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Research article

The value of vaccine co-administration in the Northeast of Italy

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Abstract: Vaccine co-administration is safe and convenient, and it is recommended for ensuring timely age-appropriate vaccinations and offering the best protection against vaccine-preventable infectious diseases both to the pediatric and to the adult population. The purpose of this study is to assess the compliance of the vaccination services of a 500000-inhabitant local health agency of the Northeast of Italy with such a recommendation and the value of co-administrations. This was a population-based analysis of an anonymous vaccination database containing complete information on all the vaccines administered in 2023 to the population of the study area. The frequency and types of vaccine co-administration were assessed and the advantage in terms of healthcare-time spare was estimated. Co-administration regarded 18% of the 27922 persons vaccinated in 2023. Co-administration was routine in the pediatric age, where it showed 3 peaks at 0–2, 5–6, and 12–14 years. It was less common among adults, with a peak at age 65. Frequent patterns of vaccine co-administration were identified. In one year, co-administration resulted in a spare of 450 working days for both physicians and vaccination nurses and a time spare double than that could be obtained if co-administration was practiced whenever possible. Co-administration is an efficient strategy to provide timely protection to population groups at risk for infectious diseases and to reduce the use of healthcare resources.

Keywords: vaccination; co-administration; Italy; prevention; infectious diseases

1. Introduction

Vaccine co-administration (i.e., the administration of more than one vaccine on the same clinic day, at different anatomic sites, and not combined in the same syringe) is promoted as a desirable strategy that can be theoretically applied to all vaccine combinations unless explicitly contraindicated. This approach to vaccinations reduces the number of vaccination encounters, thus allowing a spare of

healthcare worker-hours, and increases timeliness of vaccine administration, avoiding delays from the administration of a vaccine to the next one. Co-administration has become routine in infant vaccination, since the pediatric vaccination schedule is particularly challenging. It has also been shown to be safe and effective in the pediatric setting [1].

Among adults, on the other hand, co-administration is still relatively uncommon, despite the advantages including effectiveness in improving vaccine coverages and in turn protection of individuals at risk for infections. Bonanni et al. reviewed key data on vaccine co-administration and showed that it is effective in improving vaccine coverages [2]. In addition, the same review reported that, among adult travelers in various settings, simultaneous administration of multiple vaccines slightly increased the frequency of transient side effects but was well tolerated and very convenient overall [2].

In Italy, co-administration is recommended by the most recent National Vaccination Plan 2023–2025, provided there are no general counterindications [3]. The possibility of co-administration was explicitly considered by the Ministry of Health in the Ministerial note about the 2023–24 Covid-19 vaccination campaign [4], which included a dedicated section on the co-administration of the Covid-19 vaccines.

The guide to counterindications to vaccinations issued by the Istituto Superiore di Sanità [5] also recommends routine co-administration of all the vaccine doses appropriate for age.

The Italian Veneto Region, in its most recent regional committee resolution on vaccinations [6] dedicated a whole section of the document to co-administration, in line with the guidelines from the Advisory Committee on Immunization Practices (ACIP) [7], including not only the recommendation to co-administer vaccines, but also the advantages of such approach and a figure showing where up to 3 i.m. vaccines can be administered in the same deltoid muscle.

In the Italian Friuli Venezia Giulia Region, co-administrations are included in the pediatric immunization schedule [8] whereas it is only mentioned as regards the possibility of simultaneous administration of the measles, mumps, rubella vaccine and the varicella vaccine [9].

The purpose of this study is to assess the compliance of the vaccination services of the local health agency of Friuli Centrale (ASUFC), in the Northeastern Italian Region Friuli Venezia Giulia, with the recommendation to propose co-administration of vaccines in pediatric and adult population in 2023.

2. Materials and methods

This population-based prevalence study used several health administrative databases of the Friuli Venezia Giulia Region as the source of information. In particular, the following databases were analyzed: the list of potential healthcare beneficiaries, residencies, and vaccinations, referred to the population living in the ASUFC catchment area (approximately 520000 inhabitants). Those databases are anonymous but can be linked deterministically at the individual level through a stochastic periodically modified key which, at a given time, is univocal for each person across all databases. For researchers, there is no way to discover the identity of subjects.

