workers (WHO Alert level 4).
[2] Impact of an outbreak from a single index case that was not detected by hospital surveillance and was found in general ward was modelled.
[3] Clinical data were generated by modelling of undetected single index case.
[4] A patient with undiagnosed infection at base case with no protection measure will result in 2,580 infected patients at 30 days in this model.
[5] Costs reported in 2009 USD. US$1 (2009) = US$1.02 (2011).
[6] Resource use based on Disease Outbreak Response System and may not be generalizable to other jurisdictions.
[7] Costs were obtained from Operations and Finance Departments from hospitals; might not be reflective of other facilities. Limited information provided on methodology; information from direct charges and assumptions regarding indirect costs.
[8] Harms and attendant costs of antivirals were not included; nor was the use of antiviral prophylaxis.
[9] Minimal details were provided with respect to sensitivity analyses.

Author(s): Karen Lee, MA; Vijay Shukla, PhD; **Reviewer(s)**: John Conly, MD; Carmem Pessoa-Silva, MD, PhD
Date: 2011-03-24
Question: Cost-effectiveness of Orange strategy versus no additional measures for pandemics?
Settings: Hospital setting
Bibliography: Dan et al. Cost effectiveness analysis of hospital infection control response to an epidemic respiratory virus threat. Emerg Infect Dis 2009;15(12):1909-1916

TABLE 1D-iii

	Quality Assessment						Outcome (No. of Patients or Cost)		Difference	Quality	Comment
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Health care resources (Orange)** [1]	**Control (Yellow)**			
CEA of hospital infection control response to an epidemic respiratory virus threat (assessed with: Incremental cost per death averted by following Orange strategy)											
No. infected	Observational studies[2]	Very serious[3]	No serious inconsistency	Very serious[4]	No serious imprecision	Very strong association[4]	H1N1: 24	59	(35)	⊕OOO VERY LOW	
							Spanish flu: 59	120	(61)		
							SARS: 12	43	(31)		
Death	Modelling exercise	Inherent limitations with modelling	Not considered — single study	Based on case-fatality data from Singapore	No ranges reported	None	H1N1: 0.1	0.2	(0.1)	⊕OOO VERY LOW	• Simulation exercise
							Spanish flu: 2.95	6	(3.05)		
							SARS: 1.2	4	(2.8)		
Cost[5]	Derived from operational costs	Details on costs inputs based alert policy not provided	Jurisdiction specific	Obtained from Singapore sources[6,7]	No ranges reported	None[8]	H1N1: $1,836,000	$1,485,500	$350,500	⊕OOO VERY LOW	• Costs reported in USD
							Spanish flu: $2,856,000	$2,212,000	$644,000		
							SARS: $1,537,000	$1,188,000	$349,000		
Cost per case prevented	Calculation	Prone to same limitations as inputs	Prone to same limitations as inputs	Prone to same limitations as inputs	Serious[9]	Minimal details were provided with respect to sensitivity analyses			H1N1: $7,153	-	• Results sensitive to rate of exposure, transmissibility, fatality rate, transmission from atypical cases
									Spanish flu: $7,541		
									SARS: $8,041		

	Quality Assessment						Outcome (No. of Patients or Cost)				
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Health care resources (Orange)** [1]	**Control (Yellow)**	**Difference**	**Quality**	**Comment**
CEA of hospital infection control response to an epidemic respiratory virus threat (assessed with: Incremental cost per death averted by following Orange strategy)											
Cost per death avoided	Calculation	Prone to same limitations as inputs	Prone to same limitations as inputs	Prone to same limitations as inputs	Serious[9]	Minimal details were provided with respect to sensitivity analyses			H1N1: $2,503,600	-	• Reported cost-effectiveness estimates could not be replicated. Values present recalculated estimates.
									Spanish flu: $153,333		
									SARS: $7,541		

CEA = cost-effectiveness analysis; PPE = personal protective equipment; SARS = severe acute respiratory syndrome; USD = US dollars.

