Review

The burden of seasonal influenza in Italy: a systematic review of influenza-related complications, hospitalizations, and mortality

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**Abstract:** Background: reliable country-specific data on influenza burden play a crucial role in informing prevention and control measures. Our purpose was to provide a comprehensive summary of the available evidence on the burden of seasonal influenza in Italy. Methods: we performed a systematic literature review of articles published until 31 July 2020. PubMed, Embase and Web of Science were searched using terms related to burden, influenza, and Italian population. We included studies investigating seasonal influenza-related complications, hospitalizations and/or mortality. Results: sixteen studies were included: eight (50%) analyzed influenza-related complications, eight (50%) hospitalizations, while seven (43.8%) influenza-related deaths. Only three studies (19.7%) concerned pediatric age. The synthesis of results showed that patients with chronic conditions have an increased risk for complications up to almost three times as compared to healthy people. Hospitalizations due to influenza can occur in as much as 5% of infected people depending on the study setting. Excess deaths rates were over six-fold higher in the elderly as compared to the rest of population. Conclusions: although there are still gaps in existing data, there is evidence of the significant burden that influenza places each year especially on high-risk groups. These data should be used to inform public health decision-making.

**Keywords:** influenza, burden, Italy, mortality, complications, systematic review

1. Introduction

Seasonal influenza is an infectious disease that highly impact on population health in the Europe 1. Worldwide, annual influenza epidemics are estimated to result in about 3 to 5 million cases of severe illness, especially among older adults, young children (< 5 years), pregnant women, and individuals with chronic medical conditions 2. In high-income countries, most influenza-related deaths occur among people aged 65 years or older 3. Respiratory complications are the most common sequelae 4 and it has been estimated that about 290,000 to 650,000 deaths from respiratory causes 5,6 and 99,000 to 200,000 deaths from lower respiratory tract infections (LRTIs) are attributable to influenza annually 7. Furthermore, several extra-respiratory complications, such as cardiovascular and nervous system play an important role 8. Worryingly, seasonal influenza generally represents an underappreciated public health problem with significant socio-economic implications 9.

The monitoring and surveillance of seasonal influenza is possible through data collection and sharing systems, such as FluView in the United States (www.cdc.gov/flu/weekly) and FluNews in Europe (www.flunewseurope.org), that systematically collect data on seasonal influenza and publish periodic reports to inform on epidemiological trends. InfluNet is the Italian nationwide sentinel surveillance system for influenza, coordinated by the Italian National Institute of Health. It collects epidemiological (InfluNet-Epi) and virological (InfluNet-Vir) data that are weekly published on FluNews-Italy (https://www.epicentro.iss.it/influenza/FluNews) reports and uploaded into the European database coordinated by the European Centre for Disease Prevention and Control (ECDC). FluNews-Italy also integrates findings from other surveillance systems, such as the monitoring system of severe and complicated laboratory-confirmed cases of influenza, daily mortality among the elderly and InfluWeb (a web-based surveillance system of influenza-like illness – ILI). More information on influenza burden (e.g., complications and hospitalizations) can be gathered from other sources, such as Health for All database (https://www.istat.it/it/archivio/14562) or published papers. However, the available evidence is still suboptimal. For instance, Health technology assessment (HTA) projects of different preventive interventions against influenza have brought to light the need for more data 10-14.

In sum, reliable country-specific data on influenza burden play a crucial role in informing the planning of prevention and control measures to limit the spread of the disease and minimize associated costs. For this reason, in scientific literature, there are some country specific reviews aiming to assess influenza incidence and clinical and economic burden. The published reviews focus either on a specific geographical area, such as Latin America, Sub-Saharan Africa, Japan, or West Europe, or on a specific age range, such as elderly or pediatric age 15-21. To the best of our knowledge, no review has focused on Italy. Consequently, the present study aims to provide an overview of available data on the burden of seasonal influenza in Italy. Alongside the above-described Italian databases, this comprehensive review may be of aid for policy makers, health economists, public health practitioners and other relevant stakeholders.

2. Materials and Methods

This systematic review of the literature (PROSPERO registration number: CRD42021272644) was conducted following the 2020 PRISMA guidelines (Appendix 1: Check List PRISMA).

