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COMMENTARY



Vaccine co-administration in adults: An effective way to improve vaccination coverage

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ABSTRACT

The ongoing COVID-19 pandemic highlights that complications and mortality associated with infectious diseases increase with age. Various vaccines are recommended for adults, but coverage rates remain suboptimal. Although co-administration would improve vaccine uptake and timely immunization, this is not routine practice in adults. We review key data on co-administration of vaccines in children and adults to reassure healthcare providers about its safety and advantages. In European countries and the United States, combined tetanus, diphtheria, and acellular pertussis boosters as well as meningococcal and human papillomavirus vaccines are recommended for healthy adolescents and adults of certain ages. Vaccination against influenza (annually), pneumococcal disease, and herpes zoster is recommended for older adults and specific risk groups. While co-administration is well established in children, it is less common in adults. Travelers can also receive multiple co-administered vaccines. Pediatric and travel vaccine co-administration has a well-established positive benefit-risk profile and is an efficient and cost-saving strategy to improve coverage. Healthcare providers could more often recommend and practice vaccine co-administration; this would not risk patient safety and health, would improve protection against vaccine-preventable diseases, and would help comply with national vaccination calendars. Recommending bodies may consider revising vaccination schedules to reduce the number of visits.

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Background

The ongoing global coronavirus disease 2019 (COVID-19) pandemic highlights that susceptibility of adults to infectious diseases and associated complications or mortality increase with age. The world's population is aging; in Europe, the proportion of people aged 65 years and above is forecasted to increase from 20.6% in 2020 to approximately 30% in 2050.¹

The COVID-19 pandemic also confirms that vaccination programs are highly effective,² underscoring that well-implemented vaccination strategies are a crucial determinant in fostering the health and independence of the aging population.³ Currently, several vaccines are available and recommended to European adolescents and adults in certain age groups, such as those against influenza (annually), pneumococcal or meningococcal disease, herpes zoster, diphtheria, tetanus, pertussis, and human papillomavirus, and also against tick-borne encephalitis in endemic regions.⁴ Other adult vaccines are expected to enter the market in the future, further crowding vaccination calendars. Because the success of vaccination programs is highly dependent on vaccine uptake, strategies to improve coverage are becoming increasingly important.^{5,6}

Although COVID-19 vaccines have only been on the market since late 2020, their coverage was the highest reached across Europe (>70%) in a record time (i.e., one year).⁷ Despite existing recommendations, such a broad coverage in adults has not been reached in decades for influenza vaccination, not even in risk groups or elderly populations.⁸ Low vaccination rates in adults are frequently associated with missed opportunities to vaccinate.^{6,9} Therefore, co-administration of vaccines has a substantial role to play in decreasing the number of consultations and hence missed opportunities, and can increase timeliness of vaccination.¹⁰ After an initial observation period of widespread COVID-19 vaccine use in the real-world setting, national and international health authorities have started recommending co-administration of COVID-19 vaccines with vaccines against other diseases based on the limited data available along with general vaccinology principles.^{11,12} The Advisory Committee on Immunization Practices (ACIP) in the United States was first to issue recommendations for co-administration of COVID-19 vaccines with other vaccines.¹¹ European countries later issued recommendations on co-administration of influenza and

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COVID-19 vaccines before the influenza season in the Northern Hemisphere.^{13,14} However, in adults, co-administration of vaccines has not yet become a routine practice, and related recommendations keep evolving. In this non-systematic literature review, we present key data on co-administered vaccines, with the aim of reassuring healthcare providers and thus potentially improving uptake and timely administration of adult vaccines. The cited references were selected by the authors based on their expert opinion and knowledge of the field, as well as from the results of a broad literature search in PubMed using various combinations of the terms “co-administration,” “vaccine,” “adult,” “children,” and “travel.”

A plain language summary contextualizing the relevance, the results, and the impact of our work is presented in [Figure 1](#).