Among subjects living in the area of the ASUFC vaccinated in 2023, we assessed the frequency of co-administrations and the most frequently co-administered vaccines. In addition, groups of population more frequently receiving vaccines in co-administration were identified, as well as the Vaccination Centers where co-administration was a more common practice.

Differences in the prevalence of co-administrations in 2023 between groups of population were assessed using the chi-square test. Differences in continuous variables such as age between subjects

receiving vaccines in co-administration and those receiving single vaccines were assessed using the t-test. P-values < 0.05 were considered statistically significant.

We also estimated the person-time that was spared in 2023 thanks to co-administering vaccines, assuming that vaccination encounters are usually scheduled every 12 minutes and that at least one vaccination nurse and one medical doctor are required to be on site during the encounter.

All the analyses were conducted using SAS Enterprise Guide v7.15 (SAS Institute Inc. Cary, NC, USA).

2.1. Ethics approval of research

The study protocol was approved by the Ethics Committee of the Friuli Venezia Giulia Region (Parere CEUR-2024-Os-98).

3. Results

In 2023, 155821 persons living in the area of ASUFC received at least one vaccine. The overall number of vaccines administered to those people was 266126, in 228023 encounters. Mean age of the vaccinated persons was 58.4 ± 26.6 years, median 67 years. Of them, 27922 persons (17.9%) received vaccines in co-administration. The age distribution of all persons vaccinated and of those receiving at least one co-administration of vaccines in 2023 is shown in Figure 1.

Three peaks can be observed in the frequency of vaccination during the pediatric age: the first at 0–2 years of age (78.2%), the second at 5–6 (61.3%), and the third at 12–14 (74.2%). Exactly in the same ages, three peaks, almost as high as the previous ones, were observed among persons receiving at least one vaccine co-administration.

In older ages, there is a very high and wide peak among the elderly, but the frequency of those receiving co-administrations was much smaller, with a minor peak corresponding to age 65.

There were 488 different combinations of vaccines that were co-administered. Co-administration encounters were 35363. Table 1 shows the 30 most frequent co-administration patterns, accounting for 32681 co-administration encounters (92.4%).

The most common co-administration pattern included Covid-19 and influenza vaccination in adults; the second one is the canonical 6-in-1, pneumococcal and rotavirus vaccine co-administration according to the Friuli Venezia Giulia pediatric immunization schedule [8].

The maximum number of vaccines that were co-administered in the same encounter was 5 (5 cases, all travelers, receiving cholera, oral typhoid, and three additional vaccines, such as yellow fever, rabies, hepatitis A, polio, meningococcal ACWY, influenza or adult diphtheria, tetanus, pertussis, or polio vaccine). In an additional 70 encounters, 4 vaccines were co-administered. Again, all except 4 regarded travelers. Of them, 64 included a typhoid vaccine, 53 the adult hepatitis A vaccine, 44 the cholera vaccine, 30 the yellow fever vaccine, and 15 the rabies vaccine. 26 cases included either the Salk polio vaccine or the adult diphtheria, tetanus, pertussis, or polio vaccine. The mean age of the 71 travelers receiving 4 or 5 vaccines simultaneously was 36.6 ± 14.1 years. Thirty-five were males (49.3%).

Of the 4 non-travelers, 3 cases were 1-year-old children receiving 4 age-appropriate vaccines (6-in-1, pneumococcal vaccine, meningococcus B vaccine, and rotavirus vaccine in one case and 6-in-1, meningococcus ACWY vaccine, measles, mumps, rubella, varicella vaccine, and pneumococcal vaccine in another; meningococcus B, meningococcus ACWY, pneumococcus, and measles, mumps, and rubella

vaccine in the last one). The fourth non-traveler and adult person receiving recombinant Herpes Zoster, pneumococcus, meningococcus ACWY and the diphtheria, tetanus, and acellular pertussis booster.

