THE BURDEN OF RESPIRATORY INFECTIONS AMONG OLDER ADULTS IN LONG-TERM CARE: A SYSTEMATIC REVIEW

By

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B.A., Smith College, 2014

Thesis

Submitted in partial fulfillment of the requirements for the Degree of Master of Science in the Department of Epidemiology in the School of Public Health at Brown University

PROVIDENCE, RHODE ISLAND

MAY 2019
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Arielle Childs
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Abstract of Epidemiology of Respiratory Infections Among Older Adults in Long-Term Care: A Systematic Review, by Arielle Childs, ScM, Brown University, May 2019.

Background: There is no existing rigorous synthesis of the current literature on respiratory infections in LTCFs that permits a comprehensive understanding of their burden.

Purpose: To review the burden of respiratory infections in LTCF residents.

Data Sources: PubMed (MEDLINE), EMBASE, and the Cochrane Library between April 1964 and October 2017.

Study Selection: Experimental and observational studies that were published in English, included adults >60 years of age who were unvaccinated or reported no record of vaccination, resided in a LTCF, and reported measures of occurrence for influenza, respiratory syncytial virus, or pneumonia.

Data Extraction: Machine-learning-assisted screening of articles was performed by X reviewers, and study characteristics and quality were independently evaluated by two reviewers.

Data Synthesis: Of the 26 studies, 18 reported an incidence estimate, 7 reported a prevalence estimate, and 1 reported both. Studies reported respiratory infection incidences from 1.1% to 85.2% and prevalences from 1.4% to 55.8%.

Limitations: Lack of literature and inconsistent measures of occurrence.

Conclusion: Respiratory infections are highly prevalent and incident among older LTCF residents. Existing literature assessing the natural progression of respiratory infections in LTCF settings is scarce, therefore resources might be more advantageous when implemented in surveillance programs in long-term care populations.

Primary Funding Source: Sanofi Pasteur
INTRODUCTION

The burden of acute respiratory infections is estimated to cause approximately 4 million global deaths per year, which is more than twice that of any other respiratory condition [1]. In the United States alone, influenza, pneumonia, and respiratory syncytial virus (RSV) are projected to infect more than 13 million people annually, with a mortality burden of more than 100,000 [2-4]. Respiratory infections are significantly more harmful to older adults due to their compromised immune systems, which based on limited data, results in more severe illness, a greater number of subsequent hospitalizations, and more deaths than other populations [5, 6]. These prior findings of increased risk among older individuals are of great concern because pneumonia, influenza, and RSV are common in elderly populations [7, 8]. By 2050, the population of individuals 65 years of age and older is expected to nearly double the population estimated in 2012, which is why it is essential to understand the burden of respiratory infections in aging populations [9].

An estimated 40% of the global population of adults are expected to live in a LTCF at some point within the next 30 years, so residents are necessary targets for research [10]. Older adults are at increased risk for acquiring infections, so those in LTCFs might be more susceptible to severe complications [11]. Institutionalized older adults are an important target population because they represent an average of 2 million illnesses recorded every year, including high rates of respiratory infections [12]. The clustering of aged individuals in close living quarters allows infections to spread quickly, possibly due to low vaccination rates [13].

Unvaccinated LTCF residents are an important population to understand because they are genuinely at-risk compared to those who have been vaccinated. Although individual studies have collected data regarding incidence and prevalence of respiratory infections among unvaccinated LTCF residents, no systematic reviews have been conducted to display these findings. Leaders in the field of geriatrics recommend clinicians review existing literature in the event of an outbreak, therefore there is
a need to synthesize the literature in a way that clinicians can easily access. The findings from our review will guide future interventions regarding respiratory illnesses in LTCF residents and offer alternative methods for establishing the distribution of respiratory infections in LTCFs. Our objective was to conduct a systematic review of published literature quantifying the prevalence and incidence of respiratory infections for unvaccinated populations in LTCF settings.
METHODS

This systematic review concentrates on studies and existing systematic reviews examining respiratory infections and contributing risk factors in LTCF settings.