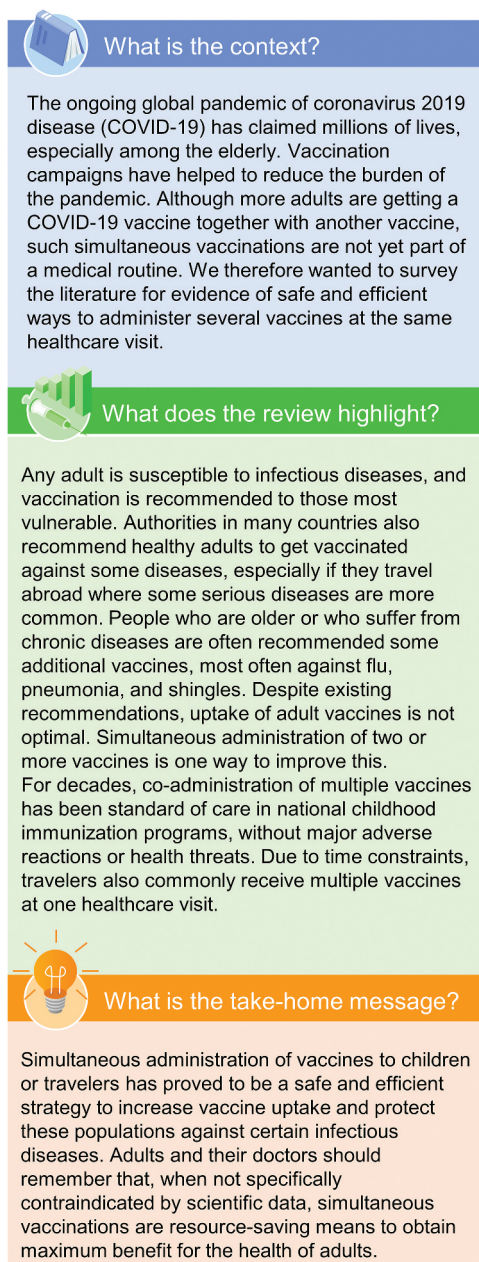


Figure 1. Plain language summary.

Importance of adult vaccination

While all adults are at risk of infectious diseases, particular risk groups include pregnant women, persons who are immunocompromised, obese, have chronic respiratory conditions, or are undergoing oncologic treatments, older adults, travelers, sexual minorities, intravenous drug users, alcohol abusers, and smokers.^{15–25} Vaccine-preventable diseases such as influenza, pneumococcal disease, or herpes zoster have the highest incidence and severity in older adults because of comorbidities and immunosenescence, but younger populations are also susceptible.^{26–30} Although the true incidence of pertussis in adults is unclear due to underdiagnosis and underreporting, older adults and those with asthma or chronic obstructive pulmonary disease (COPD) are also at increased risk for pertussis and severe outcomes.^{31–33}

Combined tetanus, diphtheria, and acellular pertussis boosters are recommended for healthy adults in several European countries and the United States by national recommending bodies,^{4,34} and also for patients with COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).³⁵ For patients with COPD, additionally, both the Centers for Disease Control and Prevention (CDC) in the United States and GOLD recommended vaccination against pneumococcal disease, influenza, and herpes zoster.^{35,36} Younger people may need meningococcal and human papillomavirus vaccines.^{4,34} Travelers may be recommended or even required to get vaccinated against yellow fever, meningococcal disease, poliomyelitis, hepatitis B and/or A, rabies, typhoid fever, etc., depending on endemicity of these diseases at their destinations.³⁷ Healthcare professionals in travel clinics might administer several vaccines during a single consultation,^{38,39} often due to the lack of time of travelers for multiple appointments before departure.

