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REVIEW

Recommended immunization schedules for adults: Clinical practice guidelines by the Escmid Vaccine Study Group (EVASG), European Geriatric Medicine Society (EUGMS) and the World Association for Infectious Diseases and Immunological Disorders (WAidid)

Susanna Esposito[a], Paolo Bonanni[b], Stefania Maggi[c], Litjan Tan[d], Filippo Ansaldi[e], Pier Luigi Lopalco[f], Ron Dagan[g], Jean-Pierre Michel[h], Pierre van Damme[i], Jacques Gaillat[j], Roman Prymula[k], Timo Vesikari[l], Cristina Mussini[m], Uwe Frank[n], Albert Osterhaus[o], Lucia Pastore Celentano[p], Marta Rossi[q], Valentina Guercio[q], and Gaetan Gavazzi[r]

[a]Pediatric Highly Intensive Care Unit, University of Milan, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [b]Department of Health Sciences, University of Florence, Florence, Italy; [c]CNR - Institute of Neuroscience, Aging Branch Center for Research, Padua, Italy; [d]Immunization Action Coalition, St Paul, MN, USA; [e]Department of Health Sciences, University of Genoa, IRCCS San Martino-IST University Teaching Hospital, Genoa, Italy; [f]Unit of Public Health, University of Bari, Bari, Italy; [g]Pediatric Infectious Disease Unit, Soroka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, Israel; [h]Geriatric Department, Geneva University, Geneva, Switzerland; [i]Vaccine & Infectious Disease Institute, Antwerp University, Wilrijk, Belgium; [j]Department of Infectious Disease, Annecy, France; [k]Department of Social Medicine, Faculty of Medicine, Charles University, Sokolska, Hradec Kralove, Czech Republic; [l]Vaccine Research Center, Tampere University Hospital, Tampere, Finland; [m]Clinic of Infectious Diseases, University of Modena and Reggio Emilia, Modena, Italy; [n]Division of Infection Control and Hospital Epidemiology, Department of Infectious Diseases, Heidelberg University, Heidelberg, Germany ; [o]University of Veterinary Medicine Hannover, Hannover, Germany; [p]European Centers for Disease Control and Prevention, Stockholm, Sweden; [q]Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy; [r]University Clinic of Geriatric Medicine, University Hospital of Grenoble, and GREPI University of Grenoble-Alpes, Grenoble, France

ABSTRACT

Rapid population aging has become a major challenge in the industrialized world and progressive aging is a key reason for making improvement in vaccination a cornerstone of public health strategy. An increase in age-related disorders and conditions is likely to be seen in the near future, and these are risk factors for the occurrence of a number of vaccine-preventable diseases. An improvement in infectious diseases prevention specifically aimed at adults and the elderly can therefore also decrease the burden of these chronic conditions by reducing morbidity, disability, hospital admissions, health costs, mortality rates and, perhaps most importantly, by improving the quality of life. Among adults, it is necessary to identify groups at increased risk of vaccine-preventable diseases and highlight the epidemiological impact and benefits of vaccinations using an evidence-based approach. This document provides clinical practice guidance on immunization for adults in order to provide recommendations for decision makers and healthcare workers in Europe. Although immunization is considered one of the most impactful and cost-effective public health measures that can be undertaken, vaccination coverage rates among adults are largely lower than the stated goal of $\geq$ 95% among adults, and stronger efforts are needed to increase coverage in this population. Active surveillance of adult vaccine-preventable diseases, determining the effectiveness of the vaccines approved for marketing in the last 5 y, the efficacy and safety of vaccines in immunocompromised patients, as well as in pregnant women, represent the priorities for future research.

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Introduction

There is little doubt that rapid population aging, which is primarily due to the decrease in age-specific mortality during the fourth quarter of life, has become a major challenge in the industrialized world.[1] Such aging has also led to an increase in the number of individuals over 80 y in age; this number is expected to triple over the next 50 y, making them the largest at-risk category of adults globally for whom vaccines are currently recommended. Immuno-senescence (i.e., age-related deterioration of the innate and adaptive immune systems) affects antibody responses to vaccine components in many elderly patients and limits the immunogenicity and effectiveness of vaccines in this group.[2] Together with poor immune responses and the effectiveness of some vaccines, progressive aging is therefore a key reason for making an improvement in vaccination a cornerstone of public health strategy.[3] Moreover, it is generally accepted that the near future will see an increase in age-related disorders and conditions such as cancer, cardiovascular diseases, diabetes, obesity, malnutrition, dementia, and multimorbidity, all of which are risk factors for the occurrence of a number of vaccine-preventable diseases.[4] An improvement in vaccination strategies specifically aimed at adults and the elderly can therefore also decrease the burden of these chronic conditions by reducing morbidity, hospital