Nineteen thousand seven hundred and ninety-five encounters with co-administrations of vaccines regarded subjects <18 year of age, in whom co-administrations are routinely indicated in the pediatric immunization schedule of the Friuli Venezia Giulia Region and for whom the presence of at least one parent is needed for immunization. An additional 15568 encounters with co-administrations of vaccines regarded the adult population (≥18 years of age), for whom no co-administration is explicitly indicated in the immunization schedule, but it is up to the doctor or the vaccination nurse to propose co-administrations when appropriate. In these 15568 encounters, 31649 vaccines were administered, thus sparing 16081 encounters that would have been needed if each vaccine had to be administered in a separate day, corresponding to 192972 minutes, that is, 3216 hours of both a vaccination nurse and an attending medical doctor (approximately 451 working days each).

Among 65-year-olds, who are actively invited for various vaccinations in Friuli Venezia Giulia (Herpes Zoster, 20-valent-pneumococcal conjugate vaccine, influenza and Covid-19 during the Autumn-Winter season) and who might also need boosters of various vaccines (e.g., the diphtheria, tetanus, and acellular pertussis vaccine, the tick borne encephalitis vaccine), we found that in 2023 there were 2810 persons who received only one vaccine per encounter but overall accounted for 4346 encounters in the year (excluding those needed for second doses of the same vaccine), indicating that 1535 encounters could have been avoided if vaccines were co-administered.

Considering the entire adult population (age ≥18 years) who did not receive any co-administration in the year, 124006 persons accounted for 158697 encounters (excluding those needed for second doses of the same vaccine), indicating that 34691 encounters could have been avoided if vaccines were co-administered, corresponding to 416292 minutes, that is, 6938 hours of a vaccination nurse and a doctor (almost 1000 days each). Of subjects reporting more than one encounter with no co-administrations, 25622 had 2 encounters, 3332 had 3, 605 had 4, and 137 had 5–8 encounters to receive one vaccine in each of them. Their mean age was 69.7 ± 14.9 years, median 72; 53% were females.

The proportion of adult (age ≥18 years) encounters with co-administration was variable across the 9 vaccination services of the local health agency ASUFC area: 7.3% in area A, 5.9% in area B, 7.9% in area C, 8.1% in area D, 10.6% in area E, 9.1% in area F, 8.0% in area G, 6.2% in area H, and 6.3% in area I (P-value of chi-square test < 0.0001).

The proportion of co-administrations was also variable according to the place of the vaccinal encounter: it was 5.9% when the vaccination was administered in General Practitioner ambulatories (mostly influenza vaccines, Covid-19 vaccines, 20-valent pneumococcal vaccines, and diphtheria, tetanus, and acellular pertussis vaccine), 1.5% in pharmacies (influenza and Covid-19), 15.1% in hospitals (mostly influenza vaccines, Covid-19 vaccines, 20-valent pneumococcal vaccines, and diphtheria, tetanus, and acellular pertussis vaccine), and 16.1% in the dedicated vaccination services (any vaccine).

Table 1. The 30 most frequent vaccine co-administration patterns in the population of ASUFC, Italy, in 2023.