[1] The Singapore Ministry of Health evaluated the impact of different alert levels. Based on hospital measures, the levels are defined as follows: Yellow = PPE for health care workers: for middle-risk, PPE included N95 mask, gown, and gloves (eye protection if risk of splashes), PPE including N95 mask in all patient areas, and gown and gloves, and eye protection if risk of splashes; if high-risk activity (high probability of close contact to aerosol-generating procedures), then PPE included N95 mask in all patient areas, and gown and gloves, and eye protection; if contact tracing for confirmed cases, visitor restriction, restricted movement of patients and health care workers (WHO Alert level 4). Orange: for middle risk, PPE included N95 mask, gown, and gloves (eye protection if risk of splashes); full PPE for health care workers in high-risk contact (high probability of close contact to aerosol-generating procedures), including N95 mask, gown and gloves, and eye protection, and visitor restriction; no inter-hospital movement of patients or health care workers, prophylaxis for contacts (WHO Alert level 5).
[2] Impact of an outbreak from a single index case that was not detected by hospital surveillance and was found in general ward was modelled.
[3] Clinical data are generated by modelling of undetected single index case.
[4] A patient with undiagnosed infection at base case with no protection measure will result in 2,580 infected patients at 30 days, based on this model.
[5] Costs reported in 2009 USD. US$1 (2009) = US$1.02 (2011).
[6] Resource use based on Disease Outbreak Response System and may not be generalizable to other jurisdictions.
[7] Costs were obtained from hospital operations and finance departments; might not be reflective of other facilities. Limited information provided on methodology; information from direct charges and assumptions regarding indirect costs.
[8] Harms and attendant costs of antivirals were not included; nor was the use of antiviral prophylaxis.
[9] Minimal details were provided with respect to sensitivity analyses.

Author(s): Karen Lee, MA; Vijay Shukla, PhD; **Reviewer(s)**: John Conly, MD; Carmem Pessoa-Silva, MD, PhD
Date: 2011-03-24
Question: Social interventions in the community and hospital to reduce the spread of influenza pandemic.
Settings: Community/hospital setting
Bibliography: Perlroth et al. Health outcomes and cost of community mitigation strategies for an influenza pandemic in the US. Clin Infect Dis 2010; 50(2):165-74

TABLE 1E

	Quality Assessment						Health Care Resources[1]				Quality	Comment
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Social distancing**	**Quarantine**	**School closure**	**Do nothing**		
Resource use using social network agent based model[2] (assessed with: Cost per QALY)												
Cases	Observational studies[2]	Very serious[2]	No serious inconsistency	Very serious[2]	No serious imprecision	Assumed infection rate of 2.1	3,212	3,317	3,169	3,515	⊕OOO **VERY LOW**	
Total cost[3] (per person)	Observational study[4]	Very serious[5]	No serious inconsistency	• Based on US study of influenza tmt[6] • Pneumonia and influenza ICD-9 codes	None[7]	None	$420	$720	$1,330	$540	⊕OOO **VERY LOW**	• Costs based on 2007 study of Medstat Marketscan database for 2001-2003 • Costs were reported by age and risk group.
Quality adjusted life expectancy	Modelling exercise	Inherent limitations with modelling	Not considered – single study	May not accurately reflect loss in quality with influenza	Disutilities may be over-estimated	None[8]	20.159	20.158	20.161	20.153	⊕OOO **VERY LOW**	• Utility values based on published literature. Some disutilities associated with influenza symptoms appear large, potentially overestimating quality adjustment.

	Quality Assessment						Health Care Resources[1]				Quality	Comment
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Social distancing**	**Quarantine**	**School closure**	**Do nothing**		
Resource use using social network agent based model[2] (assessed with: Cost per QALY)												
Cost per case averted	Calculation	Prone same limitations as inputs	Prone same limitations as inputs	Prone same limitations as inputs	Serious[9]	None	$5,600	$15,300	$32,100	-	–	• Model based on previously developed model (agent-based, social network) • Assume case-fatality rate of 1%.
Cost per QALY	Calculation	Prone same limitations as inputs	Prone same limitations as inputs	Prone same limitations as inputs	Serious[9]	None	Dominant[10]	$36,000[10]	$98,750[10]	-	–	

QALY = quality-adjusted life-year; USD = US dollars.

