SHORT ARTICLE

Bacterial carriage and respiratory tract infections in subjects ≥ 60 years during an influenza season: implications for the epidemiology of Community Acquired Pneumonia and influenza vaccine effectiveness

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Key words

Influenza • Pneumococcus • Elderly

Summary

Introduction. *During the 2010/11 influenza season an epidemiological prospective cohort active study was organized, to evaluate etiologic role due to the main bacteria and viruses causing Community Acquired Pneumonia (CAP) and Influenza like-illness (ILI) in elderly and to explore the role of the bacterial nose-pharingeal carriage in subjects with respiratory tract infections.*
Methods. *An integrated active surveillance of a cohort of adults aged ≥ 60 y based on a double prospective and retrospective mechanisms of capture of ILI and CAP cases was organized. Samples were collected from all ILI and CAP prospectively identified. The samples were be tested by multiplex PCR for detection of the main respiratory bacteria and viruses.*
Results and discussion. *The study population amounted to 2,551 adults. During the 2010/11 influenza season, the ILI cumulative incidence was 4.2%, that was twice higher than that calculated by regional sentinel–based Influenza surveillance system during the 2010/11 season in the elderly (2.2%). Among 45 patients with ILI of which had been collected the swab, 17 (37.8%) were positive for influenza viruses and 2 (4.4%) for RSV, 6 (13.3%) patients carried Streptococcus pn and 6 (13.3%) Haemophilus in. In the same period, 7 CAP cases were observed; 3 cases were prospectively identified and samples were collected, while 4 cases were retrospectively detected. The CAP cumulative incidence was 0,3%. The influenza vaccine effectiveness in prevention of laboratory-confirmed influenza emerged by our study was 61%, in condition of good antigenic matching between vaccine and circulating strains observed during the 2010/11. These data contribute to better defining the epidemiological picture of upper and lower respiratory tract infections, fundamental information in light of the recent introduction of new vaccines for prevention of pneumonia in the elderly, including 13-valent conjugate pneumococcal vaccine.*

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Introduction

Community Acquired Pneumonia (CAP) and Influenza have a relevant impact in terms of Public Health especially in elderly and high risk groups. Combined, influenza and pneumonia rank as the sixth leading cause of death worldwide and as the leading infectious cause of death [1, 2]. Synergism exists between influenza virus and bacterial pathogens, in particular Streptococcus pn, accounting for excess mortality during influenza epidemics. The synergistic interaction between influenza virus and streptococcus pn is a multifactorial process. What these factors are and what the relative contribution of each is to excess morbidity and mortality is poorly understood [3]. Furthermore, other respiratory viral infections may facilitate secondary bacterial infections through different mechanisms, largely little known [4]. Further comprehensive studies of the viral and bacterial etiology of upper and lower respiratory tract infections are required both for estimate the real burden of the different agents and for setting up a prevention and control strategies for CAP. In order to evaluate etiologic role due to the main bacteria and viruses causing CAP and Influenza like-illness (ILI) in elderly and to explore the role of the bacterial nose-pharingeal carriage in subjects with respiratory tract infections, an epidemiological, lab-based, population-based, prospective cohort active study was organized during the 2010/11 influenza season. The secondary aims of the study included the estimation of the incidence of CAP and ILI in adults older than 60 years, the evaluation of the role of the potential risk-factors associated with CAP and ILI and the study of the pattern of co-infections between respiratory viruses and bacteria.

Methods

Procedures of the Study. Twenty General Practitioners (estimated surveyed ≥ 60 year adults: > 9,000) invited eligible subjects aged ≥ 60 years to participate into the

study, coordinated by the Department of Health Sciences, University of Genoa. At this Centre, subjects received information about aims and procedures of the study; inclusion and exclusion criteria were checked by the investigators of the Centre and written informed consent was obtained for each participants. Inclusion criteria included age ≥60 years, written informed consent, availability to follow study procedures, vaccination with 23-valent polysaccharides pneumococcal vaccine performed not less than 5 years before the study entry, participation to any other clinical trial, any particular clinical conditions that could interfere with the study activities and aims. Demographic and medical data were collected by the investigators and the case definitions of clinically suspected CAP and ILI were illustrated to the eligible participants (see the following section). Between November 2010 and April 2011, each participant who presented a respiratory tract infection episode should phone to the Department of Health Sciences, using a dedicated phone-number (on call seven days per week, between 8 a.m. to 8 p.m.). A health care worker of the Department of Health Sciences, in agreement with the general practitioner, went to the patient home or to hospital to obtain further information about her/his clinical conditions and to collect biological samples for the virological and microbiological assays: these procedures included a nase-pharingeal swab, a urine and a blood (0.5 ml) sample for patients with suspected CAP and a nase-pharingeal swab for all the patients presenting ILI. Moreover, an active phone-survey was performed by the study personnel of the Department of Health Sciences, to monitor the medical conditions of the enrolled participants, and to verify the potential occurrence of any suspected clinical respiratory syndrome not signaled by phone by the patient, yet. A risk-assessment analysis of all the main factors and conditions reported by the patients presenting CAP and ILI will be performed.

