Intranasal Live Attenuated Influenza Vaccine

Subjects: Infectious Diseases

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Although influenza is a major public health concern, little is known about the use of spray live attenuated influenza vaccine (LAIV) among adults. For this reason, we conducted a systematic review and meta-analysis to investigate the efficacy and safety of LAIV, especially in adults with/without clinical conditions and children <2 years, with the final aim of possibly extending the clinical indications. PubMed/MEDLINE and Scopus were the two databases consulted through February 2021. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. A critical appraisal was conducted. Analyses were performed by using ProMeta3 software. Twenty-two studies were included, showing that LAIV was associated with a higher probability of seroconversion when compared with a placebo and considering the A/H1N1 serotype (pooled OR = 2.26 (95% CI = 1.12–4.54), p-value = 0.022; based on 488 participants, without heterogeneity (I2 = 0.0%)). The meta-analysis also confirmed no significant association with systemic adverse events. Only rhinorrhea, nasal congestion, and sore throat were significantly associated with LAIV compared to the placebo. Despite the limited available evidence, LAIV has proved to be a safe and effective flu vaccination, also due to its very low invasiveness, and our review's results can be considered a starting point for guiding future research and shaping forthcoming vaccination campaigns.

Keywords: intranasal live attenuated influenza vaccine ; inactivated influenza vaccine ; immune response

1. Introduction

Influenza is an acute respiratory infection caused by influenza viruses, which belong to the single stranded-RNA genome family of *Orthomyxoviridae*. It is one of the most significant and commonly occurring vaccine-preventable diseases. Thus, it is a significant source of morbidity and mortality worldwide, with an attributable estimate of 54.5 million lower respiratory tract infections (LRTIs) in 2017 [1]. It causes illnesses that range from mild to severe, occasionally requiring hospitalisation and, at times, leading to death. The disease severity may vary according to the seasonal flu viral strain, the specific strains in the vaccine, and patients' characteristics, such as age, comorbidities, or underlying chronic conditions. As recommended by the World Health Organisation (WHO), annual vaccination is currently the most effective strategy to control seasonal influenza infections [2][3], especially for people at a greater risk of severe disease or complications when infected, i.e., pregnant women, children aged <5 years old, the elderly (>65 years old), or subjects with underlying clinical conditions [4][5]. To reduce their risk of contracting influenza [6] and prevent transmission to susceptible patients [7], influenza vaccination on healthcare workers is strongly encouraged, if not required, in many hospitals. Despite the development and widespread availability of safe and efficient vaccines, vaccination coverage, especially among the most vulnerable populations, is still far from the recommended threshold (at least 75% of the population) [8]. This low coverage is one of the leading causes of the high burden of influenza, with a range of 250,000–645,000 estimated deaths every year from seasonal influenza-associated respiratory complications worldwide [9][10].

Nowadays, there are two types of flu vaccines currently available: inactivated influenza vaccines (IIVs) and live attenuated influenza vaccines (LAIVs). On the one hand, IIV is approved for use in subjects aged six months and older, including persons with underlying chronic medical conditions and pregnant women, and it is administered by intramuscular injection [11]. On the other hand, LAIV, being a live attenuated virus, is approved in the USA for use in healthy individuals between 2 and 49 years [12], and in Europe for individuals between 2 to 18 years [13], and should not be administered to pregnant women [10]. The most significant advantage of LAIV is the non-invasive route of administration by nasal spray. Furthermore, it imitates natural infection, conferring mucosal immunity, and therefore enabling this vaccine to be the most suitable candidate for mass immunisation, especially in pandemics [14].

Despite being primarily designed for children, other categories may also benefit from live attenuated vaccines. LAIV efficacy and its impact on vulnerable groups are still debated. This systematic review aims to investigate whether the LAIV is safe and effective in adults, including those with underlying clinical conditions, pregnant women, and children younger than 24 months.