Vaccine 1	Vaccine 2	Vaccine 3	Nencounters
Covid-19	Inluenza		6610
DTaP/IPV/Hib/HepB[a]	13- or 15-valent pneumococcal conjugate	Rotavirus live attenuated	4129
Meningococcal ACWY	9-valent Human Papillomavirus		3651
DTaP/IPV/Hib/HepB[a]	13- or 15-valent pneumococcal conjugate		3132
DTaP-IPV[b]	9-valent Human Papillomavirus		2898
DTaP/IPV[c]	Measles, mumps, rubella, varicella		2760
Inluenza	13- or 20-valent pneumococcal conjugate		2540
Meningococcal ACWY	Measles, mumps, rubella, varicella		2386
Adult dTap[d]	Recombinant Herpes Zoster		1026
Adult dTap[d]	Tick borne encephalitis		859
Recombinant Herpes Zoster	23-valent polysaccharide pneumococcal		533
Meningococcal ACWY	Meningococcal B		337
Recombinant Herpes Zoster	20-valent pneumococcal conjugate		202
Adult dTap[d]	Live attenuated Herpes Zoster		201
Adult dTap[d]	9-valent Human Papillomavirus		166
Adult dTaP/IPV[e]	Measles, mumps, rubella, varicella		140
Adult dTaP/IPV[e]	Meningococcal ACWY		122
Adult dTap[d]	Adult Hepatitis B		116
Adult dTap[d]	Inluenza		110
Adult Hepatitis A	Oral typhoid		110
Adult dTap[d]	23-valent polysaccharide pneumococcal		94
Tick borne encephalitis	9-valent Human Papillomavirus		93
Tick borne encephalitis	Recombinant Herpes Zoster		67
Adult dTap[d]	Adult Hepatitis A		63
DTaP-IPV[b]	Measles, mumps, rubella		63
DTaP/IPV/Hib/HepB[a]	Rotavirus live attenuated		63
Adult Hepatitis A	Typhoid parenteral		63
13- or 15-valent pneumococcal conjugate	Rotavirus live attenuated		54
Cholera	Oral typhoid		47
DTaP/IPV/Hib/HepB[a]	Measles, mumps, rubella, varicella		46

*Note: [a]Diphtheria, tetanus, pertussis (whooping cough), polio, Haemophilus influenzae type b (Hib) and hepatitis B, or "6-in-1" vaccine; [b]Diphtheria, tetanus, acellular pertussis (DTaP) and inactivated poliomyelitis vaccine; [c]Diphtheria, tetanus, pertussis (whooping cough), polio or "4-in-1" vaccine; [d]Adult diphtheria, tetanus, and acellular pertussis vaccine; [e]Adult diphtheria, tetanus, pertussis (whooping cough), polio vaccine.

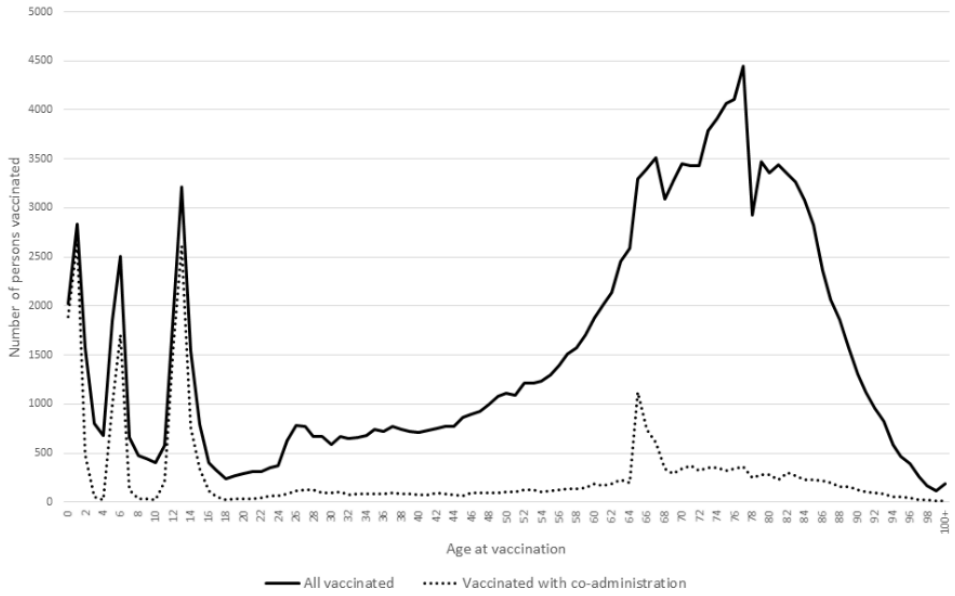

Figure 1. Age distribution of all persons living in the ASUFC area, Italy, vaccinated in 2023 and of those receiving at least one vaccine co-administration in the same year.