CONTACT Susanna Esposito susanna.esposito@unimi.it Pediatric High Intensity Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milano, Italy.

admissions, health costs, mortality rates and, perhaps most importantly, by improving the quality of life in this age category. On the other hand, high vaccination coverage in the population may further reduce morbidity and mortality of vaccine-preventable diseases in adults through the mechanism of herd immunity.[5] Furthermore, several data highlighted the cost-effectiveness of influenza and pneumococcal prevention as well as the importance of maintaining high vaccination coverage against diphtheria, tetanus, and pertussis.[6]

Among adults, it is necessary to identify groups at increased risk of vaccine preventable diseases and highlight the epidemiological impact and benefits of vaccinations using an evidence-based approach. This document provides clinical practice guidance on immunization for adults to provide recommendations for decision makers and healthcare workers in Europe. The travelers were not considered in the document because the panel considered that this cathegory requires a dedicated paper.

Methodology

We conducted a systematic review of the literature regarding different categories of vaccines among 5 populations of interest, according to the vaccine groups seen in Table 1. The final string used was "Vaccines"[Mesh] AND cohort, restricted to humans, English language, adults (≥ 18 y old) and from 2000 to 2014. We identified a total 1,396 studies in the MEDLINE, SCOPUS and EMBASE databases, updated until December 2014.

Table 1. Categories of populations and vaccine type.

Population	Type of vaccines
Adults	Influenza
	Pneumococcal
	dTp
	HPV
	MMR and V
Old adults	Influenza
	Pneumococcal
	dTp
	Herpes zoster
	TBE
Immunocompromised adults	Influenza
	Pneumococcal
	dTp
	HPV
	MMR
	V and herpes zoster
	Hib
	Meningococcal
	HAV
	HBV
	Yellow fever
Pregnant	Influenza
	Pneumococcal
	dTp
	MMR and V
	HPV
	Meningococcal
	HAV
	HBV
Healthcare workers	Influenza
	Pneumococcal
	dTp
	MMR and V
	HPV
	Meningococcal
	HBV

dTp: diphtheria, tetanus, pertussis; HAV: hepatitis A virus; HBV: hepatitis B virus; Hib: *Haemophilus influenzae* type b; MMR: measles, mumps, rubella; HPV: human papillomavirus; TBE: tick born encephalitis; V: varicella.

For each group, we developed a specific table comprising selected information of interest. For each paper, the following information was retrieved in a standard format: last name of the first author, year of publication, gender (if needed), type of cohort, country, cohort size, age at vaccination, enrolment period, follow-up, type of vaccine, outcome, and estimate of the relative risk (RR) and its corresponding 95% confidence interval (CI). For each study, we also provided an appraisal of the available evidence according to the lines of reasoning used in the previously developed guidelines for the management of adult lower respiratory tract infections.[7] The studies were evaluated as follows, according to the strength of evidence they provided: 1) +, when the numerical results unequivocally supported a positive answer to the research question (i.e., determinant-outcome relation of interest clearly established); 2) -, when the numerical results unequivocally did not support a positive answer to the research question (i.e., determinant-outcome relation of interest not established); 3) ?, when the numerical results were unclear. Moreover, we created a folder containing all the papers in .pdf format through a web store (i.e., Dropbox).

In addition, we evaluated the safety of each vaccine type by considering clinical trials. We searched the last reliable review of each clinical trial, published in peer-reviewed journals with a high/medium impact factor after 2012, and, if missing, we provided the last 2 published clinical trials in the high/medium impact peer reviewed journals on the issue. Final recommendations were for adults in Europe.

Adults

Vaccination programmes usually target vulnerable populations such as children, the elderly, and people with underlying chronic conditions. In addition, specific groups that are considered to be at higher risk of contracting severe form of the disease and its complication represent the primary targets of vaccination, e.g., those subject to professional exposure and pregnant women. Healthy adults, not included in any of the aforementioned categories, are often neglected. However, there are several good reasons for reconsidering vaccination strategies that include the total adult population. Firstly, adults represent the largest proportion of the population, accounting for 50–60% of the entire resident population of Europe, and therefore they either produce a significant burden of disease (i.e., influenza and pneumococcal infections) or represent an important reservoir for the infectious agent (i.e., pertussis and human papillomavirus [HPV]). Moreover, vaccination strategies targeting specific at-risk population groups are often very difficult to implement, and vaccination coverage rarely reaches the expected levels.

In this section, we included all the articles referring to adults 18–64 y old.