2. Current Insight on Live Attenuated Influenza Vaccine

To the best of our knowledge, this is the first systematic review with meta-analysis that specifically assessed both the efficacy and safety of a LAIV intranasally administered via spray. In total, we identified 22 studies, of which 18 assessed LAIV efficacy and 16 LAIV safety (the sum is higher than the total because some studies assessed both efficacy and safety). In particular, focusing on efficacy (as a 4-fold increase in antibody titer), our results showed a high probability of seroconversion after administration of the LAIV intranasally spray when compared against the placebo, but particularly for A/H1N1 serotype and only referring to healthy adults. Indeed, this finding was not confirmed when another serotype—for instance, A/H3N2—was considered. Nevertheless, in the latter analysis, only four studies were retrieved [15][16][17][18], and for this reason, caution is needed in the interpretation of data. Moreover, a smaller sample size was reached in this case, and the wide confidence interval might be explained because of this statistical element. Meanwhile, only two studies [19][16] assessed the efficacy of LAIV intranasally spray compared to placebo in groups different from healthy adults, in particular, people with HIV [16] and the elderly [19]. In this case, no conclusions can be drawn due to the differences in subjects' characteristics and the paucity of the studies; however, the two studies both found a lower probability of seroconversion in those subjects with LAIV compared to a placebo. Similar and predictable results were also found in studies assessing the efficacy of LAIV in comparison with IIV in subjects with comorbidities, which showed a lower probability of seroconversion among those who received LAIV, regardless of the virus serotype analysed.

Concerning the safety of LAIV, all the included studies compared LAIV vs placebo, and all the results supported a very high level of safety since most of the assessed symptoms did not differ between the two groups (fever and cough in both healthy and immunocompromised subjects, fatigue/tiredness, myalgia, and headache only in healthy adults). Only local symptoms, such as sore throat, nasal congestion, and rhinorrhea, showed a significantly higher rate among the intervention group than the placebo, mainly in fixed-effect models.

Results of this review highlighted a critical gap in knowledge. In particular, we failed to identify randomised control studies involving vulnerable subjects. Indeed, in our meta-analysis, we combined simultaneously breastfeeding women, immunocompromised patients because of cancer or HIV, and the elderly. No studies were conducted on healthcare workers, also considered at higher risk of influenza because of professional exposure. At the same time, an age-stratified analysis was not possible because only two studies were conducted in subjects older than 65 years, and none of the retrieved studies was conducted in subjects younger than two years of age.

Regarding the geographic distribution of the studies, almost all countries were well covered (America, Asia, Europe, and Africa). However, the highest number of studies was conducted in America, whereas the lowest was in Africa, highlighting a disequilibrium between developed and developing countries.

Considering the study design, almost all included studies were trials, but two were observational; however, the quality of included studies was quite good. The overall risk of bias was judged low or arising moderate concern for all the included studies: no severe or critical risk of bias was identified in any domain of the assessments. This generally medium/high quality of included studies allowed us to be confident about results obtained in our meta-analysis.

Generally speaking, the results of our review should be taken with caution because we did not assess the matching between serotypes contained in administered vaccines and circulating serotypes in the respective influenza season. Moreover, in most cases, studies did not verify the antibody titer before subjects' allocation in the intervention or control group.

Indeed, influenza prevention is still a major public health concern, not only as a result of low vaccination rates but also due to intrinsic characteristics of the vaccines available and the virus itself. Characteristics of the vaccine are one of the main critical aspects, as proven by the low effectiveness of LAIV from 2013 through 2016 seasons. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunisation Practices (ACIP) voted down the use of LAIV for the 2016/2017 flu season [20]. The instability of the vaccine was speculated to have caused the reduced efficacy, which could also contribute to the safety outcome. However, after a 2-year absence, the LAIV vaccine was reintroduced in the 2018/2019 influenza vaccine schedule. This new decision was taken based on additional studies performed, according to which no statistical differences were detected between LAIV and IIV efficacy [21]. Regarding the characteristics of the virus itself, random genetic mutations constantly occur in the genome while the influenza virus replicates in a cell. These alterations can lead to changes in the virus's surface proteins, the HA (hemagglutinin) and NA (neuraminidase), causing the immune system to no longer recognise them. This process, called "antigenic drift", complicates the management of flu vaccination campaigns, determining the need to update vaccines annually and re-administer vaccines to the whole population [8]. On the other hand, there is another process called "antigenic shift", consisting of major changes in HA and

NA proteins of the virus that, although being less frequent, might lead to a potential pandemic effect [8]. This high virus variability creates a great challenge for public health in terms of both adequate and sufficient vaccine procurement and an efficient vaccination strategy. The immunisation drive is crucial if other cases are to be avoided, and we need to try every possibility of increasing the vaccination rates. For this purpose, it is essential to fight vaccine hesitancy, understanding the determinants of it, but also to provide the easiest and safest way to administer the vaccines. Moreover, it should be considered that influenza immunisation not only protects vaccinated individuals but provides some level of indirect protection, called “herd effects” or “herd immunity”. Even if indirect effects are assumed to provide a little additional benefit, it might make the difference when a large portion of the population is immunised [22]. In this perspective, and considering that intranasal spray administration is readily accepted, systematic delivery of influenza vaccine in all possible settings and with a large target population would greatly enhance the epidemic control [23].

