Globally, lower respiratory tract infections (LRTIs), including community-acquired pneumonia (CAP), cause considerable morbidity and mortality in adults, especially in the elderly. In addition to age, underlying medical conditions are associated with an increased risk of CAP. From an aetiological point of view, Streptococcus pneumoniae is the leading cause of adult CAP throughout the world. Two types of vaccine are available for the prevention of pneumococcal diseases: the pneumococcal polysaccharide vaccine (PPV23) and the pneumococcal conjugate vaccine (PCV7, PCV10 and PCV13). An accurate understanding of the LRTIs burden and the types of subjects at risk of CAP, allow to find an appropriately targeted immunization strategy and provide baseline data to evaluate pneumococcal vaccine effectiveness. Given the high variability in available estimates of LRTIs burden and associated risk factors, the objective of the study was to discuss the methodological criticism in its evaluation, in the light of the gradual introduction of PCV13 immunization strategy targeted to elderly and risk groups in middle-high income countries.

**Introduction**

Globally, LRTIs, including CAP, are a major cause of morbidity and mortality in adults in developed countries, leading to high hospitalizations rates, especially in the elderly [1-4]. According to recent estimates, LRTIs are the fourth most common cause of death, exceeded only by ischemic heart disease, strokes and chronic obstructive pulmonary disease (COPD), and 1.9 million adults aged ≥15 years die from LRTIs every year worldwide. The 2010 Global Burden of Disease Study reported also that LRTIs are the second most frequent reason for years of life lost [5]. Among Europe, CAP is the leading cause of death due to infection [4], with almost 90% of deaths due to pneumonia occurring in subjects > 65 years-old [6]. Pneumonia has also a substantial burden on healthcare resources and society, with associated annual costs in Europe estimated at approximately €10 billion, mostly due to hospitalization and lost working days [7]. Studies have shown that the risks of CAP and CAP-related deaths increase with age and are highest among the elderly [2, 3], indicating that the burden of pneumonia is growing in this era of global population aging [8-11]. The “oldest old” (≥ 85 years) are at particularly high risk of infections, due to comorbidities and waning immune function [12]. Moreover, in these subjects CAP can have serious consequences and aggravate underlying comorbidities [13].

In addition to age >65 years, other risk factors for CAP are recognized, such as chronic cardiovascular or respiratory diseases, cerebrovascular diseases, epilepsy, dementia, dysphagia, chronic liver or renal diseases, lifestyle factors (smoking, alcohol consumption, being underweight, regular contact with children and dental hygiene), and immunosuppressive conditions [14, 15]. From an aetiological point of view, Streptococcus pneumoniae is the leading cause of adult CAP throughout the world [3, 16, 17], and has been estimated to be the cause of 30-50% cases of CAP requiring hospitalization in adults in developed countries [18]. Nevertheless, in high-income countries it has been decreasing as a consequence of the wide use of antibiotics and of the introduction of pneumococcal vaccines [19]. From the clinical and public health perspectives, estimates of the overall health care burden and aetiological patterns of CAP are crucial for effective disease control programs [1, 2]; however, available estimates largely vary, so that its true burden remains unclear. The objective of the present study is to discuss the methodological criticism in the evaluation of the burden of LRTIs, including pneumonia, and of the pneumococcal vaccine effectiveness, in the light of the gradual introduction of PCV13 immunization strategy targeted to elderly and risk groups in middle-high income countries.
Knowledge gap for PCV introduction in adults: criticisms in the definition of the burden of pneumonia and LRTIs

Although LRTIs, including pneumonia, are common diseases, the real burden and their related risk factors remain unclear, even in high-income countries [20]. Available incidence estimates largely vary, making the comparison of LRTIs and CAP incidence obtained from different studies difficult (Fig. 1) [15]. Epidemiological studies conducted in the second half of 2000 among adults have reported hospitalization rate of about 1.1 and 2.8 per 1,000 year in the UK and in Germany, respectively [21, 22]. The overall incidence estimated in hospitalized adult patients for CAP who lived in two countries in Ohio, USA, was 2.6 per 1,000 inhabitants year [23]. Furthermore, a study conducted in Denmark between 1993 and 2008 reported rate of hospitalization for pneumonia lower than 4 per 1,000 in adults aged >50 years [24].

Several factors explain the variation of available CAP estimates and they are deepen below. First, the performance of surveillance system in terms of specificity and sensitivity in capturing LRTI cases is suboptimal. This limit could be overcome using a syndromic surveillance system that combines high sensitivity in identifying suspected cases obtained by scanning the chief complaint field for the word strings assigned to the single syndrome and automatic review of ED acceptance data folders and high specificity as a result of critical revision of each reported case according to the operative case definition [15].