[1] Study considered multi-layering interventions, but only the individual interventions have been reported in this table. When considering all treatment strategies and multi-layering options, social distancing, school closure, and antiretroviral treatment and prophylaxis were found to be dominant over all other multi-layer and single treatments.
[2] Modelling-based study. Data on different interventions, such as social distancing, school closure, household quarantine and antiviral treatment, taken from different sources to feed into model.
[3] Costs reported in 2009 USD. US$1 (2009) = US$1.02 (2011)
[4] Molinari N-A et al. The annual impact of seasonal influenza in the US: Measuring disease burden and cost. Vaccine 2007;25:5086-5096.
[5] Database study subject to bias due to lack of randomization. Large sample of claims were used (N = 179,718) to address potential biases and uncertainty.
[6] Resource use based on US study and may not be generalizable to other jurisdictions.
[7] Dataset included 179,718 medically attended cases from four influenza seasons (2000-2001,2001-2002, 2002-2003, 2003-2004) involving outpatient treatment, hospitalization, or death.
[8] Harms and attendant costs of antivirals were not included in reported values.
[9] Results were sensitive to infection rates, case-fatality rate, compliance. Results were sensitive to changes in parameters with cost per QALY estimates increasing to over $150,000 (compared with < $32,000 in the base case) when case fatality = 0.25% and infection rate is reduced to 1.6.
[10] Incremental cost per QALY estimates reported compared with doing nothing. Note, in study, all three options (quarantine, school closure, and social distancing) were ruled out by extended dominance compared with multi-layering treatment options.

Author(s): Karen Lee, MA; Vijay Shukla, PhD; **Reviewer(s)**: John Conly, MD; Carmem Pessoa-Silva, MD, PhD
Date: 2011-03-24
Question: Economic impact of quarantine in the community during SARS.
Settings: Community/hospital setting
Bibliography: Gupta et al. The economic impact of quarantine: SARS in Toronto as a case study. J Inf 2005; 50(5):386-393

TABLE 1F

	Quality Assessment						Cases (or Health Care Resources)			Quality	Comment
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cases**	**Control**	**Difference**[1]		
Impact of quarantine on spread of SARS (assessed with: Number of people with SARS)											
Number of SARS cases	Observational studies[2]	Very serious[2]	No serious inconsistency	Very serious[2]	No serious imprecision	None	73	584	(511)	⊕OOO **VERY LOW**	• Aggregate of primary, secondary, tertiary, and quaternary infections • Assumes transmission rate of 8% • Modelled based on data from the Toronto case study • Educated estimates and data were used in the development of the model to inform transmission rate, population density, number of contacts, and incubation period of SARS.
Total costs[3]	Modelling	Inherent limitations with modelling	Not considered; single study	Very serious[4]	Very serious[5]	None	Direct costs $12 million	Direct costs $48 million	($36 million)	⊕OOO **VERY LOW**	• Costs reported in CAD • Educated estimates and data were used to estimate the cost of SARS and quarantine.
							Indirect costs $0.2 million	Indirect costs $24 million	($23.8 million)		
							TOTAL $12.2 million	TOTAL $72 million	($59.8 million)		

CAD = Canadian dollars; SARS = severe acute respiratory syndrome.
[1] Parentheses () indicate reduction in cases or cost savings.
[2] Modelling base studies on the impact of quarantine on spread of SARS. Rough estimates used for transmission of SARS in different situations to run the model. Results may also be subject to recall bias, as information was collected retrospectively by interview.
[3] Year and country of costs not explicitly stated, but appears to be CAD 2003. C$1 (2003) = US$0.98 (2011)
[4] Cost calculations based on a number of sources, as well as opinion. Costs and resource use were largely obtained from sources specific to Toronto and may not be generalizable to other jurisdictions.
[5] Cost inputs are based on a number of sources, including interviews with health care workers, which could be subject to recall bias.

Author(s): Karen Lee, MA; Vijay Shukla, PhD; **Reviewer(s)**: John Conly, MD; Carmem Pessoa-Silva, MD, PhD
Date: 2011-04-25
Question: Should health system resources be used for potential influenza pandemic?
Settings: Any setting
Bibliography: Putthasri et al. Capacity of Thailand to contain an emerging influenza pandemic. Emerg Infect Dis 2009; 15(3):423-432

TABLE 1G

	Quality Assessment						Use of Physical Interventions	Quality	Comment
Viewpoint: health system	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Total expected resource use[1,2]**		
Potential health resources (measured with: Different health resources related to infrastructure, personnel and material[3])									
Resources required	Observational studies[4]	Very serious[5]	No serious inconsistency	Serious[6,7]	No serious imprecision	Reporting bias[8]	Disposable gowns: 1,377 N95 masks: 7,181 Surgical masks: 16,440 Plastic face shields: 567 Goggles: 961 Surgical gloves: 66,201	⊕OOO **VERY LOW**	• Major flaw of study: results combine 3 scenarios for transmission of infection (related to WHO Phase 4 and 5).[9] • Results not reported separately.