Data Sources and Searches

We systematically searched three online databases (PubMed, Cochrane, and EMBASE) for published systematic reviews on the prevalence and incidence of influenza, pneumonia, and respiratory syncytial virus (RSV) among LTCF residents in any country (Figure 1.). There were no parameters for geographic location, but systematic reviews were restricted to those published in English between April 1964 and October 10, 2017. The same restrictions were implemented for our principal search for individual articles. We systematically searched PubMed and EMBASE for relevant observational and experimental studies published in English. We further supplemented this search by skimming references for related systematic reviews. The database search strategy included a combination of terms including “respiratory”, specifications exchangeable for “nursing home” and “institutionalized elderly”, with a restriction for studies including children or infants.

Study Selection

Potential systematic reviews were screened by one author due to the minimal number of reviews found, and none were found to be eligible. For individual articles, a semi-automated abstract screening was performed using a machine-learning algorithm, which was trained by two to four reviewers to prioritize abstracts for screening from highest to lowest relevance [14]. Abstracts for individual articles were independently assessed for inclusion by at least two reviewers through a systematic evaluation using the protocol criteria. Eligible articles were included if they were observational (retrospective or prospective) or interventional (vaccination or treatment), and published
in English. We only included studies that specified participants were aged 60 or older, or that had a mean age of study participants (≥ 75 years) with an SD (≤ 6 years) that reasonably suggested all individuals in the study cohort were over the age of 60. Further inclusion criteria required that the studies be conducted in a population that included information on participants institutionalized in a LTCF or care facility setting not linked to a hospital. Studies were only included if they provided data on an unvaccinated population which had not received the vaccine corresponding to the respiratory infection of interest. Similarly, we attempted to only include studies if the population was not taking prophylactic medications, for example, antiviral medications (oseltamivir, zanamivir, peramivir, amantadine, and rimantidine) for influenza. Studies examining RSV had no such requirements because there was no vaccination for the virus at the time of this review. If the reported study did not describe any vaccination or antiviral medication data and met the remaining criteria, we assumed the study population was unvaccinated or unexposed to antiviral medications and included the article in our review. We did not exclude studies based on the method that a respiratory infection was identified because several methods are often all considered valid. For example, for influenza, viral testing is not necessary to diagnose influenza and clinicians often make a diagnosis based on evaluation of symptoms, clinical judgement, and local influenza activity[15].

The main outcomes of interest were the most common communicable respiratory infections, specifically influenza, RSV, and pneumonia. Additional topics of interest were expenses and illness patterns associated with the previously defined outcomes. We excluded studies that did not report our infections of interest, had an incorrect age range, or reported on a population in a LTCF facility that was associated with or received care from a hospital. Studies were not included if they were case reports, editorials, case series, or commentaries. Disagreements about exclusions between reviewers were resolved through discussion.
Data Extraction and Quality Assessment

For each included study, one reviewer extracted study characteristics and respiratory outcomes. Study characteristics included author, publication year, study design, geographical location, study dates, inclusion and exclusion criteria specific to the study, and type of study. Further characteristics included data about the study population, such as risk factors for infection, mean age of the unvaccinated population, number of outcomes in unvaccinated population compared to those at risk, and the appropriate measure of occurrence (incidence proportion, prevalence proportion, incidence rate, prevalence rate). Other collected characteristics were not reported at this time. Data was extracted into the Systematic Review Data Repository from the Agency for Healthcare Research and Quality of the U.S. Department of Health & Human Services.

Data Synthesis and Analysis

Our systematic review consisted of a qualitative assessment. Data of infection occurrence was compared between studies classified as outbreaks within the individual literature and non-outbreak studies, which were generally epidemiological, or performed to observe vaccine efficacy. Based on the inconsistency of included data, the difference in outcome measures, and the heterogeneity of the global populations, quantitative synthesis was nearly impossible.

Role of the Funding Source

Sanofi Pasteur provided an unrestricted research grant to support this systematic review as part of a larger project aiming to estimate the burden of infections in long-term care. Brown University retained the right to publish and publicly present all results. Sanofi Pasteur was not involved in establishing the scope of the systematic review, creating the initial protocol, extracting data, or performing qualitative analysis, but was involved in suggesting edits to the final review protocol and
reviewing the final manuscript. Incorporation of any edits suggested by Sanofi Pasteur was not compulsory. One employee of Sanofi Pasteur was a 4th screener and helped to screen 164 of the abstracts.
RESULTS

Literature Search

Our search for existing systematic reviews yielded 46 results. For the search of individual articles, out of 1,451 which were initially generated from PubMed, 345 were selected for further review. No new articles were identified from EMBASE.