Second, the definition of pneumonia differs among studies [25]: some studies used chest X-ray findings to determine pneumonia [9, 11, 26], whereas others used clinically defined criteria or simply relied on reported cases at the sentinel sites [25, 27]. Additionally, the diagnosis of pneumonia is not standardized in clinical settings [20]. Furthermore some studies have reported incidences of CAP including both outpatients and hospitalized patients [11, 29], while other studies evaluated hospitalized cases only [21, 30], introducing a selective bias towards severe patients. Lastly, mild cases must be overlooked in countries in which access to health care is limited, affecting the incidence estimates by the health care-seeking pattern [20].

Third, the heterogeneity of study design and difference in the underlying risk profile and age categorizations of the populations studied [12, 31-33] produce different estimates [20]. Furthermore, some studies of regional and socio-economic variations in LRTIs incidence have not age-stratified further after 65 years, but this group include very different subjects, both people working full-time and those that require round-the clock care [12]. Last but not the least, available incidence estimates also vary from setting to setting, reflecting national differences in health systems and medical practice [3, 11, 12, 21, 28-30, 34-35].

The pneumococcal immunization strategies in adults

Currently, two type of vaccines are available to prevent pneumococcal-related disease in adults: a polysaccharide vaccine and pneumococcal conjugate vaccines [36]. During 1970s the PPV-23 was introduced in high-income countries for the prevention of pneumococcal...
diseases caused by the 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F) in adults and children aged ≥2 years [37].

Furthermore, in many countries the PPV23 has been recommended for high-risk groups, including the elderly [38, 39]. However, there is little evidence that it is effective in adults with chronic diseases and in the elderly [40, 41]. Although available systematic reviews and meta-analyses demonstrate that PPV23 confer protection against invasive pneumococcal disease (IPDs) [38, 41], its duration is limited [42, 43], and its effectiveness against pneumococcal pneumonia is still controversial, particularly for the elderly [40, 41].

The first pneumococcal conjugate vaccine (PCV7) was licensed in 2000 for protection against IPDs, including sepsis, meningitis, and non-invasive diseases, such as pneumonia and acute otitis media (AOM), caused by the seven serotypes contained in the vaccine (4, 6B, 9V, 14, 18C, 19F and 23F) in infants and children aged 2 months to 5 years [44]. In 2009 PCV10 (serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F) was approved for protection against IPDs, pneumonia and AOM in infants and children aged from 6 weeks up to 5 years [45].

Today a PCV13 vaccine, including six additional serotypes to PCV7 (1, 3, 5, 6A, 7F and 19A) is available for the prevention of IPDs and pneumococcal pneumonia in adults aged ≥18 years and the elderly, and for the prevention of IPDs, pneumonia and AOM in infants and children aged between 6 weeks and 17 years [46]. Since 2006, the WHO has recommended that PCV be included in all routine childhood immunization programs [47]. Of the European region member states, 49% had introduced PCV by 2012.

In countries with high immunization coverage the benefits of childhood immunization have been observed over time also in unvaccinated children and adults, as a result of the “herd immunity” effect [48-51]. However, despite extensive childhood immunization plan, the burden in the elderly and high risk groups remains high [15, 52].

Since the indication of PCV13 use has been extended to adults ≥ 50 years-old in 2011, its gradual inclusion in adults immunization plan has been observed in high-income countries, in addition to childhood immunization programs [53]. Nevertheless, pneumococcal immunization strategies vary with regards to age groups and risk groups to be immunized, the type vaccine (PPV and/or PCV) and the eligibility for reimbursement [15, 53].

Based on available epidemiological evidence, the best pneumococcal immunization strategy to reduce the burden of LRTIs should be age- and risk-based. In fact, although “at-risk strategy” has many disadvantages (i.e. difficult access to health services, involvement of different healthcare professionals, difficult to achieve high levels of vaccine uptake), it should be greatly implemented and coupled by age-based strategy [15]. The majority of the Western European countries has implemented this coupled strategy [53-54], however the number of identified risk groups and the age group eligible for vaccination varies in the different countries [36, 53].