[1] Resource use estimates based on a mapping exercise using information obtained from surveys from different provinces and institutional settings.
[2] Simulation exercise with no control group.
[3] List of 39 resources generated through previous experiences, literature searches.
[4] Survey was conducted for potential resource use in different provinces of Thailand. Survey questionnaire was developed based on past experiences in Thailand and information available in literature.
[5] Survey study.
[6] Study was done in Thailand, which has a different health system to other countries.
[7] There is potential to have another survey on the same issue.
[8] Fourteen provinces participated in the survey.
[9] Phase 4 refers to human-to-human transmission from case patient to caregiver. Phase 5 refers to human-to-human transmission in localized clusters.

APPENDIX 2 : LITERATURE SEARCH STRATEGY AND RESULTS

Research Areas

1. Cost or resource use (utilization) studies and respiratory virus (of any type)
2. Cost of physical interventions (isolation, quarantine, social distancing, barriers, personal protection, and hygiene) to control the spread of respiratory viruses.

OVERVIEW	
Interface:	OvidSP
Databases:	EMBASE 1980 to 2010 Week 43 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 2, 2010
Alerts:	Weekly search updates began November 3, 2009 and ran until September 19, 2011
Study Types:	Economic studies
Limits:	Publication years 1995 – 2010 Humans

SYNTAX GUIDE	
/	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
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.pt	Publication type
.mp	Mapping alias (searches title, abstract, heading words, table of contents and key phrase identifiers)

ECONOMIC MULTI-DATABASE STRATEGY	
#	Searches
Question #1: Cost or resource use for respiratory viruses	
Concept: Respiratory viruses	
1	exp *Influenza/
2	influenza.ti.
3	flu.ti.
4	exp *Common Cold/
5	common cold.ti.
6	exp *Rhinovirus/
7	exp *human rhinovirus/
8	(rhinovirus* or rhino virus*).ti.
9	RSV.ti.
10	exp *Adenoviridae/
11	exp *Adenovirus/
12	(adenovirus* or adeno virus* or adenoviridae infection*).ti.
13	exp *Coronavirus/
14	exp *Coronavirus Infections/
15	(coronavirus* or corona virus*).ti.
16	exp *Respiratory Syncytial Viruses/
17	exp *Respiratory Syncytial Virus Infections/
18	exp *respiratory syncytial virus infection/
19	respiratory syncytial virus*.ti.
20	respiratory syncythial virus*.ti.
21	(respirosyncytial virus* or respirosyncythial virus*).ti.
22	exp *Parainfluenza Virus 1, Human/
23	exp *Parainfluenza Virus 2, Human/
24	exp *Parainfluenza Virus 3, Human/
25	exp *Parainfluenza Virus 4, Human/
26	exp *Parainfluenza virus/
27	(parainfluenza or para-influenza).ti.
28	((croup or laryngotracheobronchitis or bronchitis) adj2 (virus* or viral)).ti.
29	exp *Severe Acute Respiratory Syndrome/
30	exp *SARS virus/
31	(severe acute respiratory syndrome* or SARS or sudden acute respiratory syndrome*).ti.
32	acute respiratory infection*.ti.
33	acute respiratory tract infection*.ti.
34	or/1-33
Concept: Human filter	
35	exp animals/
36	exp animal experimentation/
37	exp models animal/
38	exp animal experiment/
39	nonhuman/
40	exp vertebrate/
41	animal.po.
42	or/35-41
43	exp humans/
44	exp human experiment/
45	human.po.
46	or/43-45

