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Influenza vaccine effectiveness in Italy: Age, subtype-specific and vaccine type estimates 2014/15 season

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ABSTRACT

The 2014/15 influenza season in Europe was characterised by the circulation of influenza A(H3N2) viruses with an antigenic and genetic mismatch from the vaccine strain A/Texas/50/2012(H3N2) recommended for the Northern hemisphere for the 2014/15 season. Italy, differently from other EU countries where most of the subtyped influenza A viruses were H3N2, experienced a 2014/15 season characterized by an extended circulation of two influenza viruses: A(H1N1)pdm09 and A(H3N2), that both contributed substantially to morbidity.

Within the context of the existing National sentinel influenza surveillance system (InfluNet) a test-negative case-control study was established in order to produce vaccine effectiveness (VE) estimates. The point estimates VE were adjusted by age group (<5; 5–15; 15–64; 65+ years), the presence of at least one chronic condition, target group for vaccination and need help for walking or bathing. In Italy, adjusted estimates of the 2014/15 seasonal influenza VE against medically attended influenza-like illness (ILI) laboratory-confirmed as influenza for all age groups were 6.0% (95%CI: −36.5 to 35.2%), 43.6% (95%CI: −3.7 to 69.3%), −84.5% (95%CI: (−190.4 to −17.2%) and 50.7% (95% CI: −2.5 to 76.3%) against any influenza virus, A(H1N1)pdm09, A(H3N2) and B, respectively. These results suggest evidence of good VE against A(H1N1)pdm09 and B viruses in Italy and evidence of lack of VE against A(H3N2) virus due to antigenic and genetic mismatch between circulating A(H3N2) and the respective 2014/15 vaccine strain.

1. Introduction

The 2014/15 influenza season in Europe was characterised by the circulation of influenza A(H3N2) viruses with an antigenic and genetic mismatch from the Northern hemisphere vaccine strain A/Texas/50/2012(H3N2) and more closely related to the vaccine strain A/Switzerland/9715293/2013(H3N2) recommended for the 2014/15 season of the Southern hemisphere [1]. The observed antigenic mismatch between circulating and vaccine A(H3N2) viruses well explained the preliminary estimates of influenza vaccine effectiveness (IVE) in the general population [Canada, UK and USA] [2–4] and in hospitalised patients [5], of −8%, −16.8%, 3.4% and 22% respectively.

Italy, differently from other EU countries where most of the subtyped influenza A viruses (78%) were A(H3N2), experienced a 2014/15 season characterized by an extended circulation of two influenza viruses: A(H1N1)pdm09 and A(H3N2), that both contributed substantially to morbidity. In the first phase of the season

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(from week 50-2014) only the A(H1N1)pdm09 circulated, then (from week 2-2015) the A(H3N2) virus started co-circulating (52% and 41%, respectively) [6].

IVE studies are essential to monitor how the vaccine performs in the target populations. Since 2009 Italy has been providing IVE estimates using the screening method, and the test-negative case–control (TNCC) study for monitoring influenza vaccine effectiveness, to the I-MOVE (Monitoring Vaccine Effectiveness in Europe) network [7,8].

Results of the case–control study, conducted during the 2009/10 season, were unable to provide pandemic and seasonal IVE estimates at national level but contributed with data to the multicentric study [8]. However, the screening method study design provided IVE estimates of 92.4% (95%CI: 46.3–98.9%), suggesting that the pandemic vaccine offered good protection against medically attended laboratory-confirmed A(H1N1)pdm09 infections [7]. During the 2010/11 season, results permitted national estimates of IVE and also contributed to the pooled analysis [9,10]. At national level, results suggested that the 2010/11 and 2011/12 seasonal vaccines used in Italy conferred low protection against medically attended laboratory-confirmed influenza infections, but the sample size was not sufficient to reach conclusive results.

Aims of the present study were to provide estimates of IVE in Italy by influenza type/subtype and age group for the overall population and for the target group for vaccination.

2. Methods

We used similar methods to those already described [11,12]. The study was conducted within the context of the existing National sentinel influenza surveillance system (InfluNet) implemented in the 1999/2000 season [13,14], that is based on voluntary participation of an average of 1046 (range: 955–1305) general practitioners (GPs) and paediatricians (Ps) per season, covering about 2% of the general population by region and age group. Within the InfluNet system, a test-negative case–control study was established in order to produce IVE estimates in preventing primary care consultation due to laboratory-confirmed influenza infection [7,11].