Definitions of CAP and ILI. Suspected CAP was considered in any patient with an acute illness and symptoms suggesting lower respiratory tract infection, including a new cough with high fever or chills, pleuritic chest pain, dyspnea or prolonged fever.

Confirmed CAP was defined as a new radiological infiltrate associated with one major criteria (cough, expectoration and fever) or two minor criteria (dyspnea, pleuritic pain, altered mental status, pulmonary consolidation on auscultation, and leukocytosis).

ILI was defined by the presence of fever > 38°C and at least one other symptom (headache, malaise, myalgia, chills or sweats, asthenia) and one respiratory symptom (cough, sore throat, nasal congestion or runny nose), according Italian surveillance network guideline.

Laboratory assays. Collected biological samples will be tested by multiplex PCR for detection of the main respiratory bacteria and viruses. The detection of Streptococcus pn, Legionella pn, Chlamidia pn, Haemophilus in, Mycoplasma pn, Bordetella pertussis and by type A and B Influenza Virus, Respiratory Syncytial Virus, Parainfluenza virus, Adenovirus, Coronavirus, Metapneumovirus, Rhinovirus will be performed using molecular tests of genic amplification multiplex Seeplex PneumoBacter ACE (Seegene) and Seeplex RV12 ACE (Seegene), respectively [5]. Influenza viruses will be characterized using HI assay and sequence analysis of genes codifying surface glycoproteins (HA and NA).

Results

The study population amounted to 2,551 adults aged more than 59 years (≥ 60 years). Age distribution, risk factors for influenza complication and pneumonia, and influenza vaccination coverage in the study population is reported in Table I. Age group including subjects older than 79 years was the largest and showed the highest prevalence of patients with chronic heart failure (8%) and the highest influenza vaccine coverage (87%). Subjects aged between 75 and 79 years showed the highest prevalence of chronic heart (13%) and pulmonary chronic (8%) diseases, while diabetes was more frequent in 70-74 year adults (19%). The influenza vaccine coverage observed among the 2,551 ≥ 60 year adults (74%) was very close to the 2010 WHO objective for subjects older than 65 years (75%). The WHO objective was reached in 70-74 (78%), 75-79 (81%) and ≥ 80 (87%) year age groups.

Tab. I. Age distribution, risk factors for influenza complication and pneumonia, and influenza vaccination coverage in the study population.

	Age group (yrs)						
	60-64	65-69	70-74	75-79	≥80	Unknown	All
Enrolled subjects	378 (15%)	438 (17%)	547 (21%)	481 (19%)	628 (25%)	79 (3%)	2,551 (100%)
Risk factors							
Chronic heart disease (%)	6	7	10	13	11		10
Chronic heart failure (%)	1	2	1	3	8		3
Pulmonary chronic dis. (%)	2	4	6	8	7		5
Diabetes (%)	14	15	19	16	15		16
Previous Hospital. (%)	17	16	17	17	17		17
Influenza vaccination* (%)	48	67	77	81	87		74

* considering only subjects whose age was known

During the 2010/11 influenza season, 108 ILI cases were observed; 45 cases were prospectively identified and samples were collected, while 63 cases were retrospectively detected by the active phone-survey foreseen by the protocol. The cumulative incidence of ILI was 4.2% (95% C.I. 3.5-5.1%). ILI cumulative incidence according age groups was shown in Figure 1. Among 45 patients with ILI of which had been collected the swab, 17 (37.8%) were positive for influenza viruses and 2 (4.4%) for RSV. Typing and sub-typing of influenza viruses allowed to identify 10 A(H1N1) pdm 09, 3 A(H3N2) and 4 B viruses; molecular characterization of hemagglutinine confirmed the good matching between circulating strains and vaccine viruses.
The cumulative incidence of laboratory-confirmed influenza was 0.7% (95% C.I. 0.4-1.1%). If the proportion of samples positive for influenza we observed among patients with ILI of which had been collected the swab was applied to all cases of ILI, the incidence of laboratory-confirmed influenza would rise to 1.6% (95% C.I. 1.2-2.2%).
According influenza vaccination status, 0.5% (95% C.I. 0.2-0.9%) and 1.2% (95% C.I. 0.6-2.2%) among vaccinated and non-vaccinated subjects, respectively, had laboratory-confirmed influenza. The influenza vaccine effectiveness in prevention of laboratory-confirmed influenza was 61.3% (95% C.I. 0.1-85%).
Among 45 adults with ILI of which had been collected the swab, 6 (13.3%) patients carried Streptococcus pn and 6 (13.3%) Haemophilus in.
Between November 2010 and April 2011, 7 CAP cases were observed; 3 cases were prospectively identified and samples were collected, while 4 cases were retrospectively detected by the active phone-survey foreseen by the protocol. The cumulative incidence of CAP was 0.3% (95% C.I. 0.1-0.6%). Among 3 patients with CAP of which had been collected the swab, 1 was positive for A(H1N1) pdm 09 influenza virus.