2.1 Identification of eligible studies

All studies quantifying the burden of seasonal influenza in Italy were potentially eligible, independently by initial influenza clinical presentation. The study outcome was the burden of influenza defined here as influenza-attributable complications, hospitalizations, or deaths. The study population was the entire Italian population, independently of age, health status and any other variable affected by both laboratory-confirmed influenza and clinical proxies (e.g., ILI). No formal limits were established for study design. By contrast, the following exclusion criteria were applied: (i) studies evaluating the burden of pandemic influenza; (ii) case reports and case series with no possibility to establish the population burden of influenza; (iii) economic modelling with no original data; (iv) narrative reviews and other forms of the second-hand research; (v) original studies focusing only on epidemiological and/or virological surveillance of the laboratory-confirmed influenza and/or ILI.

The literature search was performed by consulting three databases, namely PubMed, Web of Science (WoS) and Embase. The following search string was used on PubMed: “(epidemiology OR epidemiological OR virolog\* OR surveillance OR incidence OR (“attack” AND rate) OR complicat\* OR hospitalization OR (inpatient AND (admission OR care)) OR (outpatient AND (admission OR care)) OR (hospital AND (admission OR care OR discharge)) OR ambulatory OR mortality OR death OR sequelae OR visit) AND (influenza OR flu) AND (Italy OR italian)”. This spelling was then adapted to WoS and Embase. No search restrictions were applied. The search was updated to July 31st, 2020.

After removing duplicates, papers were screened by title and abstract first. Clearly ineligible studies were discarded. The remaining records were assessed in the full-text modality.

2.2 Data extraction and synthesis

From the articles definitively included in the literature review, the following information were extracted: bibliographic record, study location, study setting (i.e., outpatient, inpatient, institutionalized, mixed), main demographic characteristics of the study population (e.g., sample size, age, and sex distribution); study period/influenza season, type of outcomes and their occurrence. Moreover, if available, data were stratified by viral (sub)type and type of outcome.

A meta-analysis of data was not planned because of the expected heterogeneity in study populations and endpoints. Indeed, data were summarized in a narrative way.

2.3 Quality Assessment

The Newcastle-Ottawa Scale (NOS) was used for evaluating the quality of included studies. NOS adopts a star system, with a total score ranging from 0 to 9 and a score ≥7 indicating a high-quality study. Two investigators separately performed the quality evaluation of each study and disagreements were settled by a joint re-evaluation of the original article with a third author. No study was excluded based on quality criteria.

3. Results

The search of the three databases yielded a total of 9,268 articles. After duplicates removal, 6,640 articles were screened for title and abstract and 28 were selected for full text screening. It was not possible to retrieve 4 articles. Twenty-four articles were then screened by full text and 8 studies were excluded with the following reasons: did not meet the inclusion criteria (n=2), not related to the topic (n=4), reviews (=2). Eventually, 16 articles 22-33 published from 2001 to 2020 were included in the qualitative synthesis. Details about the study selection process are shown in the flowchart (Figure 1).

3.1 Studies’ characteristics and quality

Seven studies (43.7%) were conducted in the Northern Italy 22, 23, 25, 27, 28, 30, 33, three (19.7%) in Central Italy 26, 31, 32 and one in Southern Italy 29. Four (25%) were nationwide studies 24, 34-36 and one (6.2%) was conducted both in Lombardy (in Northern Italy) and Apulia (in Southern Italy) 37.

Five studies (31.2%) were set into a hospital 22, 25, 27, 32, 33, one (6.2%) in a residential drug-rehabilitation community 26, six (37.5%) in a primary care setting 23, 28, 29-31, 37 and four (25%) were based on administrative health data 24, 34-36. Regarding studies set in a primary care setting, one (16.67%) was set into a health care unit 33, one (16.67%) in the district of a local health authority (LHA) 30 and four (66.67%) based on General Practitioners (GPs) or Primary Care Pediatricians (PCPs) 28, 29, 31, 37.

Three articles (19.7%) concerned the pediatric age 27, 28, 32, three articles (18.7%) concerned adulthood 22, 26, 37 and four (25%) old age 33, 25, 30, 31, while four (25%) articles referred to the entire population without age distinction 24, 34, 35, 36.

Eight studies reported data on only one season 22, 26-29, 31, 33, 37; Rizzo et al. reported data from 1970 to 2001 34, 35 and Bertolani et al. reported data from 2008 to 2015 24. The other studies reported data on a period of up to four seasons 23, 24, 30, 32, 36. The characteristics of included studies are reported in Table 1.