Influenza vaccination

The Cochrane review on the efficacy and effectiveness of influenza vaccination in adults included reports on inactivated parenteral vaccines (20 studies), live attenuated intranasal vaccines (8 studies) and the inactivated intranasal vaccine (1 study).[8] Vaccines both with and without an adjuvant were considered. According to the review, the overall effectiveness of the inactivated influenza vaccine against influenza-like illness (ILI) when strains contained in the vaccine antigenically matched those circulating is 16% (95% confidence interval [CI] 5% to 25%), with a corresponding number needed to vaccinate (NNV) of 40 (95% CI 26 to 128). The inactivated vaccines were not significantly protective against ILI when the degree of matching between the vaccines and circulating influenza strains was absent or unknown. The overall effectiveness of the live attenuated influenza vaccines (LAIV) in preventing confirmed influenza was 60% (95% CI 53% to 66%), with an NNV of 71 (95% CI 64 to 80). The effectiveness increased to 62% (95% CI 52% to 69%) when the vaccine content matched the circulating strain and the NNV was 58 (95% CI 52 to 69).

Reported effectiveness estimates of the inactivated influenza vaccine against ILI varied significantly across the different studies. Hardelid et al. reported 31.9% (95% CI 11.9–47.3%) effectiveness in the 15–44 y age group and 19.9% (95% CI 5.7%–31.9%) in the 45–64 y age group.[9] Kafatos et al. reported 45.5% (95% CI 34.6%–54.6%) in the 15–44 y age group and 32.2% (95% CI 22.4–40.8%) in the 45–64 y age group.[10] Kawai et al. reported 54.9% (95% CI 30.8–78.5%) and 82.1% (95% CI 56.6–96.2%) with the 1- and 2-dose regimens, respectively, in the 16–64 y age group.[11] Nichol at al. reported a significant reduction in the rate of ILI (adjusted odds ratio, 0.48; 95% CI, 0.27–0.86) in people 50–64 y of age.[12] Castilla et al. reported adjusted hazard ratio values of 0.61 (95% CI 0.40–0.94) using the adjuvanted inactivated influenza vaccine during the 2009 pandemic in the 18–59 y age group.[13] High (87–95%) vaccine efficacy has been reported by Örtqvist when using the adjuvanted inactivated influenza vaccine during the 2009 pandemic in Stockholm county.[14]

Reported effectiveness estimates for laboratory-confirmed influenza varied between 69.6% (95% CI 34.8–93.3%) and 78.5% (95% CI 40.0–97.2%), respectively, with the one- and 2-dose regimens, in the 16–64 y age group.[11]

Vaccine effectiveness for influenza hospitalisation was reported by Baxter et al. as 12.4% (95% CI 1.6–22.0%) in persons aged 50–64 y.[15] McLean et al. reported no association between influenza vaccination and hospitalisation (odds ratio [OR] 1.08; 95% CI 0.62–1.88),[16] whereas Seo et al. reported an overall vaccine effectiveness for preventing hospitalisation of 32.5% (OR 0.675; 95% CI 0.486–0.937; $p = 0.019$), with no significance in the age groups 18–49 y (OR 0.82; 95% CI 0.34–1.99) and 50–64 y (OR 1.09; 95% CI 0.59–2.04).[17]

In summary, the effectiveness of seasonal influenza vaccination for preventing ILI and influenza hospitalisations in healthy adults is sub-optimal but increases significantly for laboratory-confirmed influenza.[8] No evidence of an association with serious adverse events was found.[9] However, vaccines provide not only individual immunity but also community protection when vaccine coverage is high.[18] Yearly influenza vaccination should be recommended for all healthy adults both for individual protection and for the overall reduction of disease burden and virus circulation, which is demonstrated in the presence of a good match between the vaccine and the circulating strains.[18] Within this large population, it is important to continue to ensure that the most vulnerable adults, for example, those with cardiovascular disease, diabetes, pregnant, etc. are vaccinated.[18] Among these vulnerable adults, also institutionalized subjects and prisoners should be included.[19,20] A previous anaphylactic reaction to the influenza vaccine represents the only contraindication to receiving the vaccine.[2] Precautions should be taken in cases of moderate or severe acute illness and a history of Guillain-Barré syndrome (GBS) within 6 weeks following a previous influenza vaccination.[2]

Pneumococcal vaccination

Two pneumococcal vaccines are currently available for use in adults: the pneumococcal polysaccharide vaccine (PPV), covering 23 serotypes (PPV23), and the pneumococcal conjugate vaccine, covering 13 serotypes (PCV13).