Efficiently implemented adult immunization strategies provide an opportunity to maintain functional ability of adults, their families, their communities, and their countries, and hence to improve medical, social, and economic outcomes.⁶ However, coverage of adult vaccination remains suboptimal and varies highly depending on vaccine, geographic region, or other factors.^{40,41} Therefore, further efforts from the global community and governments are needed to improve implementation of adult immunization programs.⁶ Healthcare professionals are the first line of contact with patients, and their contribution is a cornerstone for the implementation of strategies to increase vaccination coverage in adults.⁴²

Principles of vaccine co-administration

Simultaneous administration of two or more vaccines at different injection sites during the same appointment is generally referred to as concomitant or co-administration. It is one of the most efficient approaches to foster vaccination coverage rate, reduce the number of vaccination consultations and thus costs, raise compliance with recommendations, guarantee the timely administration of vaccines according to the recommended age or needs, and to adopt and implement new vaccines.⁴³ Co-administration reduces the number of missed vaccination opportunities,¹⁰ which are frequently the cause of low vaccination rates⁹ or of incomplete primary vaccination.⁴⁴

Furthermore, if vaccines were administered separately, transient adverse events would be reported at each visit, and the total cumulative number of transient adverse events would likely be greater than after co-administration of multiple vaccines. Because co-administration is convenient for both patients and healthcare providers, it contributes to the first of the four pillars (Convenience & Easy Access, Patient Communication, Enhanced Vaccination Systems, and Motivation) proposed to convert “vaccine availability” to “vaccination acceptance” throughout life.^{9,37}

Concerns with vaccine co-administration

In Europe, vaccines may be co-administered as indicated in the Summary of Product Characteristics or if no specific contraindications or scientific evidence to discourage simultaneous administration exist.⁴³ However, there are some concerns about potential negative immunological interference and adverse reactions.

In theory, immunologic interference between co-administered vaccines can enhance or impair the immunogenicity of vaccine antigens. In reality, there are very few vaccine combinations and scenarios for which co-administration is contraindicated because of negative immunologic interference. In the United States, such contraindications for currently used vaccines comprise simultaneous administration of the 13-valent pneumococcal conjugate vaccine (PCV13) with the meningococcal diphtheria conjugate vaccine in persons with functional or anatomic asplenia and/or human immunodeficiency virus infection, and PCV13 with the 23-valent pneumococcal polysaccharide vaccine (Table 1).⁴⁵

By contrast, co-administration in adults is supported by numerous studies that evaluated simultaneous administration of the most widely recommended adult vaccines (i.e., those against influenza, pneumococcal infections, herpes zoster, combined diphtheria and tetanus, and COVID-19 vaccines).^{46–49} The general principles for timing and spacing of immunobiologics published by the ACIP, including co-administration recommendations for live and inactivated vaccines (Table 1),⁴⁵ could also be adopted more widely in Europe. Except for the few aforementioned specific situations,⁴⁵ contraindications for co-administration could be the same as those for each vaccine alone. While in the United States the ACIP provides a detailed overview on contraindications for all licensed vaccines,⁵⁰ in Europe no such comprehensive general guidelines exist.

Safety of vaccine co-administration is detailed in subsequent sections.

Proven co-administration strategies

Throughout the life of an individual, the vaccination schedule is most challenging in infancy and childhood. Co-administration of pediatric vaccines demonstrated an excellent safety and immunogenicity profile, and has consequently become a widely accepted practice worldwide.⁵¹ In the United States, the CDC recommends co-administration of routine pediatric vaccines, and supports this recommendation without concerns about immunogenicity and safety.⁵² Co-administration of pediatric vaccines is also foreseen in immunization schedules across European countries, and infants may simultaneously receive up to four vaccines included in national immunization programs.⁴ Co-administration of childhood vaccines has been common practice for decades and proved to be an efficient strategy to maintain or even increase vaccine uptake. Despite some regional and sociodemographic differences, the coverage of the vast majority of pediatric vaccines exceeds 90% in both the United States and in Europe.^{53,54}