As regards the safety of LAIV, healthy adults did not report a higher risk of adverse events when compared with placebo, opening up prospects for new targets. The LAIV appears to be manageable and particularly suitable for easy administration, being minimally invasive. Would this help increase vaccines acceptance? Indeed, appropriate communication of this information [24], and widespread dispersal of this knowledge among the general population, including social network channels [25], are essential. The flu vaccination coverage threshold is rarely achieved, but during the COVID-19 pandemic, great attention was also raised around flu vaccination [26], especially during the 2020/2021 flu vaccination campaign, while the COVID-19 vaccination was still not available. An extensive flu vaccination campaign was conducted in 2020 to better differentiate between flu and COVID-19 due to the similar symptomatology and consequently to be more sensitive in differential diagnoses among the two [27]. In this context, the flu vaccination request highly increased, obtaining a vaccination rate never reached before [28], but also causing procurement issues and vaccine shortages. In this case, would it be helpful to extend the use of LAIV to other groups, particularly healthy adults? Moreover, it should be considered that the LAIV spray vaccine can also be self-administered, reducing the efforts usually needed in planning, organising and implementing an injection vaccination campaign and overstepping the fear of needles that is recurrent among the general population.

3. Limits and Strengths

The main limitation of our study is relatively high heterogeneity in the characteristics of the included studies that allow us to only combine in meta-analysis a low number of studies or to quantitatively assess efficacy and safety of LAIV only for some serotypes, only in healthy adults, or not wholly exploring differences between LAIV compared with placebo and LAIV compared with IIV. Indeed, in our analysis, we previously combined studies that used IIV and placebo as control groups; however, in sensitivity analysis, we then only included studies with IIV as control or only including the placebo as a control, based on the number of studies available (usually in case of less than three or four studies, meta-analysis is not recommended). Indeed, in most of our sensitivity analyses, very few studies were retrieved for each viral strain. Another potential limitation concerns the different populations included in our review. However, we believe that this element can represent both a limitation but also a strength. Having a so broad population can lead to heterogeneity. However, at the same time, it can allow us to explore different target populations simultaneously. Indeed, our study intended to stratify analysis based on a specific target population. Nevertheless, it was not possible due to the low number of studies retrieved for each specific population subgroup. Therefore, we could only stratify the analysis among healthy and immunocompromised subgroups of subjects. Moreover, since the results were expressed in several different ways in the original manuscript, we calculated the ES (expressed as OR) based on the reported events and total sample size in the two groups (intervention and control). This aspect might represent a limit since we use raw data without any adjustment for potential confounders. In other words, our calculated ES for each study and the overall result should be considered as a crude value. However, since the participants’ characteristics recruited in intervention groups and those in the control groups were similar, we believe that this does not affect the interpretation of our results. On the contrary, our study is the first systematic review with meta-analysis to assess the association between efficacy and safety of LAIV in target groups different from children older than 2 years [29][30][31]. In particular, we aimed to explore efficacy and safety in children below 2 years, adults, subjects at higher risk (as those immunocompromised, subjects with comorbidities, or pregnant/breastfeeding women). Moreover, this review has a systematic and comprehensive approach used to retrieve as much evidence as possible. Indeed, we consulted two different medical/scientific databases, and, in addition, we manually checked the listed references. Furthermore, we conducted the review in agreement with the international guidelines and followed the approved checklist. In addition, our analyses showed no statistical heterogeneity (in most of the analyses, we found an I^2 equal to zero), and no publication bias was detected by visual inspection of the funnel and performing the Egger’s regression test. Lastly, we performed both fixed and random effect models, allowing us a comparison among the two estimated ES values. However, since the I^2 was equal to zero in most of the performed analyses, the two estimated ES were identical in almost all the analyses.

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