Study Characteristics

We ultimately identified 26 studies: 3 on influenza, 7 on RSV, and 16 on pneumonia. Fifteen studies were from North American countries, 6 from Asian countries, and 5 from European countries. There were 11 prospective cohort studies [16-26], 10 retrospective cohort studies [27-36], 3 randomized controlled trials [37-39], and 2 cross-sectional studies [40, 41]. The mean age of the unvaccinated populations ranged from 70.8 to 90.1 years, with 6 studies reporting different measures of age data. Male sex ranged from 16.5% to 54% of study participants, with no data for 8 studies. The years of the data used in the studies ranged from February 1979 and the winter of 2014, with no data for one study. The range of study sizes was 52 – 102,842 participants, and follow-up period lengths ranged from 30 days to up to 4 years. Two studies were industry funded, 17 were not industry funded, and the remaining 7 did not report the source of funding. Of the included studies, 18 reported an incidence estimate, 7 reported a prevalence estimate, and 1 reported both measures. The accompanying search for associated expenses and illness patterns found no relevant literature.

Respiratory Infections

Influenza

Three included studies addressed the occurrence of influenza in unvaccinated LTCF individuals as seen in Table 1. Two studies were retrospective and 1 was a randomized controlled trial. Out of these
3 studies, two reported specifically on outbreaks. One retrospective study looked at an outbreak of influenza A among a LTCF with 170 subjects in the United States, with infected individuals divided into two categories of illness. Definition I represented those with more severe symptoms (high fever and either chest congestion or cough) and Definition II denoted those with milder symptoms (high fever or chest congestion or cough). Incidence proportions were identified for both categories: Definition I had an incidence of 20.3% and Definition II had an incidence of 47.4% [27]. Another retrospective outbreak study reported a high incidence of 85% among 27 unvaccinated LTCF residents [28]. The only randomized controlled trial investigated the efficacy of the influenza vaccine amongst elderly individuals in Japanese LTCFs. Within the control group of 11,723 unvaccinated LTCF residents, the incidence of influenza was 5.9%, which was significantly higher than in the vaccinated cohort [37].

*Respiratory Syncytial Virus*

As presented in Table 2., the incidence of RSV among LTCF populations was evaluated in 4 prospective studies, 2 retrospective studies, and 1 randomized controlled trial. Among these 7 studies, 6 reported incidence proportions and 1 reported an incidence rate. Five measures of occurrence were from non-outbreak studies, with incidence ranging from 1.1% to 10.8%, and an incidence rate of 12.4 cases per 1,000 person-years [16, 18, 19, 30, 38]. The two outbreak studies reported higher incidence proportions of 12.9% and 13.5% [17, 29].

*Pneumonia*

Seventeen studies reported incidence and prevalence data for pneumonia among unvaccinated LTCF populations in the form of 7 prospective studies, 6 retrospective studies, 2 cross-sectional studies, and 1 randomized controlled trial in Table 3. The majority of studies were conducted as non-outbreak studies with incidence ranging from 4.8% to 41.2% and prevalence was reported from 1.4% to 55.8%.
Incidence rates were 0.07 and 0.17 cases per 1,000 bed-days, as well as 9.17 cases per 100 person-years [31, 39]. Prevalence rates of 4.61 and 5.21 cases per person-year were reported [35]. For the 3 outbreak studies, incidence ranged from 6.4% to 19.8% and prevalence was reported as 5.1% [23, 32, 36]. Risk factors showed that the Barthel Index Score, swallowing disorders, ischemic heart disease, and dementia significantly increased risk of pneumonia [26].
DISCUSSION

Our systematic review found 26 studies that showed respiratory incidence of 1.21% to 85.2% and prevalence of 1.4% to 55.8%. Out of the included literature, 7 articles were labeled as outbreaks. The majority of the included studies reported incidence data and most were from North America, which could result from our strict definition of a LTCF that is not associated with a hospital. Our results show that healthcare providers should promote immunization against influenza and pneumonia, and follow rigorous prevention practices to avoid the spread of infections, particularly in unvaccinated populations. These indications suggest that policy makers should be more rigorous when defining and enforcing guidelines for vaccinations within LTCFs, particularly the pneumococcal vaccine. Our findings demonstrate that there is a gap in available respiratory vaccines for elderly LTCF residents. Pharmaceutical companies could implement our findings to target LTCFs for future vaccine development.