A Cochrane review included 25 studies involving approximately 127,000 participants equally distributed between randomized controlled trials (RCTs) and non-RCTs.[21] Different vaccine types (from 6- to 23-valent PPV) were included in the review. A review by Conaty et al. included 13 observational studies on PPV.[22] Moreover, PPV23 has also been assessed in 3 further studies.[23-25]

In recent years, the age indication for PCV13 was first extended from subjects aged $\leq$ 5 y to include those aged $\geq$ 50 y, and subsequently further extended to include all ages based on comparative immunogenicity data, including also the 18–64 y age group.[26] In the comparison of opsonophagocytic activity (OPA) titres between subjects 60–64 y of age, vaccinated either with PCV13 or PPV23, superiority was demonstrated for PCV13 with 9 of 12 common serotypes and non-inferiority for the remaining 3, whereas the comparison between younger subjects only immunized with PCV13 and subjects in the 60–64 y age group vaccinated with PCV13 demonstrated consistently higher titres in younger vaccines.[26]

The meta-analysis conducted in the Cochrane review found strong evidence of PPV23 efficacy against invasive pneumococcal disease (IPD).[21] In particular, 11 studies involving 36,489 participants found a protective vaccine efficacy of 74% (95% CI 55% to 86%). Non-RCTs provided evidence for protection against IPD in populations for whom the vaccine is currently utilized (OR 0.48, 95% CI 0.37 to 0.61). Efficacy was demonstrated against all-cause pneumonia in low-income (OR 0.54, 95% CI 0.43 to 0.67) but not high-income countries. The review by Conaty et al. found the vaccine efficacy against IPD to be an estimated 53% (95% CI 46–59%).[22] Singleton et al. found 100% (95% CI 78–100%) vaccine efficacy against IPD in the 20–39 y age group and 73% (95% CI < 0–96%) in the 40–54 y age group.[25] Hechter et al. did not find a significant level of protection against pneumococcal bacteraemia, but did find significant levels of protection against hospitalisation for all-cause pneumonia (hazard ratio 1.18; 95% CI 1.02–1.37; $p = 0.03$) in the population overall and in patients without chronic obstructive

pulmonary disease (COPD; hazard ratio 1.21; 95% CI 1.02–1.43; p = 0.03) but not in patients with COPD.[24]

The efficacy data for PCV13 in the elderly age group were published recently and showed 75% efficacy against IPD due to vaccine serotypes, 45% efficacy against the first episode of community-acquired pneumonia (CAP) due to vaccine serotypes and 45% against non-invasive CAP due to vaccine serotypes.[27] No similar data are available for the age group comprising healthy young adults.

In summary, PPV23 vaccination showed a clear protective effect against IPD and some protection against CAP, as well as the ability to prevent all-cause CAP hospitalisation among healthy adults. PCV13 was shown to be effective against IPD and CAP due to vaccine serotypes in a recent study in elderly subjects (≥65 y) who developed lower OPA antibody titres compared with the younger adults. Both PCV13 and PPV23 vaccination are clinically effective, in addition to being well tolerated, and may be used for individual protection of healthy adults against IPD, as they may reduce the hospitalisation burden for all-cause pneumonia in the population of healthy adults. However, although pneumococcal disease may occur, it is rare and does not justify undergoing vaccination as a public health measure. Therefore, as an age-based recommendation, no pneumococcal vaccines are recommended for adults < 65 y with no underlying risk factors.

Diphtheria, tetanus, pertussis (dTp) vaccination

Diphtheria has been virtually eliminated from most European countries; however, resurgence of the disease has occurred in places where vaccination coverage rates have declined.[28] The threshold over which re-circulation of diphtheria may be possible appears to be a 30% fraction of the population without detectable antitoxin.

Tetanus immunity relies on anti-toxin antibodies, whereas immunological memory cannot contribute to disease prevention if antibody titres are below the threshold.[29] However, tetanus is often demonstrably less severe in vaccinated compared with unvaccinated subjects, even several decades after the last booster dose.

One study has been selected to support the recommendations on the use of the pertussis vaccine in healthy adults.[30] A total 263,496 persons aged 8–20 y were selected from the Kaiser Permanente study population in United States. A total of 904 pertussis cases were identified among these individuals. The vaccination history was determined for all cases, which had all been vaccinated with different combinations of acellular pertussis (ap) and whole cell pertussis (wp) vaccines. For those vaccinated with ap only, the relative risk of disease was 6.67, 2.46 and 3.81 (having received 5 total doses, 6 total doses, or 5 or more total doses, respectively) compared with those who received one or more wp doses in the schedule. Therefore, this study showed that waning immunity among adolescents and young adults is more evident in those vaccinated with ap only and depends on the number of vaccine doses received in the past.[31] Because most European children have received only ap vaccine doses, the risk of waning immunity is high in the European population.

In summary, a policy of receiving a dTp vaccination booster every 10 y is recommended for adults to limit the waning immunity against the 3 diseases and improve community protection against pertussis.