The quality of studies varied in the range from 4 to 6 stars (median: 4; mean: 4.562) (Table 2). All the studies were judged to have a representative exposed cohort and a follow up long enough for outcomes to occur. The quality assessment was penalized by the absence of the non-exposed cohort that prevented assigning three stars for all the studies.

3.2 Health burden of influenza

3.2.1 Complications

Eight articles (50%) evaluated influenza-related complications 22, 25-28, 32, 33, 37; all of them analyzed respiratory complications, while five articles also analyzed non-respiratory ones 32, 26-28, 32, 37.

In the general population, complications occurred in 35.1% of patients visited by GPs for clinical influenza; elderly and patients with concomitant chronic diseases had a significant increased risk (OR respectively of 1.7 and 2.9) 37. According to the study setting, the percentage of people incurring complications fluctuated between 19.6% 26 and 65.5% in adulthood 22, 19.8% 28 and 44.4% in pediatric age 27, and 32.3% 25 and 57.8% 37 in the elderly. Fluctuations were due to both the severity of the disease and the study setting (hospital as compared to primary care). In particular, studies performed at the hospital setting 22, 25, 27 released higher estimates.

Respiratory complications were the most frequently described and, in the general adult population, bronchitis and pneumonia accounted for 43.2% of complications 37. As far as pneumonia is concerned, this occurred in 1.4% of people with clinical influenza visited by GPs 32 but in 5% of outpatients who underwent hematopoietic stem cell transplantation and former drug users 26, 32. In the pediatric age, 0.4-8.1% of children develop pneumonia 27, 28. Also, non-respiratory complications, such as cardiac and neurological, were reported in 6.8% and 3.4% out of 29 patients admitted to hospital with severe influenza 22. Nevertheless, the frequency of other complications was lower in the other studies 26, 37. Acute otitis media was mostly described in children and occurred in a percentage ranging from 10.8% and 13.9% of patients 27, 28.

3.2.2 Hospitalizations

Eight articles (50%) evaluated influenza-related hospitalizations 23, 24, 27-31, 37.

In the general population, hospitalization occurred in 0.43% of patients visited by GPs for clinical influenza, mostly (76.9%) in at-risk patients; pneumonia and bronchitis were the most reported causes of hospitalization 37. Influenza-related hospitalizations in pediatric population occurred in 0.7% out of 2,143 healthy children without severe chronic medical condition 28 and in 5.4% of children attending the emergency room 27.

Loconsole et al. 29 detected 8.85% hospitalizations in intensive care unit (ICU) for acute respiratory distress syndrome (ARDS) among people with a laboratory-confirmed diagnosis of influenza in Apulia region in the 2017/18 season, but it should be observed that this percentage refer to the subgroup of patients with influenza-like illness tested for influenza viruses because either hospitalized or for surveillance purpose. Eighty-four per cent of these people were not vaccinated. Another interesting information related to vaccination comes from Bellino et al. [23] that demonstrated a 34%, 22%, 14% and 12% reduction in hospitalization rates for influenza, pneumonia, respiratory causes, and cardiovascular diseases in vaccinated people in respect to unvaccinated. Mannino et al. 30 detected a very small number of hospitalizations in vaccinated people (<0.2%) and Manzoli et al. found even lower hospitalization rates in the elderly population 31. These last two studies relied on the consultation of hospital administrative databases and looked only at admissions for influenza and/or pneumonia. Bertolani et al. 24 pointed out an underestimate of influenza-related hospital admissions, estimating an average of 15,206 hospital admissions for respiratory and cardiovascular complications of influenza in addition to the 4,407 admissions reporting influenza specific codes during influenza seasons from 2008/09 to 2014/15.

3.2.3 Mortality

Four articles (25%) evaluated the number of deaths due to influenza in the study population 22, 23, 25, 29. Death occurred in 4.1 % of patients with laboratory-confirmed influenza [29], but in a higher percentage of patients with severe influenza or ARDS, namely 24.1% and 46% of cases 22, 29. Death occurred in 13.9% of hospitalized oldest-old patients with laboratory-confirmed influenza and/or respiratory syncytial virus infection 25. The risk of death was decreased by 33-39% by vaccination 23.