47	42 not 46
48	34 not 47
Concept: Economic filter	
49	(economic adj2 model*).mp.
50	(cost minimi* or cost-utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s).ti,ab.
51	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit).ti.
52	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab.
53	(cost or costs or economic*).ti. and (costs or cost effectiveness or markov).ab.
54	or/49-53
55	((Cost or costs) adj2 estimat*).ti,ab.
56	54 or 55
Concept: Utilization filter	
57	physician's practice patterns/
58	((prescrib* or resourcing or prescription) adj3 (practice* or pattern or patterns or frequency or proportion or habit or habits or trend or trends or behaviour)).ti,ab.
59	(practice adj2 (pattern or patterns or habit or habits or trend or trends or behaviour)).ti,ab.
60	(utilization or utilize* or utilisation or utilise* or dispens*).ti.
61	("clinician use" or "clinical use" or "physician use").ti.
62	("resource use" or "resource utilization" or "resource utilisation").ti,ab.
63	or/57-62
64	48 and (56 or 63)
65	limit 64 to yr=1995-2010
66	remove duplicates from 65
67	(comment or newspaper article or editorial or letter or note).pt.
68	66 not 67
Question #2: cost of physical interventions to control the spread of respiratory viruses	
Concept: Respiratory viruses	
1	exp Influenza/
2	influenza.ti,ab.
3	flu.ti,ab.
4	exp Common Cold/
5	common cold.ti,ab.
6	exp Rhinovirus/
7	exp human rhinovirus/
8	(rhinovirus* or rhino virus*).ti,ab.
9	RSV.ti,ab.
10	exp Adenoviridae/
11	exp Adenovirus/
12	(adenovirus* or adeno virus* or adenoviridae infection*).ti,ab.
13	exp Coronavirus/
14	exp Coronavirus Infections/
15	(coronavirus* or corona virus*).ti,ab.
16	exp Respiratory Syncytial Viruses/
17	exp Respiratory Syncytial Virus Infections/
18	exp respiratory syncytial virus infection/
19	respiratory syncytial virus*.ti,ab.
20	respiratory syncythial virus*.ti,ab.
21	(respirosyncytial virus* or respirosyncythial virus*).ti,ab.
22	exp Parainfluenza Virus 1, Human/
23	exp Parainfluenza Virus 2, Human/
24	exp Parainfluenza Virus 3, Human/

25	exp Parainfluenza Virus 4, Human/
26	exp Parainfluenza virus/
27	(parainfluenza or para-influenza).ti,ab.
28	((croup or laryngotracheobronchitis or bronchitis) adj2 (virus* or viral)).ti,ab.
29	exp Severe Acute Respiratory Syndrome/
30	exp SARS virus/
31	(severe acute respiratory syndrome* or SARS or sudden acute respiratory syndrome*).ti,ab.
32	acute respiratory infection*.ti,ab.
33	acute respiratory tract infection*.ti,ab.
34	or/1-33
Concept: Physical intervention	
35	exp Handwashing/
36	exp Hand washing/
37	(handwashing or hand washing or hand-washing or hand cleaning* or hand scrubbing* or handscrubbing*).ti,ab.
38	hand hygiene.ti,ab.
39	(sanitizer* or sanitiser*).ti,ab.
40	(cleanser* or disinfectant*).ti,ab.
41	exp Gloves, Protective/
42	exp Glove/
43	exp Gloves, Surgical/
44	exp surgical glove/
45	(glove or gloves).ti,ab.
46	exp Masks/
47	(mask or masks).ti,ab.
48	(n95 or n99).ti,ab.
49	exp Patient Isolators/
50	exp Patient Isolation/
51	patient isolat*.ti,ab.
52	(barrier* or curtain* or partition*).ti,ab.
53	negative pressure room*.ti,ab.
54	reverse barrier nursing.ti,ab.
55	cross Infection/pc [Prevention]
56	exp Infection control/
57	school closure*.ti,ab.
58	(clos* adj3 school*).ti,ab.
59	mass gathering*.ti,ab.
60	exp Crowding/
61	overcrowding.ti,ab.
62	public gathering*.ti,ab.
63	(ban or bans or banned or banning).ti,ab.
64	(outbreak* adj3 control*).ti,ab.
65	distancing.ti,ab.
66	exp Quarantine/
67	(quarantine* or quarantaine*).ti,ab.
68	or/35-67
69	34 and 68
Concept: Human filter	
70	exp animals/
71	exp animal experimentation/
72	exp models animal/
73	exp animal experiment/
74	nonhuman/