Human papillomavirus (HPV) vaccination

Research in the HPV field has contributed to the worldwide implementation of 2 prophylactic HPV vaccines, namely, a bivalent (Cervarix, GlaxoSmithKline Biologicals) and a quadrivalent (Gardasil, Merck & CO., Inc.) vaccine, protecting against HPV 16 and 18 and HPV 6, 11, 16, and 18, respectively. Since the introduction of these 2 HPV vaccines in 2007, a third prophylactic HPV vaccine has been developed (Gardasil 9, Merck & CO., Inc.) and approved by the U.S. Food and Drug Administration (FDA),[32] and recently, was also been recommended by the European Medicines Agency (EMA).[33] The vaccine provides broader protection against HPV-related cancers due to its protection against 5 additional HPV genotypes. Administration of the currently available HPV vaccines in individuals older than 26 y of age (denoted here as healthy adults) is not mentioned in the package inserts, nor do they note that the safety and effectiveness of the vaccines have not been assessed in this cohort.[34-36]

Drolet et al. recently examined the efficacy of prophylactic HPV vaccination in a systematic review and meta-analysis that included 20 studies in 9 high-income countries.[37] A significant decrease in both HPV 16/18 infections (68% [95% CI 0.19, 0.52]) and anogenital warts (condylomata acuminata) (61% [0.39; 95% CI 0.22, 0.71]) was reported in girls under age 20 y with female vaccination coverage of at least 50%. Significant reductions in anogenital warts were also recorded in boys under age 20 y (34% [95% CI: 0.47, 0.91]) and females between 20 and 39 y (31% [95% CI: 0.51, 0.89]). This beneficial effect of HPV vaccination is secondary to the herd effect.[37]

The end-of-study results of a phase III efficacy, safety, and immunogenicity study involving the quadrivalent vaccine in women aged 24–45 y reported a vaccine efficacy against disease or infection related to HPV 6, 11, 16, and 18 in the according-to-protocol (ATP) population of 88.7% (95% CI: 78.1, 94.8), and 66.9% (95% CI: 4.3, 90.6) in the intention-to-treat population (ITT), i.e., women who were seropositive and DNA negative for the HPV vaccine type at the time of enrolment, who received at least one dose of the vaccine.[38] In the intermediate analysis of this study, Munoz et al.[39] reported a 30.9% (95% CI 11.1–46.5) efficacy of the quadrivalent vaccine against disease or infection related to HPV 6/11/16/18 in the ITT population, here including women aged 24–45 y with infection or disease present at baseline. This low percentage, with reference to the 90.5% (95% CI 73.7–97.5) efficacy observed in the ATP population, confirms that HPV vaccines are most effective when administered before exposure to HPV because they have no therapeutic effect and can only protect against HPV types not already acquired at the time of vaccination.[40] However, most HPV-positive women included in this study were positive to only one HPV genotype at enrollment, and could therefore still potentially benefit from the HPV vaccine genotypes with which they were not yet infected.[39]

A follow-up of the phase III efficacy, safety, and immunogenicity study involving the bivalent vaccine in women older than 25 y has recently been published and reported a vaccine efficacy against persistent HPV 16/18 - related infection and CIN1+ of 81.1% (97.7% CI 52.1–91.0) in the ATP cohort. This study included a subset of women with a history of HPV infection or disease, and as such, supported the contention that women older than 25 y can also benefit from HPV vaccination when they have been previously exposed to HPV.[41] Furthermore, decreasing efficacy with age was observed in the ITT population in the Costa Rica HPV trial, where the efficacy fell from 68.9% (95% CI 53.1–79.9) in women aged 18–19 y, to 21.8% (95% CI: 16.9, 47.9) in 24–25 year-olds.[42]

Similar findings were observed for the quadrivalent HPV vaccine in a study including over 2.2 million females aged 10–44 y, where increased vaccine effectiveness with decreasing age was noted.[43]

Together with the fact that 5–15% of sexually active, middle-aged adult women acquire a new oncogenic HPV infection each year (1–2% HPV 16/18),[40] these outcomes confirm that mid-adult women could potentially benefit from the vaccine. However, vaccination in this group of women cannot replace screening.

