EDITORIAL

Exploring the pathway toward the reduction of paediatric seasonal influenza burden: school-based vaccination and surveillance

MARIA GORI[1,2], CLARA FAPPANI[1,2,3], SILVIA BIANCHI[1,2], ELISABETTA TANZI[1,2,4], GIANVINCENZO ZUCCOTTI[5], ANTONELLA AMENDOLA[1,2,4]

[1] Department of Health Sciences, Università degli Studi di Milano, Milan, Italy; [2] Coordinate Research Centre EpiSoMI (Epidemiology and Molecular Surveillance of Infections), Università degli Studi di Milano, Milan, Italy; [3] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy; [4] Coordinate Research Centre MACH (Centre for Multidisciplinary Research in Health Sciences), Università degli Studi di Milano, Milan, Italy; [5] Department of Pediatrics, V. Buzzi Children's Hospital, Università degli Studi di Milano, Milan, Italy

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Dear Editor,

Influenza is a highly contagious infectious disease and a major health problem in the paediatric population, especially in preschool-aged children, who are at increased risk for severe influenza-related illness and complications [1]. Children have the highest influenza attack rates, up to 30%, especially because of the immaturity of their immune system and the wide attendance of school and other community settings [1, 2]. Indeed, seasonal influenza can spread easily in crowded areas such as schools. Influenza viruses can also be spread by contaminated hands, and children can have poor hygiene habits [1].

Children, especially those in preschool-age, are the primary source of influenza transmission within the community [3, 4]. Indeed, it has been demonstrated that influenza viruses shedding is higher in children compared with adults [1, 5]. Additionally, Ng et al. reported that preschoolers started and kept shedding influenza viruses earlier and for a longer period than adults, because they have low pre-existing influenza-specific immunity [6].

Annually 870,000 children under 5 years of age seek care in emergency settings because of influenza and related conditions worldwide, with an associated hospitalisation rate of 20% [7, 8]. Between 28,000 and 111,500 deaths in such age group are imputable to influenza-related causes, with the majority occurring in children under 4 years of age [3].

Influenza epidemics can result in high levels of work and school absenteeism, leading to significant burden in terms of financial and health outcomes [3]. In particular, childhood seasonal influenza impacts on absenteeism both of sick children and their parents, who often need to miss several working days for taking care of their children [7, 8].

In children with good health, influenza often manifests with non-specific and mild symptoms, which do not require medical care. In these conditions, without proper testing, influenza may be mistaken for other respiratory illnesses and is frequently underestimated. Indeed, during periods of low influenza activity or outside of epidemics situations, the infection of other respiratory viruses can also present as influenza-like illness (ILI), which makes the clinical differentiation of influenza from other pathogens difficult [8]. Hence, assessing the real impact burden of influenza among children is still challenging.

To reduce the burden of influenza infections, vaccination coverage has to be necessarily increased and large-scale surveillance has to be implemented.

Influenza vaccination is the most important public health tool to reduce virus spread and the morbidity and mortality associated with influenza and related complications, particularly for the elderly. When the vaccination is not able to prevent influenza, it has been shown to reduce severity of illness in people who get vaccinated but still get sick. Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Current evidence suggests that universal childhood vaccination is a strategy of paramount importance to reduce the health and economic burden of influenza to the community as a whole, as well as that of other respiratory diseases when other viruses are co-circulating. It has been demonstrated that vaccination against influenza has a direct protective effect on children, reducing hospitalisation and mortality rates, and it also provides indirect protection to close and susceptible contacts [2]. In Japan, it has been demonstrated that vaccination against influenza among school-aged children has an important impact on the elderly [9, 10].

Several seasonal influenza vaccines have been licensed for use worldwide, including the live attenuated influenza vaccine (LAIV), approved for children and adolescents from 24 months up to 49 years of age [11], and the inactivated influenza vaccines, approved for children from six months of age [12].

The WHO recommends vaccinating children aged 6-59 months against influenza [13].