4. Discussion

This analysis showed that in the Northeastern Italian area around the city of Udine vaccine co-administration is routinely used in infancy and childhood, consistently with the Regional immunization schedule [8], whereas among adults it is a less commonly used practice.

Among adults, in 2023 co-administration of two vaccine types was practiced by general practitioners and pharmacies during the influenza season, when the flu vaccine was often co-administered with the 20-valent pneumococcal vaccine by general practitioners and with the Covid-19 vaccine by pharmacies. In fact, in this local health agency, general practitioners had specific remunerated objectives of vaccination coverage regarding the influenza and pneumococcal vaccines in the elderly, whereas pharmacies signed an agreement with the regional health authority for administering influenza and Covid-19 vaccines. Both for general practitioners and for pharmacies, co-administration was the most efficient strategy to fulfill their goals. Despite this, co-administration rates were much lower than those registered among the adult population at the vaccination centers, where medical doctors are expert in vaccinology and may be more persuasive than general practitioners and pharmacists. This is particularly true in case of multi-morbid or high-risk patients who typically attend the vaccination clinics where detailed personalized vaccination plans are provided to them. In addition, patients may be more skeptical towards co-administrations including the influenza vaccine and the COVID-19 vaccine, which are those administered by pharmacists and the most commonly administered by general practitioners. A study conducted in the USA among Medicare beneficiaries, in fact, found that among subjects vaccinated against COVID-19, influenza vaccination was high, but co-administration of both vaccines was low [10]. The same study also showed that co-administration was more frequent in frail patients and in those with some chronic conditions (e.g., chronic respiratory

diseases, mental health conditions, and diabetes) [10], who may be more likely to be vaccinated at the vaccinal centers.

Additional co-administrations in adults included Herpes Zoster vaccination: it was often co-administered with either the diphtheria, tetanus, and acellular pertussis vaccine, or the pneumococcal vaccine, or with the tick-borne encephalitis vaccine which in our region is free for the whole population since this is an endemic area.

The highest number of vaccines administered in the same encounter regarded travelers, consistently with previous literature [2]. Travelers are usually recommended to receive various vaccines, some of which require more than one dose to complete the cycle, and have limited time before starting their trip. Thus, this category of persons may benefit more than others from reducing the number of vaccination encounters, maximizing the number of vaccines in each of them, and make sure they have the best possible immunization before starting traveling. Also, on average travelers are young (mean age of those receiving 4 or 5 vaccines at a time was <40 years), thus they may be not excessively concerned about side effect or tolerability issues.

The other category of persons that may greatly benefit from co-administration of many vaccines is patients with chronic diseases (e.g., patients undergoing chemotherapy, patients on transplant waiting list, and hematological patients) who are at increased risk and may need to be quickly protected against multiple inflections.

Our analysis showed that, in a single year, co-administration of vaccines in the adult population of a 500000-inhabitant area allowed a time saving of approximately 900 health-care-worker-days and that missed opportunities to co-administer determined the waste of approximately 2000 health-care-worker-days. Thus, further implementing co-administration may improve efficiency of the vaccination services and determine a considerable sparing even in economic terms.

Our study could not assess whether vaccines induced more adverse reactions when co-administered than when administered in different encounters, since our source of data did not contain any personal identifier, and thus, we could not assess whether any adverse reaction was reported by the subjects whose vaccination data were analyzed. However, nowadays the safety of co-administration, except cases of explicit contraindication, has been widely reported [11,12] and there is no real need to prove it again. In fact, it is expected that the overall frequency of side effects may increase with the number of vaccines administered in a single encounter, but nonetheless tolerability is generally very good [2].