Three articles (18.7%) assessed nationwide excess deaths attributable to influenza 34-36. During the 1970-2001 period, estimated excess influenza-related mortality rates were 1.9-2.2 per 100,000 considering deaths caused by pneumonia and influenza and 11.6-18.6 per 100,000 considering deaths caused by all causes 35. During the same period, the age-adjusted excess deaths rates in the elderly were 13.3 per 100,000 for pneumonia and influenza and 91.1 per 100,000 for all causes 34. For the seasons from 2013/14 to 2016/17, excess influenza-related mortality rates estimated using the FluMOMO algorithm based on weekly influenza activity and environmental temperature ranged from 11.6 to 41.2 per 100,000 in the general population and from 65.0 to 147.3 per 100,000 in the elderly 36.

3.3 Viral strains contribution

Seven articles (43.8%) analyzed the contribution of viral strains 22, 25, 28, 29, 34-36 correlating the complications or the mortality to them (Table 3). In detail, one article evaluated the number of hospitalized and complicated cases of influenza A and B in the pediatric population 28, one the number of ARDS hospitalization in ICU caused by Influenza A or B 29, one the number of complicated patients requiring Non-Invasive Ventilation (NIV) 25, three articles evaluated the excess deaths in relation to viral strain 34-36 and one influenza strain found in dead people 22. As for complications, heterogeneous results emerged with B strain associated to a higher risk of NIV 20 and a higher percentage of hospitalization 28. About excess mortality there was evidence of a higher burden of A(H3N2) 34-36.

4. Discussion

This systematic review provides a comprehensive summary of the available scientific literature on the health burden of seasonal influenza in the Italian population. Seven of the sixteen papers that we identified were published within the last three years (2018-2020), suggesting an expanding interest in the topic.

As expected, respiratory complications were the most frequently described sequalae of the infection, but also non-respiratory cardiac and neurological complications were reported. On the contrary of other published systematic reviews, we extracted data on the total range of complications, independently by hospitalizations. In this regard, the studies performed at the primary care level in both pediatric and adult population 28, 37 provided a very relevant information on the type and frequency of influenza-related complications and allowed us to collect data also on those conditions that generally do not determine hospitalization, such as bronchitis and otitis. In particular bronchitis and pneumonia represented approximately half of the complications observed in adult population with clinical influenza at primary care level 37. Pneumonia affected a minor percentage of people but occurred in around 5% of individuals at risk 26, 33. As for the pediatric population, consistently with another systematic review on the topic, we found a lower probability of pneumonia in primary care-based studies as compared to hospital ones, but we were able to get a more precise estimation of the frequency of otitis media 15.

The findings of the papers included in this systematic review also showed a significant increased risk for complications among elderly (65+) and patients with at least one chronic condition 29, 37. This result is aligned with other systematic reviews on the topic 17, 21.

Influenza-related hospitalizations were shown to be as low as less than 0,1% to more than 5% according to the study setting. Considering the amount of people occurring each year influenza we should keep in mind that these results could translate to ten of thousands of hospitalizations each year. Interestingly, hospitalizations were shown to occur in a similar percentage of cases also in the pediatric population. Actually, the Italian Health For All database allows to ascertain that hospitalization rate for influenza and pneumonia in children less than 14 years old was the second highest after hospitalization rate of elderly across different age groups and this was also confirmed in other countries 21. Furthermore, another systematic review attributed 5-16% of pediatric respiratory hospitalizations to influenza 19.

In respect to mortality, the findings of this systematic review suggests that influenza is responsible for a relevant excess in mortality rate. Excess deaths rates for elderly were estimated to be over six-times higher than in general population with the most of influenza-related deaths (65-96%) occurred in persons 65+ 34, 36. These data were also confirmed by other systematic reviews 17, 38.

It is well-known that influenza is usually underreported on both death certificates and hospital discharge records either because secondary bacterial co-infections can develop or because influenza can make some chronic illnesses worse, and this information can be eventually registered as death cause in the place of influenza. Furthermore, it should be noted that patients with influenza-related complications are not always tested for influenza viruses, or they seek medical care late for influenza virus to be detected from respiratory samples. Indeed, both hospitalizations and deaths due to laboratory-confirmed influenza can be underestimated.

As far as the contribution of type of viral strain is concerned, the findings of our systematic review seem to suggest a higher mortality due to virus A, but less conclusive results may be drawn about complications and hospitalizations.