Fast approaching departure dates impose time constraints on travelers, and co-administration of several (sometimes up to six) required, routine, or recommended vaccines is thus a common practice in travel clinics.^{38,39} In a large prospective study conducted in healthy German travelers, although the overall frequency of systemic side effects increased with the number of simultaneously administered vaccines (36.7% for two, 40.3% for three, and 50.0% for more than three), the subjective rating by the study participants showed an excellent tolerability of multiple vaccinations before travel.⁵⁵ Feasibility of co-administration has also been shown in Chinese applicants for a United States immigrant visa, who had to be immunized against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, poliomyelitis, hepatitis B, measles, mumps, rubella, varicella, influenza, and pneumococcal disease.³⁸ Approximately half of the study participants (49.6%) reported side effects, all of which were transient. In Japanese travelers who received up to five simultaneous vaccines against either hepatitis A, hepatitis B, rabies, Japanese encephalitis, diphtheria, tetanus, measles, mumps, and poliomyelitis, the frequency of adverse reactions also increased with the number of simultaneously administered vaccines. However, the overall rate of adverse events was only 26.3%, of which most were transient injection site reactions.³⁹ All three studies concluded that co-administration of multiple vaccines to travelers

Table 1. Guidelines of the ACIP in the United States for spacing of live and inactivated vaccines.⁴⁵

Vaccine combination	Interval between vaccines
Two or more inactivated ^{1,2}	May be co-administered or administered at any interval
Inactivated and live ³	
Two or more live injectable ³	May be co-administered or administered sequentially ≥28 days apart

¹If not co-administered, a 28-day interval between a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine and a tetravalent meningococcal conjugate vaccine is recommended by certain experts.

²The meningococcal diphtheria conjugate vaccine and the 13-valent pneumococcal conjugate vaccine (PCV13) should be administered at a four-week interval in persons with functional or anatomic asplenia. PCV13 should not be co-administered with the 23-valent pneumococcal polysaccharide vaccine; the recommended interval is eight weeks or more and depends on the risk group.

³The live oral vaccines against typhoid fever (Ty21a) and rotavirus may be co-administered with or administered at any interval before or after inactivated or live injectable vaccines.

ACIP, Advisory Committee on Immunization Practices.

was well tolerated.^{38,39,55} Hence, the inconvenience of multiple vaccination visits before travel may outweigh the inconvenience of a slight increase of side effects after simultaneous administration of several vaccines at a single visit.

Conclusions

While simultaneous administration of multiple childhood or travel vaccines during one visit has become the standard of care, co-administration of routine vaccines for adults is only slowly becoming common practice by healthcare providers. Reluctance of routine adult vaccine co-administration with a COVID-19 vaccine can be explained by the initial contra-indication for co-administration, which was based on a lack of data in the first months of use of the novel COVID-19 vaccines. Subsequently, recommendations for co-administration of COVID-19 vaccines were issued within a year of licensure; since this practice was implemented, very few risks have been observed and no serious issues emerged. Despite this, reluctance toward co-administration remains considerable and seems to extend even to vaccines with an already established safety profile, for which extensive data on co-administration with other routine vaccines has been accrued. Increasing awareness on the safety of vaccine co-administration may lead to an improvement in compliance to recommendations and ultimately, improved coverage rates for routine adult vaccines.

Having separate appointments, whether they are requested by patients or offered by healthcare providers for each vaccine, is detrimental for vaccination coverage among adults and may lead to increased use of resources. Co-administration of routine childhood vaccines and adult vaccines to travelers has proved to be a safe and efficient strategy to improve coverage and protect these populations against vaccine-preventable diseases for which they are at risk. The success of these strategies may increase confidence of healthcare providers in routine adult vaccine co-administration, which might be of significant added value once integrated into regular practices to ensure compliance with recommendations. This is especially important considering the recent licensure of new pneumococcal conjugate vaccines and potential future licensure of respiratory syncytial virus vaccines, which will make adult vaccination calendars even more challenging.

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Authors' contributions

LB-J wrote the first draft of the manuscript. All authors reviewed the drafts critically and provided invaluable feedback for the development of the present manuscript. All authors approved the final submitted version.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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