An efficacy study of the quadrivalent HPV vaccine in men 16–26 y of age for the prevention of external genital lesions (EGLs), defined as anogenital warts or penile, perianal or perineal intraepithelial neoplasia of any grade, or cancer at these sites related to HPV 6/11/16/18, revealed 90.4% (95% CI 69.2–98.1) and 65.5% (95% CI 45.8–78.6) protection in the ATP and ITT cohorts, respectively.[44] The majority of the EGLs were HPV 6/11 - associated anogenital warts, reflecting the large proportion of anogenital warts caused by HPV 6/11, and hence the beneficial effect of the quadrivalent vaccine use in males is evident. The reduced efficacy of the vaccine in the ITT cohort with respect to the ATP cohort reinforces the desirability to vaccinate males before their first sexual encounter. However, significant efficacies were reported for anal intraepithelial neoplasia (AIN) of any grade, AIN2+, and persistent infection by HPV 6, 11, 16, and 18, supporting the use of the vaccine in males regardless of their sexual activity. In addition, for men who have sex with men, this study reported on the quadrivalent HPV vaccine efficacious in protecting against HPV 6, 11, 16, and 18 -related AIN of any grade (77.5% [95% CI 39.6–93.3]) in the ATP population.[44] The results of this study led to the licensure in several countries of the quadrivalent vaccine for men for the prevention of EGLs.[40] The Advisory Committee on Immunization Practices (ACIP) had previously been recommended licensure for males aged 9 through 26 y to reduce their likelihood of acquiring anogenital warts. To our knowledge, no efficacy, safety, and immunogenicity trials have been published investigating vaccine efficacy in males older than 26 y.

HPV vaccines are well tolerated.[41-44] However, episodes of mass psychogenic syndrome have been reported and it is therefore important to carefully plan the setting where mass vaccination campaigns will be implemented.

In summary, HPV vaccines are effective in preventing persistent infections and cervical disease associated with vaccine types. The highest efficacy is observed in those uninfected at the time of vaccination, but some protection is still observed among those already infected at baseline. The quadrivalent vaccine is effective in preventing condyloma in women receiving the first vaccine dose prior to 20 y of age and in men 16–26 y old. HPV vaccination of all adolescent women and men before their sexual debut should be recommended, and universal vaccination of the entire population up to 20 y of age should be considered. Vaccination of older women up to 45 y of age is advised as an individual protective measure but is not reimbursed by public health programmes.

Measles, mumps, rubella (MMR) and varicella (V) vaccination

No cohort study or clinical trial is available on the MMR and V vaccine efficacy or effectiveness in adults. However, the MMR and V vaccines also provide a strong immune response in adults, and vaccination of susceptible adults is crucial in order to meet the European Region of the World Health Organization goal of measles and congenital rubella elimination.[45,46] Moreover, addressing the immunity gaps for measles, mumps and rubella in the population of each European country is considered a priority, and without a strong recommendation and a special focus on immunizing susceptible adults, measles and congenital rubella elimination might be delayed for many years to come, because the low coverage achieved against measles and rubella in the last decades in many countries has allowed the creation of wide pockets of susceptibility in the adult population.[45]

All susceptible adults should receive 2 doses of the V vaccine because the risk of disease complications is increased in adulthood.[46]

In summary, all adults lacking evidence of immunity against any of measles, mumps and rubella (whether natural or acquired secondary to prior vaccination) receive 2 doses of the MMR vaccine with a minimum interval of 4 weeks. Similarly, healthy adults lacking anamnestic recall of receiving the V vaccine should receive 2 doses with a minimum interval of 4 weeks. The MMR and V vaccines are contraindicated during pregnancy and in case of immune deficiency or immune suppression.[45,46] However, the risk-to-benefit profile of immunization should be carefully evaluated in each specific condition.

Tick-borne encephalitis (TBE) vaccination

There are 2 safe and effective TBE vaccines available.[47-49] High vaccination coverage may decrease significantly TBE incidence, as it was proven in Austria.[48]

At least 2 doses of TBE vaccine are required for development of protection. Protection is significantly lower (about 95%) in those with a record of irregular vaccination. TBE vaccine failure infections are reported rarely.[49]

In areas where the disease is highly endemic ($\geq$ 5 cases/100,000 per year), implying that there is a high individual risk of infection, World Health Organization recommends vaccination of all age groups.[50] The primary vaccination series consists of 3 doses (day 0, 1 to 3 months after the first dose, 5 to 12 months after the second dose) and booster dose should be administered every 5 y, in Switzerland even every 10 y.[49] If a rapid immune response is required, accelerated schedule based

on immunization on day 0, day 14 and month 5–7, or on day 0, day 7 and day 21 according to vaccine may be used.

In summary, in areas where the disease is highly endemic TBE vaccination is recommended in all age groups.