Given this, although gaps in existing data still exist, there is evidence of the significant burden that influenza places each year on the Italian population across all age groups. This is even more important considering that a projected increase of more than 30% of cases of influenza has been estimated in a 30 years’ time horizon in the US adult population aged 50 years and older 39. Similarly, an increase in costs is forecasted and approximately 50% of productivity loss costs will be attributed to influenza-related mortality while 75% of direct costs will be due to hospitalized cases. Indeed, the prevention of influenza is of utmost importance in particular among people with higher risk for these two outcomes. Recommendations for vaccinating high-risk groups are already implemented in most countries and generally encompass elderly albeit with different age cut-off 40, but attention should be paid also to children because mostly affected by the disease each year 41 and at risk of complications and hospitalizations. Nevertheless, more, and much standardized data would be worthwhile to inform the decision-making process at national level.

The findings of this systematic review should be interpreted considering the following limits. Because we restricted our review to published data available on three databases, it is not possible to exclude that we might have missed some articles. However, we believe that it is unlikely that additional relevant data could be found. Another limit is represented by the lack of pooled estimates that were not obtainable. Studies reported data across a range of seasons and settings and considered various endpoints, therefore they used different methods for evaluating the burden of influenza. Considering this heterogeneity, a meta-analysis of data was not performed.

This prevents having a clear estimate of probabilities of different influenza-related complications and calls for further standardized and population-based research in the field. Nevertheless, to the best of our knowledge, this review represents the first attempts to collect and summarize italian data and could offer clues for further research. In fact, a thorough and robust understanding of influenza-related burden is necessary to both make health systems prepared to manage influenza cases and better exploit the potential impact of control measures, such as vaccination.

5. Conclusions

The evidence on influenza-related complications, hospitalizations and mortality in the Italian population is fragmented because of heterogeneity in study populations, settings, and methods. Nonetheless, it shows the relevant burden that influence places each year, in particular among elderly, people with underlying conditions but also children. The overview provided by our systematic review can inform the current planning of prevention measures against influenza and pinpoints areas of research that deserve further development, namely the risk of the whole set of complications of influenza in children and high-risk through population-based follow up studies.

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**Table 1.** Studies’ characteristics and data