75	exp vertebrate/
76	animal.po.
77	or/70-76
78	exp humans/
79	exp human experiment/
80	human.po.
81	or/78-80
82	77 not 81
83	69 not 82
Concept: Economic filter	
84	(economic adj2 model*).mp.
85	(cost minimi* or cost-utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s).ti,ab.
86	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit).ti.
87	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab.
88	(cost or costs or economic*).ti. and (costs or cost effectiveness or markov).ab.
89	or/84-88
90	((Cost or costs) adj2 estimat*).ti,ab.
91	89 or 90
92	83 and 91
93	limit 92 to yr=1995-2010
94	remove duplicates from 93
95	(comment or newspaper article or editorial or letter or note).pt.
96	94 not 95

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per Medline search, with appropriate syntax used.
Cochrane Library Issue 10, 2010 to Issue 6, 2011	Same MeSH, keywords, and date limits used as per Medline search. Syntax adjusted for Cochrane Library databases.
CINAHL (EBSCO interface)	Same keywords, and date limits used as per Medline search. Syntax adjusted for EBSCO. **Note: CINAHL was only searched for question #2**
Health Economic Evaluations Database (HEED)	Same keywords, and date limits used as per Medline search. Syntax adjusted for HEED database.

GREY LITERATURE	
Dates for Search:	November 2, 2010; limited update: June, 2011
Keywords:	Adapted from Medline search strategy
Limits:	Publication years: 1995-2010

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

- Health Technology Assessment Agencies
- Health Economic
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

32 ***Studies included economic information, but not resource use or information relevant to the GRADE resource use tables — see Appendix 4***

119 Excluded studies

19 ***Cost/resource use respiratory virus***

- 15 no resource use reported
- 3 respiratory syncytial virus alone
- 1 tuberculosis

26 ***Cost/cost-effectiveness of prophylaxis/treatment***

- 7 oseltamivir
- 2 zanamivir
- 10 palivizumab
- 7 other treatments

44 ***Cost/cost-effectiveness of vaccines***

- 26 general
- 6 infant/children
- 11 elderly
- 1 high-risk pop

2 ***Other interventions (stockpiling, school closures)***

10 ***Studies looking a resource use for respiratory viruses in infants/high-risk children***

18 ***Foreign language***

- 3 France
- 1 Switzerland (French)
- 2 Spain
- 1 Columbia
- 2 Netherlands
- 1 Germany
- 7 Taiwan/China
- 1 Italy

APPENDIX 4: INFORMATION ON EXCLUDED STUDIES

Reference	Details	Reason for exclusion
H1N1		
Ong (2010)[23] Malaysia Setting: hospital	Population: 27 million, general pop. Time frame: July to Sept 2009 Study: Retrospective cohort study of patients at University of Lamaya Medical Centre, Kuala Lumpur, Malaysia	Cost of illness study — only reported costs and length of stay information.
Schafer (2010)[24] Michigan, US Setting: hospital	Population: 222 patients diagnosed with or presumed infected with H1N1 — 66 patients receiving diagnostic imaging Time frame: May 1 to July 18, 2009 Study: Use of radiologic services during outbreak	Study specific to radiologic services, did not consider use of physical interventions — 70% patients received no imaging.
SARS		
Chang (2004)[25] Taiwan Setting: hospital/community	Population: Taiwan population, national health insurance claims Time frame: March to June 2003 Study: Impact of SARS on health use (and fears of SARS)	Study identified inpatient, ambulatory, dental, and Chinese medicine cases; did not report resource use or costs.
Ko (2004)[26] Taipei, Taiwan Setting: community	Population: patients in community Time frame: March to June 2003 Study: Prospective observational study of EMS use	Specific to EMS use, and does not report resource use or costs specific to physical interventions.
Visentin (2009)[27] Toronto, Canada Setting: community	Population: Emergency medical technicians servicing greater Toronto area (servicing 2.5 million) Time frame: March to July 2003 Study: Retrospective study of use of PPE during airway management of patients with SARS using a survey (N = 230)	Study did not report units of resources used but percentage of EMS workers using PPE (eyewear, N95, open face hood, face shield, gown).
Mubayi (2010)[28] Taiwan; Hong Kong; Singapore; Toronto, Canada Setting: community	Population: Community in various countries Time frame: 2003 SARS outbreak Study: Model to assess impact of quarantine and isolation	Study reported costs but largely driven by choice of input parameters.
Influenza		
Hassan (2009)[29] US Setting: hospital	Population: Children < = 18 years Time frame: Jan to Dec 2003 Study: Retrospective analysis of hospitalizations of national database (Health Care Cost and Utilization Project kids' Inpatient Database), sponsored by AHRQ, including 36 sites	Study reported only total costs.
Bardowski (2010)[30] US Setting: hospital	Population: General population 873-bed tertiary care facility (72 rooms) Time frame: 2006-2007 and 2007-2008 periods Study: To determine impact of enhanced isolation precautions: staff adherence, excess environmental cleaning, patient transfers	Study reported only total costs. Only abstract was available.
Ampofo (2006)[31] US Setting: hospital	Population: Children < = 18 years Time frame: July 2001 to June 2002; July 2002 to June 2003; July 2003 to June 2004 Study: Retrospective cohort study of 3 viral seasons at Primary Children's Medical Centre (Salt Lake City, UT) — 233-bed facility	Study reported only total costs.
Keren (2006)[32] US Setting: hospital (Children's Hospital of Philadelphia; 418 beds)	Population: 727 patients (children) billing data Time frame: 4 consecutive seasons (2000-2004) Study: Retrospective cohort study of patients < –21 years at children's hospital	Study reported only total costs and length of stay; did not consider physical interventions.
Xue (2010)[33]	Population: Norwegian population	Study reported only total costs