2.1. Sample size

In Italy, around 2000 throat swabs are collected each season in the framework of the InfluNet system and analysed by the Reference Laboratory Network of the Italian National Influenza Center (NIC). The overall percentage of influenza positive samples among influenza-like illness (ILI) consultations in all age groups was around 25% in 2013/14 season, but varied during the season (from around 4% positive at the beginning to over 40% positive during influenza peak weeks) [15].

Because the ratio of cases to controls varies over time according to the ratio of positive to negative influenza laboratory tests, a case–control ratio of 1:1 is used for sample size considerations.

For seasonal influenza VE among people aged ≥65 years, we expect the vaccine coverage to be around 55% [16]. A sample of at least 145 laboratory-confirmed cases (and 145 controls) are needed to detect an odds ratio (OR) of 0.5 and less (a vaccine effectiveness of 50% or more) with a power of 80% and a confidence interval of 95%.

For individuals aged 6 months–64 years, we expect a low vaccine coverage (based on data collected in season 2013/14) of approximately 5% [16]. A sample of at least 685 laboratory confirmed cases (and 685 controls) are needed to detect an OR of 0.4 and less (a vaccine effectiveness of 60% or more) with a power of 80% and a confidence interval of 95%.

2.2. Study setting and enrolment criteria

The study population consisted of patients consulting a participating practitioner for ILI and having a nasal or throat swab taken within 7 days after symptom onset. Practitioners used a systematic random sample to select the patients to swab.

A case of confirmed influenza was an ILI patient (defined according to the European Union case definition [17] who was swabbed and tested positive for influenza using real-time polymerase chain reaction (RT-PCR) or culture. Controls were ILI patients who were swabbed and tested negative for any influenza virus.

Participating sentinel practitioners interviewed ILI patients, using an on-line standardized questionnaire, to collect information on demographic, clinical and epidemiological information including: date of symptom onset, current vaccination status including date of vaccination, vaccine brand, 2012/13 and 2013/14 influenza vaccination status and a list of potential confounding factors: age, sex, presence of chronic condition(s), severity of chronic disease using the number of hospitalisations for the chronic disease(s) in the previous 12 months as a proxy, smoking history (non-smoker, past, current smoker), number of practitioner visits in the previous 12 months.

2.3. Laboratory analysis

Laboratory diagnosis was undertaken by the regional InfluNet laboratories, coordinated by the NIC located at Istituto Superiore di Sanità, by using RT-PCR assays able to detect circulating influenza A and B viruses. Influenza viruses were also isolated in MDCK or MDCK-SIAT1 cells from RT-PCR positive samples, as previously described [18]. Further strain characterisation was performed by the NIC laboratory on a selected number of influenza virus isolates. In particular, molecular characterization analyses were carried out on the available influenza strains, which belonged to the different circulating type/subtypes-A(H3N2), A(H1N1)pdm09, and B – by using nucleotide sequencing of the hemagglutinin (HA) gene. Phylogenetic analyses were conducted by using the neighbor-joining algorithm available in the Mega 6 software (http://www.megasoftware.net) [19] and HA sequences from reference strains retrieved from the EpiFlu database of the Global Initiative on Sharing Avian Influenza Data (GISAID). Antigenic characterization was performed by hemagglutination inhibition (HI) assay with specific post-infection ferret sera [18]. The results of the above virological analyses were timely sent, as soon as they were available.

2.4. Statistical analysis

We included in the study patients recruited from ISO week 46-2014 to 16-2015, meeting the European ILI case definition [17] with onset of symptoms >14 days after the start of national influenza vaccination campaigns. Individuals were considered vaccinated if they had received a dose of the seasonal vaccine more than 14 days before the date of onset of ILI symptoms.

The study period started the week of onset of the first influenza case recruited and ended the week of onset of the last influenza case after which there were at least two consecutive weeks with no further influenza positive case. We excluded from the analysis individuals with missing information on laboratory results. Using the test-negative case–control (TNCC) design we estimated the seasonal IVE as 1 minus the odds ratio (OR) using multivariate logistic regression models with influenza PCR results and seasonal vaccination status as the linear predictor.

We estimated VE for influenza virus subtypes A(H3N2), A(H1N1)pdm09, and B. Influenza A cases who were not subtypable were excluded from the analysis. Moreover, we also estimated IVE by age group and vaccine type. Variables associated with potential

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