Co-administration is already common practice in infancy and childhood; in fact, it has been established for years by the vaccination schedules of the Friuli Venezia Giulia Region, which includes ASUFC [8]. In our opinion, the fact of recommending co-administrations in the regional schedule supports the strength of the recommendation and this may explain the disparity in co-administration rate between children (co-administrations are well scheduled in an official regional document) and adults (co-administrations are proposed but not officially established, possibly giving the impression that they are less useful or less safe). However, even in the youngest age groups in which co-administrations have been recommended for years, in ASUFC they are far below 100%, indicating that a considerable proportion of parents (more than 20%) of children and adolescents are skeptical or frankly oppose co-administrations. At age 5–6 years, such proportion is even higher, suggesting strong mistrust regarding the MMRV vaccination. Missed co-administrations may impact pediatric coverages. In fact, in ASUFC in 2023 the 6-in-1 coverage of the 2021 birth cohort was 96.7% (3 doses), pneumococcal coverage was 90.6%, meningococcus B was 83.4%, and rotavirus was 85.8%, meaning

that not all newborns receiving 6-in-1 were contemporaneously immunized against pneumococcus or rotavirus. Had parents been more co-administration prone, their children would have been more protected against the other diseases, with all coverages exceeding 95%.

The newest regional schedule [13], incorporating some recommendations from the national lifetime vaccination schedule (Calendario per la Vita 2025) [14] allows the meningococcus B vaccine to be administered since day 61 of life, thus endorsing a richer co-administration in newborns, i.e. 6-in-1 + pneumococcus + rotavirus + meningococcus B vaccines. The three local health agencies of the Friuli Venezia Giulia Region will have to make a shared decision of how to translate it into operations, considering potential advantages and disadvantages of the newly proposed co-administration in the local context and how it could impact coverage. On one hand, it could be convenient for parents because it reduces the required number of accesses to the vaccination centers; on the other hand, it could increase vaccinal hesitancy because parents might fear excessive pain for the child (the number of injections in the same occasion would increase from 2 to 3) and because they might fear, as probably elderly people do, the immune overload due to the additional vaccination [15]. Certainly, from the perspective of the vaccinal center co-administering meningococcal B vaccination would be an enormous advantage in terms of spared vaccinal encounters.

Co-administration is also common and convenient for travelers and patients with chronic conditions at particular risk of infection. It could certainly be further encouraged among healthy adults and elderly since it is an effective strategy to minimize encounters and maximize coverage with age-appropriate vaccinations. Regarding concerns about the potential reduced effectiveness, the risk of increased frequency or severity of adverse effects, or the appropriateness of simultaneous vaccinations [16], it should be kept in mind that expert medical doctors constantly trained and up to date on vaccinations supervise every encounter in our vaccination centers and can banish any doubts, after careful evaluation of the subject's medical history and assessment.

In 2024, vaccine co-administration has been included among the 10 guiding principles recommended by the Hygiene Italian Scientific Society (Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica, SItI) in a document of good vaccination practices in Italy [17], since it can reduce dropout and ensure the quickest protection of the target population. The same scientific society SItI has recently issued another document, in cooperation with the Italian Society for Infectious and Tropical Diseases (Società Italiana Malattie Infettive e Tropicali, SIMIT) to stimulate urgent actions for the prevention of diseases related to Respiatory Sincitial Virus (RSV), hoping that the recently approved vaccination is included in the national vaccination schedule with a recommendation among persons ≥60 years of age with chronic diseases and in all persons ≥75 years of age [18].

5. Conclusions

In a single year, in the Italian 520000-inhabitant local health agency ASUFC, approximately 450-nurse-working days and 450-physician-working days were spared thanks to co-administrations of vaccines in the adult population (corresponding to about 200000 euro) and additional 1000 could have been spared for nurses as well as for physicians if other possible co-administrations had been offered (additional 460000 euro). With the development of new and long-awaited vaccines such as the RSV vaccine, indicated in the adult and elderly population, co-administration stands as one of the most

desirable, effective, and affordable strategies for succeeding in offering the best protection to our ageing population in a limited-resource-health system and should, therefore, be strongly encouraged.

Author contributions

Francesca Valent was responsible for the conception of the work, the acquisition, analysis, and interpretation of data for the work, the drafting the manuscript; Giulia Degani contributed to the study design and the interpretation of data and critically reviewed the manuscript. Both authors gave final approval of the version to be published.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

Francesca Valent is an editorial board member for AIMS Medical Science and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

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