

## Childhood Flu Vaccination: An Opportunity to Reduce the Burden of Disease due to Influenza Epidemics

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In recent years, many countries have faced dramatic excess deaths among the elderly. Such increase was impressive in terms of excess death rates. The excesses were concentrated in a few weeks, and specifically during the winter seasons of 2010/11, 2014/15 and 2016/17 (Euromomo 2018) [1,2]. Plausible hypotheses regarding the possible determinants of the observed excesses, especially in the very old population (i.e. aged 75+), were: i) meteorological factors (extreme -low and high- temperatures), ii) seasonal influenza, and iii) the amplitude of the at-risk population. The evidence of a possible impact of the influenza epidemics on excess mortality is more and more apparent. Among people aged 65+, European pooled data (Euromomo, 2015) [3] showed an increased excess influenza-attributable mortality rate for the season 2014/15 of 185 deaths per 100,000 (ranging from 82 to 311) corresponding to 88,9% of overall estimated excess mortality. A similar pattern was reported during the 2016/17 season, with an excess influenza-attributable mortality rate for those aged 65+ at the EU level of 137 per 100,000 deaths (ranging from 76 to 302) (Vestergaard, 2017) [4].

The mortality excess was dramatic in Italy (Rosano, 2019) [5] with more than 60,000 deaths attributable to the flu epidemics. The excess mortality in the very old population, observed during the 2014/15 and 2016/17 seasons, could be related to the presence of a drifted A/H3N2 influenza virus for which the vaccine had low vaccine effectiveness (Rizzo, 2016) [6] or to the low vaccine coverage in this age group. In Europe, between 2008–09 and 2014–15, the influenza vaccination coverage among high-risk groups has markedly dropped, with half of the countries reporting a decreased number of vaccine doses available. The average coverage in the elderly in 2014/15 was 34%, which is well below the WHO minimum target (75%). Only one country, Scotland, reached 75% coverage in older persons (2014/2015), while a number of countries

reported declining vaccination uptake (Jorgensen, 2018) [7]. In terms of amplitude of at-risk population in EU28, a large share of fragile people is represented by 47.5 million seniors aged 75+ - i.e. more than 9% of the whole population (Eurostat, 2018) [8], whose annual death rate is naturally high, around 4%. Therefore, although the observed excess deaths are not unexpected, this constitutes a serious public health issue, which can be prevented coupling personal protection measures with the influenza vaccine.

In recent years, case-control studies conducted at the EU level in the elderly population, in both primary care and hospital level, have shown, especially for the A/H3N2 component of the vaccine, moderate to low influenza vaccine effectiveness estimates in both primary care and hospital settings (Kissling, 2016; Valenciano, 2016) [9,10]. A recent research paper (Bellino 2019) [11] analysing the 2018/19 influenza season in Italy available confirms this trend. Influenza vaccines were low to moderately effective with quadrivalent vaccines conferring moderate effectiveness in preventing influenza caused by A(H1N1) pdm09, while no evidence of protection against A(H3N2) was found. Those estimates - together with increasing evidence of a potential herd effect of the influenza vaccine in the elderly - have triggered a different approach to influenza vaccination strategies. In Finland and Estonia, where public health authorities strongly promote the flu vaccination among children (Rapola, 2007; Esposito, 2012) [12,13], no increase in cumulated excess of mortality attributable to influenza has been registered in the studied period. This may indicate an appropriate path for limiting the impressive impact of deaths associated with flu epidemics in the population. Influenza vaccination is offered for free to children in US, Canada and some European countries (Austria, Finland, Slovakia, Latvia, UK) and it is recommended (but not offered for free) in other countries, such as Malta, Polonia and Slovenia. In other European countries,

vaccination is recommended and offered for free to children with particular risk from the age of 6 months (ECDC, 2018) [14,15].

In a recent systematic review, a good influenza vaccination effectiveness was reported for children and adolescents aged 2-16 years, corresponding to an estimated reduction of the proportion of children who have confirmed influenza and influenza-like illness (ILI) between 11% and 30% and between 20% and 28%, respectively (Jefferson, 2018) [16]. In addition, in the abovementioned paper regarding the 2018/19 influenza season in Italy, good effectiveness against A(H1N1) pdm09 was detected only in the age group of children/adolescents (Bellino, 2019) [11]. In countries where influenza vaccination is extended to children and adolescents, such as Canada, a reduction of 61% in influenza incidence for not vaccinated people was reported with a vaccination goal of 83% of children under the age of 15 (Loeb, 2010) [17]. Furthermore, a reduction of total medical visits and visits for ILI-associated respiratory infections was described both in the pediatric and the adult population as a consequence of children vaccination (Piedra, 2005; Pebody, 2015) [18,19]. In previous years there were questions related to vaccine effectiveness, especially in very young children, to its impact on transmission, and to the cost of implementing the integration of influenza vaccination into the routine vaccination schedule. Nevertheless, increasing evidence shows that countries with high influenza burden, high density and low levels of coverage might benefit from offering the influenza vaccine, possibly free at the point of care.

Moreover, there is also increasing evidence regarding the age group specific benefits of vaccinating children against influenza. A 2014 study showed that flu vaccine reduced children's risk of flu-related Pediatric Intensive Care Unit (PICU) admission by 74% during flu seasons from 2010-2012 (Ferdinands 2014) [20]. A 2017 CDC study published in *Pediatrics* (Flannery 2017) [21] highlighted that flu vaccination significantly reduced a child's risk of dying from influenza. Thus, evidence suggests that vaccinating school-age children would provide benefits to both vaccinated children and their unvaccinated household and community contacts. The unpredictability of the influenza virus continues to pose a major challenge to health professional and policy makers. Nonetheless, vaccination remains the most effective means to reduce the incidence and severity of influenza. Childhood vaccination could provide an opportunity to decrease the burden of disease in this age group, but may also potentially help to protect the population at risk of serious complications, due to the strategic role children play in the spread of the virus.

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