An estimated 5-15% of the general population will be infected by influenza during an epidemic [42]. Our review showed that data in United States did not support these prior findings for populations of unvaccinated LTCF residents. We found two studies that showed incidence measures of over 20% in at-risk LTCF individuals, which indicates that influenza has a higher occurrence in LTCF residents than the general population. One of the principal prevention strategies is the influenza vaccine, but although the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP) universally recommends influenza vaccination, only 75.7% of nursing home residents received the vaccine during the 2014-2015 influenza season [43, 44].

Despite the protection provided by influenza vaccines, the level of effectiveness in elderly adults varies according to type of vaccine. The quadrivalent influenza vaccine has been shown to be more cost-effective than the trivalent vaccine in the UK, China, and Spain [45-47]. However, both the high-dose trivalent inactivated influenza vaccine and the adjuvanted trivalent vaccine have been found to be more
effective than either the standard trivalent vaccine in the elderly population \([48-51]\). The higher effectiveness results from contents added to the standard trivalent influenza vaccine to induce a significantly greater antibody response. Recent developments of influenza vaccines have produced several variations of microneedle patches. A dissolvable microneedle trivalent vaccine patch showed similar effectiveness compared to intramuscular vaccines, but with the benefit of a self-administering option due and without a strict cold chain requirement \([52]\). Another microneedle patch that was not dissolvable used a quadrivalent vaccine, but was not recommended for individuals over 65 years \([53]\). By combining the dissolvability of available intradermal patches with more effective high-dose or adjuvanted trivalent influenza vaccines, an opportunity might exist to develop a more effective vaccination that is suitable for elderly individuals. Another vaccine option is a nasal spray, which uses a live attenuated vaccine. However, although live attenuated vaccines are more effective in young children, they are not recommended for immunocompromised individuals, which excludes many elderly LTCF residents \([54, 55]\). Focusing influenza vaccine research on the growing elderly population, especially those in LTCFs, would produce a larger target population.

Previous literature had shown that RSV in older adults could be responsible for nearly 12% of medically attended acute respiratory infections in older adults, while we found incidences ranging from 1.2 to 13.5%, with two studies over 12% \([56]\). Reasons contributing to the lower incidences could come from unreliable RSV test with low sensitivity, or simply untested portions of the population \([36, 57, 58]\). There have been no vaccines on the market approved to protect against RSV, although several are in the final stages of development \([59]\). In high-risk children, palivizumab has been used for prevention of RSV, but hasn’t been tested for effectiveness among elderly populations at risk in LTCFs, which could be an opportunity for expanded use of the drug \([60]\). Previous literature has demonstrated a need to identify target populations to inform implementation of RSV vaccines and therapeutics, and we have shown that
LTCF residents represent an important population when considering prevention and treatment methods for RSV [61].

Our findings of pneumonia incidence and prevalence were consistent with the existing literature [62, 63]. We found a large range of pneumonia occurrences in LTCFs, which is most likely explained by differing source populations. Reported data in populations not differentiating between vaccinated or unvaccinated are not useful because they are not truly representative of an at-risk population. The data are likely inaccurate because a portion of the population has already been vaccinated, and has at least some level of protection against the infection. Our systematic review found one relevant study that reported difficulty swallowing as a risk factor for pneumonia infection in LTCF residents with pneumonia compared to those without [20]. Similar to the influenza vaccination, the pneumococcal vaccination is an important part of a primary prevention strategy, but past research has shown that it is globally underutilized in LTCFs compared to the influenza vaccine [64]. ACIP recommends the pneumococcal vaccination for older adults, but only 78.4% of nursing home residents received the vaccine in 2014 [44, 65].

