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The risk of lower respiratory tract infection following influenza virus infection: A systematic and narrative review

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ABSTRACT

Background: Lower respiratory tract infections (LRTI) are a major cause of morbidity and mortality worldwide, particularly in young children and older adults. Influenza is known to cause severe disease but the risk of developing LRTI following influenza virus infection in various populations has not been systematically reviewed. Such data are important for estimating the impact specific influenza vaccine programs would have on LRTI outcomes in a community. We sought to review the published literature to determine the risk of developing LRTI following an influenza virus infection in individuals of any age. **Methods and findings:** We conducted a systematic review to identify prospective studies that estimated the incidence of LRTI following laboratory-confirmed influenza virus infection. We searched PubMed, Medline, and Embase databases for relevant literature. We supplemented this search with a narrative review of influenza and LRTI. The systematic review identified two prospective studies that both followed children less than 5 years. We also identified one additional pediatric study from our narrative review meeting the study inclusion criteria. Finally, we summarized recent case-control studies on the etiology of pneumonia in both adults and children.

Conclusions: There is a dearth of prospective studies evaluating the risk of developing LRTI following influenza virus infection. Determining the burden of severe LRTI that is attributable to influenza is necessary to estimate the benefits of influenza vaccine on this important public health outcome. Vaccine probe studies are an efficient way to evaluate these questions and should be encouraged going forward.

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1. Introduction

Pneumonia, bronchiolitis and other lower respiratory tract infections (LRTI) continue to be a major cause of morbidity and mortality worldwide disproportionately affecting adults ≥ 70 years and children < 5 years old. The Global Burden of Disease (GBD) project estimates that nearly 2 million of the 2.74 million LRTI-associated deaths were in these vulnerable age groups and that 10% were attributable to influenza [1]. There has been a recent increase in studies of the etiology of LRTI mostly attributable to the high sensitivity and relatively low cost of polymerase chain reaction (PCR)-based laboratory assays.

The link between severe influenza disease in adults and LRTI has been recognized for at least a century. The impact of seasonal influenza in the United States has been measured by a composite measure related to LRTI, pneumonia and influenza (P&I) mortality. P&I mortality is estimated indirectly from vital records databases,

and can be used to approximate the impact of influenza without laboratory confirmation due to the sharply seasonal nature of influenza virus infections in temperate countries. Similar methods are inconsistently applied to populations with a known number of at risk individuals, however, limiting the ability to calculate incidence of LRTI in the general population.

In children, recognition of severe outcomes following influenza virus infection has been comparatively recent. At first, this recognition relied on non-specific outcomes such as wintertime increases in acute respiratory disease hospitalizations [2–5]. Due to the non-specific presentation of LRTI in children, laboratory confirmation is essential for proper quantification of risk when other viruses, such as respiratory syncytial virus (RSV) or human metapneumovirus (HMPV), circulate at the same time as influenza.

The reliance of previous research on non-specific outcomes has resulted in uncertainty about the relative contribution of specific viruses to the overall burden. This issue can manifest as the distinction between primary viral and secondary bacterial infections or by infection with multiple viruses, among other concerns. Thus, to validly determine the risk of LRTI following influenza virus

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infection, ideally large, prospective studies with active surveillance, laboratory confirmation of infection, and long-term follow up are required. In addition, these studies must be longitudinal to capture illnesses in a series of years since incidence of influenza often varies markedly, especially in the tropics [6]. With these requirements as background, we conducted a landscape review incorporating a systematic literature search meeting the above criteria to estimate of risk of LRTI following influenza virus infection; recognizing that this estimate will represent a lower bound of the true burden. Since the systematic review identified very few articles which met these rigorous criteria we also present a narrative review with recommendations on alternative study designs to determine the potential impacts of influenza vaccine to reduce the global burden of LRTI.