During the COVID-19 pandemic, with the co-circulation of SARS-CoV-2 and influenza viruses, the Strategic Advisory Group of Experts (SAGE) of the World Health Organization (WHO) has recommended reconsidering the prioritisation of high-at-risk groups for influenza vaccination, to limit the impact on the healthcare system and avoid an additional burden on vulnerable populations [14]. Before the COVID-19 pandemic, among the risk groups for priority use of influenza vaccines, only children with underlying medical conditions were included [15]. Starting from 2020, all children aged 6 months to 6 years are considered an additional risk-group for seasonal influenza vaccination [14].

Nevertheless, influenza vaccination coverage remains suboptimal (lower than 75% [16]) in many countries, including Italy, where the coverage ranged from 10.5% in influenza season 1999/2000 to 23.7% in influenza season 2020/2021 [17]. D'Ambrosio et al., described the trend of influenza vaccination uptake in Italy along 11 influenza seasons (2010-2021), reporting a decrease in vaccination coverage in children aged 0-8 years in the period 2010-2020, followed by a significant increase during COVID-19 pandemic, especially in the age group 2-4 years (19%) [2]. This data highlights the need for prioritising strategies to implement influenza vaccination coverage in children to be in line with WHO recommendations [18].

Most paediatric influenza vaccinations are currently administered in primary care offices, hence vaccinating all children during the vaccination season can be challenging. Vaccine administration in alternative settings can be useful to overcome logistical issues, other than for reaching hard-to-reach children and adolescents and increasing families' compliance with the vaccination schedule. Also, alternative delivery options should be considered to improve adherence to vaccination campaigns. The live-attenuated influenza vaccine (LAIV) is needle-free, delivered via nasal spray, and offers protection against influenza A and B viruses. Moreover, LAIV elicits an immune response without replicating efficiently in the lower respiratory tract, reducing the risk of virus transmission [4]. For all these reasons, LAIV represents an attractive choice for mass vaccination campaigns in non-healthcare settings.

Several pilot studies have demonstrated the feasibility and effectiveness of school-based influenza vaccination (SLIV) in increasing vaccination coverage among schoolchildren [4, 19-21]. Especially for very young children, and consequently for their parents, the school represents a familiar and trusted community environment and can help to partially overcome parental hesitancy.

Furthermore, schools could reduce barriers to vaccination compared with primary case offices. It has been demonstrated that influenza vaccine uptake is lower in people, both children and elderly, living in deprived neighbourhoods, probably due to a lack of health knowledge and information and an underestimation of the risk associated with influenza virus infection [22]. Being in direct contact with families, schools could represent a key site to increase accessibility to vaccination, to overcome linguistic barriers, and for bridging the gap between different socioeconomic groups.

During the 2013/2014 influenza season, the United Kingdom started a universal childhood immunisation programme with LAIV in primary school settings (children aged 4-11 years old), achieving a relatively good uptake, ranging from 45.6% to 71.5% in different pilot areas [23, 24]. This campaign was associated with an important decrease in emergency department accesses and hospitalisation for ILIs in children vaccinated at school. Concurrently, the authors observed a reduction of 59% in adult primary care visits for respiratory symptoms, confirming the population impact of childhood vaccination [23, 24].

Similar benefits of SLIV have previously been demonstrated in North America, during the 2005/2006 influenza season, when a large immunisation campaign involving public school children from kindergarten through 12th grade (4-11 years old) was launched [23]. Importantly, it has been demonstrated that this programme, reaching a vaccination coverage of 45%, was associated with a significant reduction in morbidity attributable to influenza.

In Italy, during the 2021/2022 influenza season, when the vaccination was extended to all children aged 6 months to 6 years, a SLIV pilot study was set up in preschools (children aged 2–6 years) in the Milan municipality [25]. The percentage of adherence in the various schools ranged from 11 to 49%, resulting in a relatively good participation in the immunisation campaign, considering possible absences due to COVID-19 pandemic. An increase in childhood vaccination coverage was observed in the same geographical area during the considered influenza season compared to the previous one (from 1.9 to 22.2% in the 2-4 age group, and from 1.4 to 15.5% in the 5-8 age group). Another benefit of this study was the high participation of preschoolers with an immigrant background, most of whom with language difficulties, highlighting that the involvement of cultural mediators and the set-up of a multi-language informative were crucial for rising families' engagement.