Reference	Details	Reason for exclusion
Norway Setting: Hospital and community	Time frame: 2005-2006 flu seasons Study: Assessment of Norwegian Institute for Public Health utilization data to determine total cost	and length of stay; did not consider physical interventions.
Schull (2005)[34] Canada Setting: community/ER	Population: General population, and elderly patients with respiratory or cardiopulmonary conditions, from 20 emergency departments, serving 2.3 million Time frame: Jan 1996 to April 1999 Study: Retrospective time series analysis to assess emergency department use in Toronto	Study specific to emergency department use; did not consider physical interventions.
Carroll (2001)[35] US Setting: Long-term care facility (551 patients; 4 facilities)	Population: Elderly 65+ year-olds in Richmond, Virginia Time frame: Jan to May 1999 Study: Retrospective chart review to assess resource use and complications associated with influenza	Study did not consider use of physical interventions.
Sessa (2001)[36] Italy Setting: community	Population: General population Time frame: Dec 1998 to Mar 1999 (3-month winter epidemic period) Study: Prospectively recorded study of 197,437 visits to capture specialists' services and tests	Study did not consider use of physical interventions, and considered limited resource use.
Sander (2009)[37] US Setting: community	Population: Patients in contact with influenza Time frame: Simulation, none specified Study: Stochastic agent-based model to simulate pandemic influenza to compare 17 mitigation strategies, with targeted antiviral prophylaxis as the focus (oseltamivir)	Study reported only total cost.
Levy (1996)[38] France Setting: community	Population: General population Time frame: 1985-1989 Study: Cost of illness study based on 1985 data obtained from physician panels and claims 1989 data from Natinonal Health Insurance (NHI) system	Study reported only total cost.
Fairbrother (2010)[39] US Setting: community and hospital	Population: Young children < 5 years old in general population, through population-based surveillance program, in 3 counties including Rochester, Cincinnati, and Nashville Time frame: 2003-2004; 2004-2005; 2005-2006 Study: Assessment of the resource use and costs associated with treatment of influenza in pediatric population	Study reported only total costs and length of stay; did not consider physical interventions.
Bridges (2000)[40] Dearborn, Michigan, US Setting: community — full-time employees at Ford Motor Co.	Population: General population, healthy working adults (< 65), N = 1,184 Time frame: 1997-1998 (2 influenza seasons) Study: DB RCT to evaluate the effectiveness and cost benefit of influenza vaccine in preventing ILI and reducing societal costs	Study did not consider use of physical interventions.
Lee (2010)[41] US Setting: community and hospital	Population: Patients with ILI Time frame: Simulation, none specified Study: Computer simulation models to evaluate potential economic burden of 7 testing/treatment strategies for patients presenting to clinic or emergency departments with ILI symptoms	Study reported only total costs; did not consider physical interventions.
Newall (2008)[42] Australia Setting: community and hospital	Population: General population Time frame: July 1998 to June 2005 Study: Cost analysis combining estimates of the epidemiology of influenza with the costs associated with health care resource use	Study reported only total costs; did not consider physical interventions.
Hak et al (2006)[43] Netherlands Setting: community	Population: General population (approximately 75,000 persons recommended for influenza vaccination during 1999-2000 influenza epidemic)	Study reported only GP visits, hospitalizations, and costs; did not consider physical