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First Author, year** | **City** | **Setting** | **Study population** | **Period/influenza season** | **Mean age** | **Male gender** | **N° of participants** | **Outcome** [% calculated on the number of participants] | | |
|  |  |  |  |  |  |  |  | **N° Deaths** | **N° Hospitalizations** | **N° Complications** |
| Bassetti M, 2019 | Udine | Hospital | Patients admitted with laboratory-confirmed influenza | 2017/18 | 48 (range 0-87) | 51.7% | 29 | 7 (24.1%) | N.A. | 19 (65.5%) |
| Bellino S, 2019 | Treviso | Primary care (Local Health Unit) and hospital | Three cohorts of elderly subjects 65+ | 2014/15-2016/17 | N.A. | 43.5-44% | 249,005  person-year (125,253 for vaccinated, and 123,752 for unvaccinated) | 4,855 and 3,276 in vaccinated and unvaccinated subjects | 18,355 (11,712 and 6,643 in vaccinated and unvaccinated subjects) (ICD-9-CM 487, 480-486, 460-466, 490-496, 500-508, 510-516, 410, 422, 427, 428, in primary or secondary diagnosis) | N.A. |
| Boattini M, 2020 | Torino, Lisbon, Nicosia (Cyprus) | Hospitals | Oldest-old (> 85) patients admitted for laboratory-confirmed influenza and/or RSV infection or developing it during the course of admission for other causes | 2017/18-2018/19 | 89.4 (±3,9 SD) | 31.5% | 251 | 35 (13.9%) | N.A. | 81 (32.27 %) (radiological signs of pneumonia) |
| Boschini A, 2006 | Rimini | Residential drug-rehabilitation community | Former injecting drug users with ILI | Feb-Mar 2004 | N.A. | 82.29% | 209 | N.A. | N.A. | 41 (19.62%) |
| Bosis S, 2005 | Milan | Hospital | Children < 15 attending the emergency room | Nov 1, 2002-Mar 31, 2003 | 4.0 (± 3.7 SD) | 50.7% | 223 (influenza positive) | N.A. | 12 (5.4%) | 99 (44.39%) |
| Esposito S, 2011 | Northern Italy | Primary care (PCPs) | Healthy children <14 years of age without severe chronic medical condition but with signs and/or symptoms of ILI | Nov 1, 2008-Apr 30, 2009 | 3.8 (± 2 SD) | 51% | 2,143 (influenza positive) | N.A. | 16 (0.7%) | 424 (19.78%) |
| Loconsole D,2019 | Apulia region | Primary care (sentinel-physician network of PCPs and GPs) and hospitals | Patients with ILI, patients hospitalised with severe acute respiratory illness, patients admitted to all ICUs of the region with ARDS | 2017/18 | N.A. | N.A. | 565 (influenza positive) | 23 (4.07%) (deaths occurred in patients with ICU-ARDS) | 50 (8.85%) (ICU-ARDS hospitalizations) | N.A. |
| Mannino S, 2013 | Cremona, Bergamo, Mantova, Lecco, Pavia | Primary care (Local health authorities' district) and hospital | Residents 65+ who sought influenza vaccination (excluding those in hospital, nursing homes or rehabilitation centers) | 2006/07-2008/09 | 76.5 among aTIV; 74.9 among TIV | 43.2% | aTIV: 84,665 person-season, TIV: 79,589 person-season | N.A. | aTIV: 114 (0.135%), TIV:111 (0.139%) (ICD-9-CM 480-487) | N.A. |
| Manzoli L, 2009 | Chieti, Pescara | Primary Care (GPs) | Elderly assisted by GPs | First semester 2007 | 75.8 (± 7.4 SD) | 43.4% | 32,457 | N.A. | 142 (0.44%) (ICD-9-CM 480-487) | N.A. |
| Mastrolia M, 2019 | Florence | Hospital | Children 1 month-14 years with laboratory-confirmed influenza associated to neurological disease | 2017/18-2018/19 | 27 months (IQR 7-48) | 26.67% | 15 | N.A. | N.A. | 1 (6.7%) (impairment in motor skills) |
| Mikulska M, 2013 | Genova | Hospital (HSCT unit) | Adult outpatients seen at least once a month in the HSCT unit | Jan 1- Mar 31 2011 | N.A. | 50% | 20 (influenza positive) | N.A. | N.A. | 1 (5%) (Clinical and radiological pneumonia) |
| Sessa, 2001 | Lombardy and Puglia | Primary care (GPs) | Patients visited for clinical influenza | Dec 15 1998-Mar 15 1999 | 40 | 49.9% | 6,057 | N.A. | 26 (0.43%) | 2125 (35.1%) |
| Bertolani A, 2018 | Nationwide | N.A. | General population | 2008, 2010-2015 | N.A. | N.A. | N.A. | N.A. | Average annual number of hospitalizations: 17,488 (3,508 observed 487 codes + 13,980 estimated from other codes) (ICD-9-CM 422, 427, 428, 460-466, 481-486, 487, 481-486, 490-496, 500-508, 510-516) | N.A. |
| Rizzo C, 2006 | Nationwide | N.A. | General population | 1970-2001 | N.A. | N.A. | N.A. | Excess mortality rate (per 100,000), P&I and AC respectively: 0.72 and 5.60 age 45-64; 14.13 and 98.86 age > 65 (ICD-8 codes 480-486 and 470-474, ICD-9 480-486 and 487) | N.A. | N.A. |
| Rizzo C, 2007 | Nationwide | N.A. | General population | 1970-2001 | N.A. | N.A. | N.A. | Excess deaths attributable to influenza: 57,234 from P&I, 318,806 from AC  Excess mortality rate (per 100,000), P&I and AC respectively (age-adjusted): 1.9-2.2 and 11.6-18.6 all ages; 0.4-0.7 and 4.3-6.6 age 45-64; 12.7-14.2 and 71.2-115.7 age 65+ (ICD-8 codes 480-486 and 470-474, ICD-9 480-486 and 487) | N.A. | N.A. |
| Rosano, 2019 | Nationwide | N.A. | General population | 2013/14-2016/17 | N.A. | N.A. | 5,290,000 estimated ILI | Excess deaths attributable to influenza: 68,068 (1,29% of ILI)  Excess mortality rate (per 100,000): 11.6-41.2 all ages; 65.0-147.3 65+) | N.A. | N.A. |

AC: all cause; ARDS: acute respiratory distress syndrome; GP: general practitioner; HSCT: hematopoietic stem cell transplantation; ICU: intensive care unit; ILI: influenza-like illness; N.A.: not available; PCP: primary care pediatrician; P&I: pneumonia and influenza; RSV: Respiratory Syncytial Virus; SD: standard deviation; TIV: trivalent inactivated vaccine; aTIV: adjuvanted trivalent inactivated vaccine