### PCV13 effectiveness estimation in prevention of LRTIs in elderly and risk groups

Today, the estimation of PCV13 effectiveness in prevention of LRTIs in elderly and risk groups is of particular scientific interest due to its more recent introduction than PPV23, but it shows many methodological issues. RCTs, such as the recently published CAPITA study [55], provide the most definitive data about the efficacy of PCV13 vaccine, but performing such trials is extremely difficult [56] and expensive and entails many ethical issues. In fact, pneumococcal vaccine is recommended in the elderly, those with chronic conditions and immunosuppressed subjects, making placebo-controlled trials unethical in these groups [57]. Furthermore, pneumococcal pneumonia is a relatively uncommon outcome, so RCTs of PCV13 must consider large populations to have adequate statistical power [56].

Existing observational methods for evaluating vaccine effectiveness, such as cohort and case-control studies, are cheaper and logistically easier, but they implies the risk of introduction of biases that may interfere with vaccine effectiveness estimates [56]. Routinely collected administrative data don’t provide adequately accurate databases to estimate vaccine effectiveness. Furthermore many biases (some of which are difficult to detect) pose challenges in distinguishing vaccine-related effects from other potential confounders that may affect the same outcomes. They include differences in susceptibility to infection and differences in health care utilization in vaccinated and unvaccinated populations. In particular, vaccinated group usually include healthy subjects that have social interactions and then are exposed to LRTIs. Conversely, they have a lower risk of developing complications and serious outcome, such as deaths, than unvaccinated subjects. As demonstrated in the study published by Weycker D et al. in 2010, the annual incidence of non-bacteremic pneumococcal pneumonia requiring inpatient care is 17 and 10 folds higher in high risk subjects in 64-74 years and 75-84 years, respectively [58]. Then, the evaluation of vaccinated and unvaccinated groups should take into account the differences in LRTIs outcomes.

Otherwise proxy indicators such as antibody response are not applicable, in particular to evaluate the effectiveness against non-invasive diseases. Enzyme-linked immunosorbert assay (ELISA) can be used to measure antipneumococcal IgG antibodies [59], giving reproducible results. However, there is no consensus regarding the protective antibody levels in adults [56]. Furthermore, older adults develop antibodies characterized by reduced function [60] and ELISA cannot distinguish between functional and nonfunctional antibodies [61].
Opsonophagocytic killing (OPK) activity [56] has been shown to correlate with immune protection in animal studies [60] and have also been shown to correlate with protection better than ELISA for AOM in children [62]. However, no available studies correlates OPK assay results with protection in adults [56].

Finally, it is hard to find the correct clinical and laboratory endpoint to accurately estimate the incidence of pneumonia pneumococcal-related. The choice of clinical pneumonia as an endpoint is therefore biased in favor of high sensitivity, at the expense of specificity. Indeed, a large proportion of the cases that meet the case definitions for clinical pneumonia have a low positive predictive value and are, therefore, not pneumonia [63]. Conversely, radiologically-confirmed pneumonia is a relatively more specific measure of CAP and so evaluating vaccine efficacy on this outcome measure is a better indicator. Furthermore, the level of vaccine-induced pneumococcal antibody in adults that correlates with protection against clinical disease, including IPDs or pneumococcal pneumonia, has not been established [64]. Furthermore, classical microbiological assays, such as Gram-staining and culture from sputum and/or blood, underestimates the burden of pneumococcal pneumonia and the results are delayed. The isolation of *Streptococcus pneumoniae* from blood allows a specific aetiological diagnosis but with a detection rate of 10%-20% [36]. Urinary antigen tests for *Streptococcus pneumoniae* have been developed to overcome the limits of culture-based tests, and are characterized by high specificity and sensitivity in adults [65-68] and can help monitor changes in overall burden of pneumococcal CAP [69] but they should be developed for a broader research use and a wider range of pneumococcal serotypes, before their widespread use [64]; thus, documenting *Streptococcus pneumoniae*-specific impact is quite challenging [56].

Molecular methods represent another non-culture-based diagnostic approach that allows to rapidly and accurately quantify the bacterial load [36]. These methods are more sensitive than blood culture and may be a useful tool for the assessment of the severity of pneumococcal pneumonia [70]. Finally, molecular methods, in addition to conventional laboratory methods, are the best strategy to detect pneumococcal pneumonia [71-74].

Conclusions

Available evidence show that the burden of LRTIs, including pneumonia, in adults is relevant and strongly age- and risk factors-related [15]. Nevertheless the estimation of LRTIs and their prevalence in risk groups largely vary among published studies. Considering the availability of effective vaccine in prevention of pneumococcal pneumonia, i.e. PCV13, an accurate understanding of the LRTIs burden and the types of subjects at risk of CAP, allow to find an appropriately targeted immunization strategy that optimize the vaccine effect and provide baseline data to evaluate pneumococcal vaccine effectiveness [14, 15].

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