Discussion

By coupling a sentinel-based and active epidemiological surveillance for the detection and documentation of ILI and CAP cases with a virological and bacteriological surveillance for laboratory confirmation of the etiology, our study precisely defined the impact of upper and lower respiratory tract infections in adults aged ≥ 60 years.
Some potential limitations of this investigation should be mentioned. First, the study focused on only a single health care setting (primary care facilities) and disregarded the burden of ILI and CAP on hospitals and emergency departments. Second, only adults seeking health care or remembering ILI or CAP events were identified by surveillance system, resulting in an underestimation of incidence rates and in potential bias (because study selection may have been influenced by factors such as the socioeconomic status or the severity of the disease). Third, the small study population limited the precision of some estimates, such as vaccine effectiveness.
Despite these limitations, the design of surveillance system allowed a very high sensitivity in detection of ILI and CAP cases and an estimation both of the role played by the different etiologic agents and of vaccine effectiveness.
Our estimation of ILI cumulative incidence was 4.2%, that was twice higher than that calculated by regional sentinel-based Influenza surveillance system during the 2010/11 season in the elderly (2.2%) and was higher than the incidence registered by Italian sentinel-based Influenza surveillance system in this age-group in the last decade [6]. The incidence of laboratory-confirmed influenza estimated in the elderly if a swab was available for every ILI cases (1.6%) was higher than that observed in England, in Australia and Hong Kong and similar to that observed in Norway and New Zealand in serological studies after the first pandemic wave [7]. Although these data should be confirmed by other studies, they would change the perception of the impact of ILI and influenza in elderly populations where high vaccine coverage have been achieved.
The CAP incidence we observed, corresponding to 6.4 cases/1,000 year*person using person time of follow-up as denominators, was in line with that observed in Europe and North America: incidence rates varying between 2-40 cases/1,000 elderly person*year have been reported during the last two decades [8-12].
As far as the etiologic role played by the different viruses and bacteria, in our study, the responsibility of influenza viruses was preeminent: 38% and 33% of ILI and CAP, respectively, were due to A(H1N1) pdm 09, AH3N2) or B influenza viruses. Worthy of note and deserving of further study is the frequent carriage of Streptococcus pn and Haemophilus in observed in subjects with ILI.
The estimation of effectiveness of the seasonal influenza vaccine to prevent ILI confirmed as influenza, among the target population for the influenza vaccine is an ongoing challenge. Influenza virus is constantly evolving and the antigenic composition of vaccines requires annual update. Therefore, vaccine effectiveness estimates from previous years cannot be used to measure the performance of the current year's vaccine. The influenza vaccine effectiveness in prevention of laboratory-confirmed influenza emerged by our study winter was 61%, in condition of good antigenic matching between vaccine and circulating strains observed during the 2010/11. I-MOVE (Influenza Monitoring Vaccine Effectiveness in Europe), a multicentre case-control study based on sentinel practitioner surveillance networks in eight European Union Countries, estimated 2010/11 influenza vaccine effectiveness against medically-attended ILI laboratory-confirmed as influenza. In I-MOVE study, adjusted vaccine effectiveness in adults aged more than 60 years was 60% (95% C.I. 17-81%). Interestingly, although the approaches, the study design and the population used in our study and in I-MOVE are different, the estimation of vaccine effectiveness was overlapping, consolidating the data published by Kissling [13].
These data contribute to better defining the epidemiological picture of upper and lower respiratory tract infections, fundamental information in light of the recent

introduction of new vaccines for prevention of pneumonia in the elderly, including 13-valent conjugate pneumococcal vaccine. Continued surveillance will be crucial to further understand the mechanisms of interaction between viruses and bacteria in determining both upper and lower respiratory tract infections and the effect of the implementation of pneumococcal vaccination.

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■ Received on January 24, 2012. Accepted on March 5, 2012.

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