Old adults

Aging is a dynamic and complex process depending on genetic inheritance, time, physical activities, and nutrition.[51] The interaction of all these factors explains that defining 'who is or is not elderly' is still controversial. Moreover, socio-economic and cultural factors also play a part in determining the rate of healthy aging vs. aging with chronic diseases or/and disability. In Europe, the usual threshold for defining an elderly adult is 65 y of age. It is likely that in the next few decades, chronological age will not be the main parameter for defining an "elderly adult;" the presence of chronic disease(s) and global functional abilities (including frailty status) will be as important as the age itself.[52]

Different factors explain the increased susceptibility to infection in the elderly European population: immune-senescence; malnutrition, which has a powerful immunosuppressive effect; less effective barriers (i.e., more permeable skin and bladder, less mucus and saliva, and less active muscles); multimorbidity; and increased use of medications.[53,54] Epidemiological data regarding vaccine-preventable diseases during the last decades of life underline the need to promote vaccinations for old adults (i.e., $\geq$ 65 y old). Many European countries officially provide different guidelines for adult vaccination, which explains the initial attempt of 2 European Geriatric Societies (EUGMS and the International Association of Gerontology and Geriatrics – European section) to provide the first European guidance for elderly adult vaccinations.[55,56] However, a larger European agreement taking into account new epidemiological data, new vaccines, and the economic burden/effectiveness of adult vaccinations is required.

Influenza vaccination

The background for influenza vaccination of the elderly population is based on numerous cohort studies summarized in several meta-analyses[57-59] and only 2 randomized clinical studies.[60,61] The efficacy was found in specific elderly populations (i.e., older patients suffering from frailty, institutionalized elderly subjects, diabetes, chronic heart and chronic pulmonary disease, patients' undergoing haemodialysis and nursing home residents).[62,63] A recent Cochrane review showed the numerous biases of cohort studies that embellished the efficacy of vaccines, with the conclusion that new RCTs were needed.[64] However, a Cochrane re-arranged analysis of the same data, according to a biological and conceptual framework based on the basic sequence of events throughout the 'patient journey' (i.e., exposure, infection, clinical outcomes and observation) and using broad outcome definitions and simple frequency distributions of vaccine efficacy values, demonstrated the limitations of the Cochrane analysis.[65] This approach produced meaningful predictions for vaccine efficacy against fatal and non-fatal influenza-related complications (average ~30% with a large dispersion), ILI (~40%), disease with confirmed virus infection (~50%), and biological vaccine efficacy against infection (~60%) under conditions of virus circulation.[65]

Adjuvanted or high-dose influenza vaccines have been shown to increase the efficacy of vaccination in the old adults.[66,67] MF-59 adjuvanted influenza vaccine is licensed for persons over 65 in many countries and is probably the vaccine of choice if available. These vaccines may offer a short-term solution, although further research is required to exploit the many other new technologies.[68] No data are available to recommend LAIV in older adults.

In summary, the majority (~90%) of influenza-related deaths occur in older adults and, in addition, catastrophic disability resulting from influenza-related hospitalisation represents a significant burden in this vulnerable population.[66] The efficacy of the influenza vaccine decreases with age, reaching less than 50% in the very old population (> 80 y old), according to the severity and attack rates of influenza each year.[64] Influenza vaccines provide not only individual immunity but also community protection when vaccine coverage is high.[18] Consequently, yearly influenza vaccination using the standard-dose inactivated influenza vaccine (trivalent or quadrivalent) or, alternatively, the high-dose inactivated influenza vaccine or adjuvanted influenza vaccine, appears to be recommended in aging and elderly adults. The contraindications and precautions are those mentioned in the Adults section.

Pneumococcal vaccination

PPV23 and PCV13 are the pneumococcal vaccines on the market that are also recommended for elderly adults.

In Norway, between 1993 and 2011, the most frequent infectious invasive disease in the entire population was IPD, with an average 58.1 notifications / 100,000 inhabitants in those over 65 y of age.[69] The highest mortality rate (over 50%) of IPD was seen in older adults.[70] However, national recommendations for PPV23 use in the elderly population are controversial and are based primarily on a risk-based strategy, which likely partially explains the low vaccine coverage rates in Europe.[71] Moreover, the production of specific antibodies after vaccination decreases progressively in the extremely elderly population.[72]

Only two randomized controlled trials (RCTs) have been conducted in elderly community-dwelling adults and case control studies confirmed the vaccines' efficacy against invasive pneumonia and bacteraemic pneumonia but not against all pneumonia.[73,74] A Japanese RCT conducted in nursing home residents found a protective impact on all-cause pneumonia and IPD.[75] There was an additive effect of influenza vaccination with PPV23.[76,77]

The most common adverse reactions with PPV23, reported in less than 10% of older adults vaccinated in the clinical trials, included injection-site pain/soreness/tenderness, injection-site swelling/induration, headache, injection-site erythema, asthenia, fatigue, and myalgia.[73-77]