To our knowledge, this systematic review offers a novel perspective regarding respiratory infections in unvaccinated LTCF populations. A substantial evidence gap exists because there have been no previous systematic reviews that addressed respiratory infections specifically in unvaccinated LTCF populations. Although previous reviews have investigated methods to predict, prevent, and treat respiratory infections in the elderly, prior literature is missing information regarding respiratory infections in older individuals, LTCF residents, and true at-risk populations [10, 11, 66-68]. By including studies from North America, Europe, and Asia, our findings were more substantial and significantly more generalizable to further populations than if the review was narrowed to a single geographic location. No reviews have researched the global burden of respiratory infections in LTCFs, but our findings can be interpreted on a global scale as the distribution of incidence and prevalence for influenza, RSV, and
pneumonia in truly at-risk LTCF residents. These common respiratory infections were included to examine patterns among illnesses and allowed further generalizability to at-risk populations. Our systematic review used an innovative machine-learning program with an algorithm to help process eligible abstracts produced from the initial search. Using new technology to advance search methods is an important part of developing research techniques to be more efficient.

Despite the many strengths of our review, there are also limitations, likely due to our search restrictions. Although we were able to include studies from several geographic locations, language barriers could have decreased the availability of our eligible studies. We only included articles that were published in English, which could have caused more relevant studies or systematic reviews to be overlooked. Due to our exclusion criteria being so restrictive, it is plausible that some infection occurrences might be biased by a small sample size [27]. It is possible that some of the studies that we included, especially those studying outbreaks, had populations that were actually exposed to antivirals despite not reporting on the exposure, which could result in an underestimation of the burden of infection. This concern is reduced by research that demonstrates the ineffectiveness of chemoprophylaxis in LTCF influenza prevention [69].

There are several important limitations of our systematic review. The evidence base is limited by the heterogeneity of populations, study sites, and outcomes in the existing literature. Studies frequently had populations with large age ranges, LTCFs with hospital affiliations, or failed to report outcomes in clearly identified unvaccinated populations. We endeavored to control for this limitation by explicitly defining our inclusion and exclusion criteria to select relatively comparable studies in an attempt to reduce the impact of study heterogeneity. Exclusion of studies for not reporting data from an unvaccinated LTCF population, having a different definition for LTCF, or only presenting qualitative instead of quantitative measurements aimed to minimize variability and maximize interpretability among the existing relevant literature.
A significant limitation to our review was that the existing literature did not regularly provide specific data for unvaccinated populations. The purpose of our systematic review was to assess the current evidence base for research on respiratory infections in unvaccinated LTCF residents. This limitation is ultimately a result of our review because we determined that there is a gap in existing literature when considering these populations. Unvaccinated LTCF residents have unsatisfactory rates of immunization, which is why it is essential to identify if this population is at-risk for the infections and in need of further prevention efforts [70, 71]. There might be incomplete retrieval of identified research because many studies had populations of unvaccinated residents that were not distinguished from vaccinated residents, but for the purpose of this review, we were only able to evaluate those that separated the populations. We found no studies that included data of cost, hospitalization, or mortality for respiratory infections in LTCFs because we were only interested in data for the unvaccinated population compared to the vaccinated population. Our results should only be interpreted after consideration of these limitations.

Based on previous literature and our substantial findings, we can offer recommendations for future research. To improve upon our finding that observational studies on LTCF respiratory infections are infrequent, further research should be conducted to add to the existing literature base. It is likely that that published studies are not representative of other infections in LTCF populations, so additional observational studies investigating LTCF-specific infections would be valuable additions to previously published studies. Gastrointestinal infections, such as those resulting from Clostridium difficile and Rotavirus, and genitourinary infections, such as urinary tract infections, are known to be problematic among the elderly LTCF populations, so they would be ideal targets for future research [20, 72].

Unfortunately, it is doubtful that further studies will be conducted in unvaccinated LTCF populations based on a lack of funding and the presence of literature in LTCF populations disregarding vaccination status. We propose a more feasible and advantageous option: the use of surveillance in LTCF
populations. Due to the projected increase of elderly individuals living in LTCFs, standardized surveillance can provide an important source for data, which could be used to influence vaccination recommendations or infection protocols. Prior research has shown that establishing surveillance programs for LTCF populations would be valuable due to the high incidence of infectious disease within these facilities [73, 74].