2. Methods

2.1. Data sources and searches

We conducted a systematic review to determine the availability and quality of literature addressing the following question: What is the risk of lower respiratory tract infections or pneumonia following seasonal or pandemic influenza virus infection compared to those without influenza virus infection? (see Fig. 1). In September 2016 we searched PubMed, Medline (Ovid), and EMBASE databases using the search terms indicated in Table 1. We attempted to capture a range of clinical presentations considered LRTI including pneumonia, acute lower respiratory illness and bronchiolitis. Search results were restricted to English abstracts only and primary literature; all study designs were included in the original

search. Both articles and articles in press were included in EMBASE search parameters. Records were compiled using Endnote software and duplicates records were identified and removed. Abstracts were reviewed by a member of the study team (EM) and excluded if meeting the following exclusion criteria: (1) Not relevant to study question or not primary literature; (2) Not population-based (case report or case series); (3) Not comparative (i.e. not encompassing both influenza negative and positive; and LRTI and non-LRTI). Identified studies that met these criteria were further evaluated to determine if they met the inclusion criteria.

2.2. Narrative review

To supplement the systematic review, we also identified relevant review articles and meta-analyses and searched the lists of included studies for relevant primary literature references. Studies identified by the narrative review are summarized below but are excluded from the quality assessment and are reported separately from the systematic review results as they were not identified using the pre-defined search criteria.

2.3. Study selection

We included studies that prospectively evaluated the incidence of laboratory confirmed influenza virus infection and that followed participants with evidence of infection for development of LRTI. Studies were excluded if they tested for influenza after LRTI had already developed and been identified or if the study only included persons with laboratory-evidence of influenza. Additionally we excluded studies if they collected appropriate data but did not

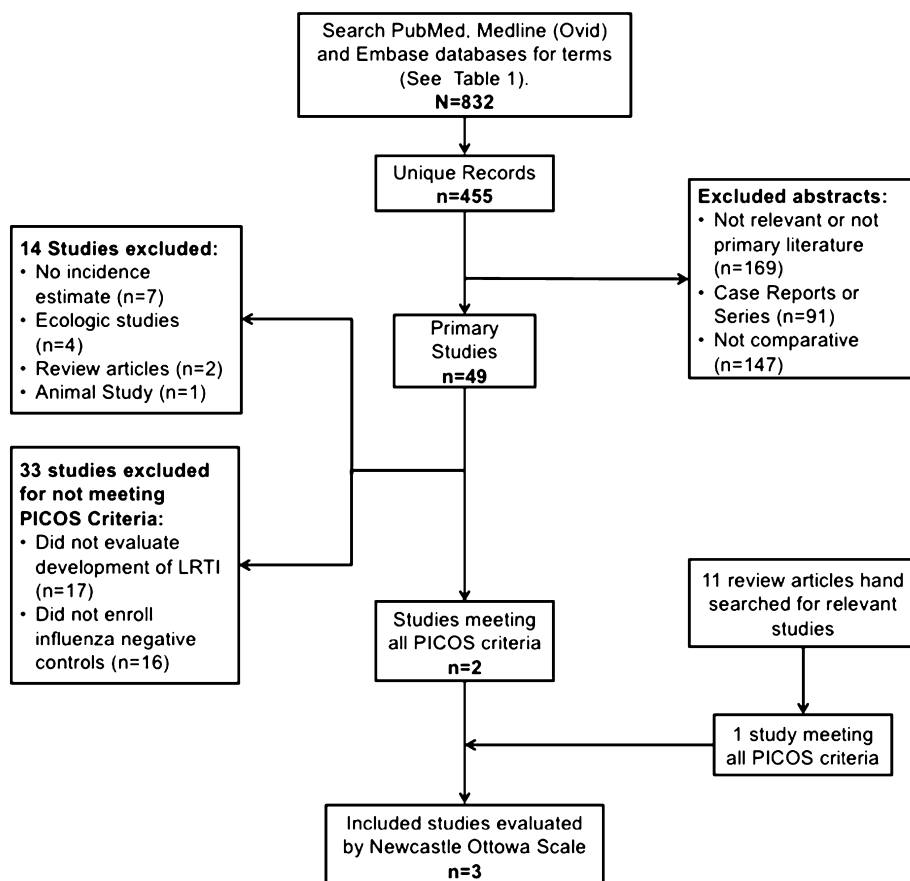


Fig. 1. Results of the systematic review.

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