Several studies have reported that saliva has high sensitivity and specificity for the detection of influenza and offer a feasible approach for testing ILI particularly in children [26]. Indeed, school has been proven to be also the ideal context for promoting influenza surveillance [21]. Additionally, another aim of this Italian study was to perform an innovative school-centred ILI surveillance by saliva self-sampling. Monitoring school absenteeism has long been proposed as a surveillance tool of influenza, but its potential remains limited [27], especially because surveillance based only on absenteeism does not allow the identification and characterization of the pathogens responsible for respiratory infections. In this sense, virological surveillance allows monitoring influenza viruses circulation and respiratory pathogens differential diagnosis, essential for adequate case management and estimating real-time vaccine effectiveness. Especially in "out-of-

season" periods, investigating not only the presence of influenza viruses, but also other more common paediatric viruses appear of utmost importance, as already suggested by other authors [28]. Importantly, this surveillance system proved to be a valuable tool, at a pandemic time, to screen for COVID-19 and influenza [25].

Additionally, implementing school-based surveillance is crucial since monitoring the school-age population provides enhanced early detection of influenza epidemics [4].

In Hong Kong, Leung et al. conducted a school-based surveillance study using nasopharyngeal swabs, which is the gold standard specimen type for influenza detection but represents a sampling method difficult to perform in the paediatric population. This translates into a reduced number of school-age children included in the surveillance [29]. Virological surveillance could be strengthened using oral fluids self-sampling or sampling under parents' supervision, which might overcome the need for the presence of medical staff, allowing virtually reaching all the school population [25, 30].

In the aforementioned Italian study, saliva-based testing was well accepted by children and their families, being able to collect an adequate amount of saliva for the purposes of molecular detection of respiratory pathogens. For this reason, the study was proposed again during the influenza season 2022/2023 [25].

Building a routinary saliva-based surveillance system could allow conducting future studies on vaccine effectiveness using the case-control test-negative design, and to assess the vaccine protection against the most severe forms of the disease.

To conclude, COVID-19 pandemic taught us that it is possible to screen with alternative biological samples (such as saliva) and to vaccinate in every setting (*e.g.*: in sports halls, in schools). In this paper, we have argued and proposed two possible key strategies to reduce the burden of influenza infections in children: i) increase universal vaccination coverage in children by offering vaccination in schools, and ii) implement large-scale influenza surveillance using an easy and painless collection method of respiratory samples. Indeed, the implementation of influenza vaccination in children through LAIV and SLIV programmes could represent the key strategy to increase vaccine uptake, and consequently to reduce hospitalisation and mortality rates in both children and, indirectly, the whole population.

Surveillance represents an important tool for monitoring influenza viruses circulation profiles and the effectiveness of influenza vaccination. Despite nasopharyngeal swabs are still the gold standard specimen type for respiratory infections detection, saliva has been proven to represent an easy, painless, and non-invasive alternative since the first COVID-19 wave [31]. The less expensive and flexible nature of saliva sampling provides better opportunities to enforce respiratory infection screening and surveillance.

Influenza affects all countries, communities, and individuals, and influenza pandemics represent a serious threat to public health. In countries such as Italy, where vaccinations are mainly provided as part of primary care, the school vaccination campaign can be seen as an important 'catch-up' intervention for those children not adequately reached by the paediatrician/territory. The use of nasal spray influenza vaccine coupled with a saliva-based surveillance for the detection of influenza viruses could represent a relevant approach to reduce the burden of influenza and other respiratory infections, achieving the goals of the WHO's Global Influenza Strategy 2019-2030 [18].

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization, AA; Writing-Original Draft Preparation, MG, CF; Writing-Review and Editing, SB, ET, GZ, AA; Supervision, AA. All authors have read and agreed to the published version of the manuscript. These first authors contributed equally to this article: MG and CF. These senior authors contributed equally to this article: GZ and AA.

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Correspondence: Antonella Amendola, Department of Health Sciences, Università degli Studi di Milano, 20142 Milan, Italy. E-mail: antonella.amendola@unimi.it

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