Reference	Details	Reason for exclusion
and hospital	Time frame: 1-year time horizon Study: Decision type model to estimate total health care burden and direct medical costs during the next pandemic	interventions.
Simmerman (2006)[44] Thailand Setting: community and hospital	Population: Patients with influenza pneumonia Time frame: Sept 2003 to Aug 2004 Study: Population-based surveillance system; patient records were reviewed to obtain information on the total cost of in- and outpatient care for influenza pneumonia	Study reported only total costs; did not consider physical interventions.
Silka (2003)[45] Los Angeles, California, US Setting: emergency department	Population: Patients presenting to ED with illness resulting from influenza Time frame: Oct 1997 to March 2000 Study: Investigate ED resource demand during widespread influenza activity	No costs or resources reported.
Sartor (2002)[46] France Setting: hospital	Population: 9 patients with ILI; 5 staff with ILI Time frame: Feb 28 to March 6, 1999 Study: Prospective cohort study to capture hospital charges associated with treatment of patients	Specific resources and numbers not reported.
Davis (2001)[47] Hawaii, US Setting: Medicare Managed Care Plan	Population: All members of a Medicare Managed Care Plan 65 years and older Time frame: 1994-1995,1995-1996,1996-1997 Study: Evaluation of vaccination for influenza	Study specific to vaccination program, not resource use report (only costs).
Cox (2000)[48] US Setting: community	Population: General population Time frame: Jan 1, 1997 to June 30, 1998 Study: Economic evaluation of antivirals (amantadine, rimantadine) using retrospective analysis of patient information from database	Number of visits (physician, ED, hospital) and costs captured. Resource not presented. Study did not consider physical interventions.
Cox (2000)[49] US Setting: community and hospital	Population: Patients with influenza who visited the ED (N = 1,362) Time frame: Jan 1, 1997 to June 30, 1998 Study: Retrospective, descriptive study, to evaluate the use of antivirals on the costs of treating influenza in ED and hospital settings	Study specific to use of antivirals; did not report resource use, did not consider physical interventions.
Mauskopf (1999)[50] US Setting: community	Population: General and high-risk population Time frame: Not explicitly stated Study: Computer model used to estimate the average per person cost and health outcomes of influenza to evaluate the use of antivirals (amantadine, rimantadine)	Study specific to use of antivirals; did not report resource use, did not consider physical interventions.
Szucs (1999)[51] Germany Setting: community and hospital	Population: General population (N = 281) Time frame: 1995-1996 Study: Retrospective data from patient records to assess the treatment and management, vaccination for influenza	Study reported only total costs; did not consider physical interventions.
Canadian Institute for Health Information (2010)[52] Canada Setting: hospital	Population: General population Time frame H1N1 pandemic 2009: April 1 to Dec 31, 2009 Study: Assessment of impact of H1N1 pandemic on Canadian hospitals using acute hospital discharge data	Study did not report units or total costs (presented graphically).
Molinari (2007)[21]* US Setting: community and hospital	Population: Patients with influenza (N = 179,718) Time frame: 2001-2003 (4 influenza seasons) Study: Medical and indirect costs attributable to annual influenza epidemics	Study reported only total costs; did not consider physical interventions.
Krumkamp (2011)[53] Thailand (2 provinces: Nakhon, Phichit) Setting: hospital	Population: Phichit N = 554,112 (985 hospital beds); Nakhon N = 1,513,163 (2,642 hospital beds) Time frame: 2009 outbreak Study: Modelling exercise based on experience of Thailand 2009 to simulate resource needs	Resource use based on study by Putthasri (2009) included in this review. The study does not offer any more information on resource use.

AHRQ = Agency for Healthcare Research and Quality; DB RCT = double-blind randomized controlled trial; ED = emergency department; EMS = emergency medical services; ILI = influenza-like illness; PPE = personal protective equipment; SARS = severe acute respiratory syndrome.
* used as input parameters for included studies