In conclusion, our systematic review was novel and showed that respiratory infections are highly incident and prevalent among frail older LTCF residents who have not been vaccinated. There is an absence of published literature for respiratory infections in this unvaccinated population, particularly influenza and RSV. Developing surveillance programs to track respiratory infections in LTCFs would contribute data to influence decisions regarding policies within LTCFs and on a national level. Additional semi-automated systematic reviews are necessary to identify the determinants of increased respiratory infection risk in LTCFs. Future research should also be expanded to investigate other types of common infections in LTCFs.
FUNDING

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest or financial ties to disclose.
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23(3): 186-8.

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3(11): 888-900.

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64. Poscia A, Collamati A, Carfi A, et al. Influenza and pneumococcal vaccination in older adults living


<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Country</th>
<th>Study Dates</th>
<th>Type of study</th>
<th>Mean Age (SD)</th>
<th>n Infected / N at Risk</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers for Disease and Prevention, 1983</td>
<td>Retrospective Cohort</td>
<td>United States</td>
<td>December 1, 1982 - January 4, 1983</td>
<td>Outbreak</td>
<td>86.4</td>
<td>23/27</td>
<td>85.2%</td>
</tr>
<tr>
<td>Horman et al., 1986</td>
<td>Retrospective Cohort</td>
<td>United States</td>
<td>December 8, 1980 - January 13, 1981</td>
<td>Outbreak</td>
<td>83.2 (range 62-100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deguchi et al., 2000</td>
<td>Randomized Controlled Trial</td>
<td>Japan</td>
<td>November 1998 - March 1999</td>
<td>Control Arm of Trial</td>
<td>81.4</td>
<td>694/11,723</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

\(^a\) Unless otherwise reported.

\(^b\) The estimates and study participants’ characteristics were calculated among the unvaccinated individuals.
Table 2. Published Global Literature on the Burden of Respiratory Syncytial Virus in Long-term Care Facilities

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Country</th>
<th>Study Dates</th>
<th>Type of study</th>
<th>Mean Age (SD)</th>
<th>n Infected / N at Risk</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnstone et al., 2014 [16]</td>
<td>Prospective Cohort</td>
<td>Canada</td>
<td>2009, 2010, 2011</td>
<td>Non-outbreak</td>
<td>Median 86 (IQR 80-90)</td>
<td>12/1,072</td>
<td>1.1%</td>
</tr>
<tr>
<td>Sorvillo et al., 1984 [29]</td>
<td>Retrospective Cohort</td>
<td>United States</td>
<td>February - April 1979</td>
<td>Outbreak</td>
<td>79.2</td>
<td>13/101</td>
<td>12.9%</td>
</tr>
<tr>
<td>Ellis et al., 2003 [30]</td>
<td>Retrospective Cohort</td>
<td>United States</td>
<td>August 1, 1995 - July 31, 1999</td>
<td>Non-outbreak</td>
<td>Age ≥65, 100%</td>
<td>1,105 infections/88,851 person-years</td>
<td>12.4 cases</td>
</tr>
<tr>
<td>McElhaney et al., 2004 [38]</td>
<td>Randomized Controlled Trial</td>
<td>United States</td>
<td>2000-2001</td>
<td>Non-outbreak</td>
<td>82.2 (8.4)</td>
<td>3/198</td>
<td>1.5%</td>
</tr>
<tr>
<td>Caram et al., 2009 [17]</td>
<td>Prospective Cohort</td>
<td>United States</td>
<td>January 29, 2008 - February 26, 2008</td>
<td>Outbreak</td>
<td>70.8 (15.0)</td>
<td>7/52</td>
<td>13.5%</td>
</tr>
<tr>
<td>Uršič et al., 2016 [18]</td>
<td>Prospective Cohort</td>
<td>Slovenia</td>
<td>December 5, 2011 - May 31, 2012</td>
<td>Non-outbreak</td>
<td>Median 84 (IQR 79.8-88.8)</td>
<td>5/90</td>
<td>5.6%</td>
</tr>
<tr>
<td>Hui et al., 2008 [19]</td>
<td>Prospective Cohort</td>
<td>China</td>
<td>April 2006 - March 2007</td>
<td>Non-outbreak</td>
<td>84.9 (8.9)</td>
<td>21/194</td>
<td>10.8%</td>
</tr>
</tbody>
</table>

a Unless otherwise reported.
The estimates and study participants' characteristics were calculated among the unvaccinated individuals.