**Table 2.** Quality of included studies

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author, year | Representativeness of the exposed cohort | Selection of the unexposed cohort from the same community as the exposed | Ascertainment of exposure: secure record | Outcome of interest not present at start of study | Comparability of cohorts (on the basis of the outcome). Control for: | | Assessment of outcome | Follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts |
| important factor | additional factors |
| Bassetti., 2019 | \* | N.A. | \* |  | N.A. | N.A. | \* | \* |  |
| Bellino, 2019 | \* | N.A. | \* |  | N.A. | N.A. | \* | \* |  |
| Bertolani, 2018 | \* | N.A. | \* |  | N.A. | N.A. | \* | \* |  |
| Boattini, 2020 | \* | N.A. | \* |  | N.A. | N.A. | \* | \* |  |
| Boschini, 2006 | \* | N.A. |  | \* | N.A. | N.A. |  | \* | \* |
| Bosis, 2004 | \* | N.A. | \* | \* | N.A. | N.A. | \* | \* | \* |
| Esposito, 2011 | \* | N.A. | \* | \* | N.A. | N.A. | \* | \* | \* |
| Loconsole, 2019 | \* | N.A. | \* |  | N.A. | N.A. | \* | \* |  |
| Mannino, 2012 | \* | N.A. |  | \* | N.A. | N.A. | \* | \* | \* |
| Manzoli, 2009 | \* | N.A. | \* | \* | N.A. | N.A. | \* | \* | \* |
| Mastrolia, 2019 | \* | N.A. | \* |  | N.A. | N.A. | \* | \* |  |
| Mikulska, 2014 | \* | N.A. | \* | \* | N.A. | N.A. | \* | \* | \* |
| Rizzo, 2006 | \* | N.A. | \* |  | N.A. | N.A. | \* | \* |  |
| Rizzo, 2007 | \* | N.A. | \* |  | N.A. | N.A. | \* | \* |  |
| Rosano, 2019 | \* | N.A. | \* |  | N.A. | N.A. | \* | \* |  |
| Sessa, 2001 | \* | N.A. |  | \* | N.A. | N.A. |  | \* | \* |

N.A.: not available

Referring to the Newcastle Ottawa Scale, the star is allocated if methods adopted are considered acceptable

**Table 3.** Data on the contribution of influenza strains

|  |  |  |  |
| --- | --- | --- | --- |
| **First Author, year** | **Data stratified by influenza strain** (% calculated on the total of influenza cases by strain) | | |
|  | **Deaths** | **Hospitalizations** | **Complications** |
| Bassetti M, 2019 | **B**: 4 (21.1%) | N.A. | N.A. |
| Boattini M, 2020 | N.A. | N.A. | **B**: associated with NIV (OR 3.77; p=0.041) |
| Esposito S, 2011 | N.A. | **A**: 14 (0.8%); **B**:2 (51%) | **A**: Acute otitis media 195 (11.1%); Acute bronchitis 135 (7.7%), Wheezing 12 (0.7%), Pneumonia 8 (0.5%); **B**: Acute otitis media 36 (9.2%); Acute bronchitis 34 (8.7%), Wheezing 3 (0.8%), Pneumonia 1 (0.3%) |
| Loconsole D,2019 | N.A. | N.A. | **A/H1N1pdm09**: ICU-ARDS 25 (15.2%); **A/H3N2**: ICU-ARDS 1 (0.6%); **B**: ICU-ARDS 24 (6%) |
| Rizzo C, 2006 | **A(H3N2)**: Excess mortality rate P&I 1.04 age 45-64 / 19.37 age 65+; Excess mortality rate AC 7.53 age 45-64 / 127.69 age 65+ | N.A. | N.A. |
| Rizzo C, 2007 | **A(H3N2)**: excess deaths from AC and P&I four time higher than that for the seasons in which viruses A(H1N1) or B were predominant | N.A. | N.A. |
| Rosano, 2019 | **A(H3N2)**: Remarkable excess death attributable it in seasons 2014-15 and 2016-17 | N.A. | N.A. |

AC: all cause; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; ILI: influenza-like illness; N.A.: not available; NIV: Non Invasive Ventilation; P&I: pneumonia and influenza

**Figures legend’s: Figure 1.** Flow chart of the selection process

**Appendix legend’s: Appendix 1**: Check List PRISMA