The paper stated that study participants were enrolled in September or October and followed to the end of the respiratory viral season.

Only the number of person-years contributed by study sample was reported, not the number of individuals in the sample.

Participants were enrolled from mid-February through mid-March in 2000 for the first influenza season and trial. Then, a second trial was initiated in late December 2000 during a second influenza season, but the time period of enrollment was not reported.
<table>
<thead>
<tr>
<th>Author</th>
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<th>Study Dates</th>
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<th>n Infected / N at Riskb</th>
<th>Measure of Occurrence</th>
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<tbody>
<tr>
<td>Huybrechts et al., 2011</td>
<td>Retrospective Cohort</td>
<td>Canada</td>
<td>January 1, 1996 to March 31, 2006</td>
<td>Non-outbreak</td>
<td>83.8 (6.9)c</td>
<td>920/10,900; Incidence: 265 events/2,890 person-years</td>
<td>Prevalence: 8.4%; Incidence Rate: 9.17 per 100 person-years</td>
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<tr>
<td>Cartter et al., 1990</td>
<td>Retrospective Cohort</td>
<td>United States</td>
<td>December 1, 1984 to April 10, 1985</td>
<td>Outbreak</td>
<td>84</td>
<td>Nursing Home A: 3/16, Nursing Home C: 25/126</td>
<td>Incidence: Nursing Home A: 18.8%, Nursing Home C: 19.8%</td>
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<tr>
<td>Langmore et al., 2002</td>
<td>Cross-sectional</td>
<td>United States</td>
<td>1993-1994</td>
<td>Non-outbreak</td>
<td>Age ≥85, 49.4%; Age 65 to 84, 51.6%</td>
<td>3,118/102,755</td>
<td>Prevalence: 3.0%</td>
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<tr>
<td>Konetzka et al., 2004</td>
<td>Retrospective Cohort</td>
<td>United States</td>
<td>1996</td>
<td>Non-outbreak</td>
<td>83.5 (7.4)</td>
<td>766/5899</td>
<td>Prevalence: 13.0%</td>
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<tr>
<td>Quagliarello et al., 2005</td>
<td>Prospective Cohort</td>
<td>United States</td>
<td>February 2001 to 2001</td>
<td>Non-outbreak</td>
<td>84.7 (8)</td>
<td>112/613</td>
<td>Incidence: 18.3%</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Study Period</td>
<td>Outbreak Type</td>
<td>Prevalence Rate</td>
<td>Incidence Proportion</td>
<td>Rate</td>
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<td>Won et al., 2006[34]</td>
<td>Retrospective Cohort</td>
<td>United States</td>
<td>June 1998 to December 2000</td>
<td>Non-outbreak</td>
<td>83.4c</td>
<td>75/3,547</td>
<td>Prevalence</td>
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<tr>
<td>Givens et al., 2010[21]</td>
<td>Prospective Cohort</td>
<td>United States</td>
<td>2003 to 2009</td>
<td>Non-outbreak</td>
<td>86 (7.0)</td>
<td>133/323</td>
<td>Incidence</td>
</tr>
<tr>
<td>Aparasu et al., 2013[35]</td>
<td>Retrospective Cohort</td>
<td>United States</td>
<td>July 1, 2001 to December 31, 2003</td>
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<td>83.46 (8.1)</td>
<td>Atypical: n.d&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Typical: n.d&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Sund-Levander et al., 2007[22]</td>
<td>Prospective Cohort</td>
<td>Sweden</td>
<td>2000-2003</td>
<td>Non-outbreak</td>
<td>84.6 (6.7)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>44/234</td>
<td>Incidence Proportion: 28.9%</td>
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<tr>
<td>te Wierik et al., 2012[23]</td>
<td>Prospective Cohort</td>
<td>Netherlands</td>
<td>January to March 15, 2010</td>
<td>Outbreak</td>
<td>90.1 (1.1)</td>
<td>9/140&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Incidence Proportion: 6.4%</td>
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<tr>
<td>Rummukainen et al., 2013[41]</td>
<td>Cross-sectional</td>
<td>Finland</td>
<td>2011</td>
<td>Non-outbreak</td>
<td>Age&gt;85, 49%&lt;sup&gt;f&lt;/sup&gt;</td>
<td>75/5,262</td>
<td>Prevalence Proportion: 1.4%</td>
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<tr>
<td>Study Authors</td>
<td>Study Design</td>
<td>Location</td>
<td>Time Period</td>
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<tr>
<td>Sarabia-Cobo et al., 2016&lt;sup&gt;[24]&lt;/sup&gt;</td>
<td>Prospective Cohort</td>
<td>Spain</td>
<td>2011-2013</td>
<td>Non-outbreak</td>
<td>88.7 (6.8)</td>
<td>1,330/2,384</td>
<td>Prevalence: 55.8%</td>
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<tr>
<td>Fukushima et al., 2008&lt;sup&gt;[25]&lt;/sup&gt;</td>
<td>Prospective Cohort</td>
<td>Japan</td>
<td>December 1, 2003 to March 28, 2004</td>
<td>Non-outbreak</td>
<td>85</td>
<td>17/284</td>
<td>Incidence: 6.0%</td>
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<td>Wu et al., 2010&lt;sup&gt;[39]&lt;/sup&gt;</td>
<td>Randomized Controlled Trial</td>
<td>Taiwan</td>
<td>2004</td>
<td>Non-outbreak</td>
<td>82.3 (8.3)</td>
<td>n.d.&lt;sup&gt;d&lt;/sup&gt;/74</td>
<td>Traditional Model: Incidence Rate: 0.17 cases per 1,000 bed-days</td>
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<tr>
<td>Doi et al., 2014&lt;sup&gt;[36]&lt;/sup&gt;</td>
<td>Retrospective Cohort</td>
<td>Japan</td>
<td>Winter 2014</td>
<td>Outbreak</td>
<td>81.5 (8.5)</td>
<td>5/99</td>
<td>Prevalence: 5.1%</td>
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<td>Kikutani et al., 2015&lt;sup&gt;[26]&lt;/sup&gt;</td>
<td>Prospective Cohort</td>
<td>Japan</td>
<td>No Data</td>
<td>Non-outbreak</td>
<td>86.7 (7.8)</td>
<td>33/691</td>
<td>Incidence: 4.8%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Unless otherwise reported.
<sup>b</sup> The estimates and study participants’ characteristics were calculated among unvaccinated individuals.
<sup>c</sup> Calculated by combining group data.
<sup>d</sup> n.d. = no data
Calculated from 1-year follow-up.
Measured in the initial five weeks.
Age derived from nursing home residents.
Only rates in each arm of the trial were provided.
Figure 1. Study flow of the selection process for all papers used in the final analysis. Symbol: ‘∗’, Articles could not be evaluated because they were not written in English; the full text could not be accessed; or measures of occurrence were not presented and there were insufficient data to calculate measures of occurrence for infections of interest.
### Supplementary Table 1. PubMed Search Strategy

<table>
<thead>
<tr>
<th>Respiratory Infection</th>
<th>Search Terms</th>
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<tr>
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<tr>
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<tr>
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<tr>
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<td>&quot;elderly&quot;[All Fields]) OR residential[All Fields] OR institutionalized[All Fields] OR</td>
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<td>institutionalised[All Fields] OR geriatric[All Fields] OR NOT ((&quot;infant&quot;[MeSH Terms] OR</td>
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<td>systematic[sb] OR Technical Report[ptyp]</td>
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## Supplementary Table 2. EMBASE search strategy

<table>
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<th>Respiratory Infection</th>
<th>Search Terms</th>
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<td>[Cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim</td>
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<tr>
<td>Pneumonia</td>
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<td>[Cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim</td>
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<tr>
<td>Respiratory Syncytial virus</td>
<td>care OR home OR nursing OR elderly OR residential OR institutionalized OR institutionalized OR geriatric NOT (infants OR children)</td>
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