PCV13 appeared efficient in preventing vaccine-type pneumococcal bacteraemia and non-bacteraemia CAP in the community-dwelling elderly population, as well as vaccine-type IPD, but not in preventing CAP from any cause.[26]

PCV13 induced a higher immunological response (measured by OPA) than PPV23.[78] In addition, PPV23, followed 1 y

later by PCV13 (PPSV23/PCV13), elicited significantly lower OPA titres than those produced after only an initial dose of PCV13 for all 13 serotypes.[79] However, PCV13 protected the elderly adult population from 40 to 50% of the bacteraemic serotypes[80] and is well tolerated.[26,81]

In summary, considering the pneumococcal vaccine status of different elderly populations, the interaction between PPV23 and PCV13 and the invasive serotypes throughout the European countries, a global strategy is needed to increase the efficacy of pneumococcal protection with both the available vaccines. However, it appears reasonable, as proposed by the new American Committee on Immunization Practice (ACIP) guidelines, to start by administering PCV13 and before giving PPV23 after 1 y.[78] In cases of previous PPV23 vaccination, a new vaccination with PCV13 at least 12 months after the PPV23 vaccination should be administered.[82] PPV23 or PCV13 may be co-administered with the influenza vaccine. Henceforth, the use of PPV23 together with or before PCV13 is not recommended. If PCV13 is unavailable, the use of PPV23 for any patients aged 75 y or older and a risk-based strategy for population between 65 and 75 y is recommended.

Diphtheria, tetanus, pertussis (dTp) vaccination

Diphtheria is still present in countries where vaccination coverage has declined[28] and the cases of tetanus in Europe primarily occur in the elderly population.[29] The dT vaccine efficacy (Td) decreases with age but is still sufficient to protect a large part of the elderly population.

Pertussis in elderly adults may manifest in minimally symptomatic presentations to 6 weeks of coughing spells with weight loss, syncope, and/or rib fractures.[83] The number of notifications of pertussis infections in adults over 50 y of age increased from 2000 to 2011.[84] Notably, however, p vaccine are not equally used in Europe for the elderly population. These contrasts are related to policy decisions regarding the extent and impact of the outbreaks in this population. The efficacy has been demonstrated in elderly adults and the p vaccine can be injected with the influenza vaccine,[85] but the efficacy of co-administration is not yet been demonstrated.

Both the dT and dTp vaccines are well tolerated, with no significant differences in their adverse events.[86]

Because outbreaks in elderly adults are still rare, despite outbreaks in children,[87] the expert committee decided to recommend vaccination with dT for all elderly individuals every 10 y, whereas dTp vaccination is recommended based upon the extent of the outbreak in each country.

Zoster vaccination

The zoster vaccine currently on the market is a live, attenuated vaccine (ZLAV) with a 14-fold higher varicella zoster (VZV) attenuated virus concentration than V vaccine. The aim of this vaccine is to boost cellular immunity to protect aging individuals against herpes zoster, to decrease the rates of post-herpetic neuralgia (PHN), and to decrease the impact of herpes zoster on the quality of life.

The ZLAV efficacy was first demonstrated in the shingles prevention RCT,[88] by the Cochrane review that examined 4 placebo/vaccine studies,[89] and in a recent routine life cohort study.[90] The ZLAV reduced the zoster incidence with a risk ratio (RR) of 0.49 (95% CI 0.43–0.56).

The ZLAV efficacy decreases with age, but the incidence of zoster still decreased in the elderly population (>70 y old) and in the oldest population (>80 y old). In the USA cohort study, the age at the time of injection did not modify the magnitude of effectiveness of the vaccine (RR 0.48).[90]

The ZLAV is efficacious over a long period (although there is decreased efficiency between years 4 and 7), reducing herpes zoster by 39.6% (CI 18.2–55.5%) and PHN by 60.1% (CI −9.8–86.7%).[91] A model estimated a vaccine effectiveness over years 7 to 10 of 21.1% (CI 10.9–30.4%) for the prevention of herpes zoster and 35.4% (CI 8.8–55.8%) for the prevention of PHN.[92]

Adverse drug reactions are mainly local at the injection site, without any serious adverse reactions.[88-90]

An adjuvanted VZV gE subunit vaccine is being developed as a potential alternative to the currently approved ZLAV. A pivotal phase III study to assess the efficacy of the investigational vaccine for the prevention of shingles has met its primary endpoint and showed that HZ/su reduced the risk of shingles by 97.2% in adults aged 50 y and older compared with placebo.[93] An efficacy study on this vaccine (the Zoster Efficacy study ZOE-50), which was initiated in August 2010, is ongoing in 18 countries and involves more than 16,000 individuals.

The expert committee recommends herpes zoster vaccination for individuals aged 50 y and older, including in patients with previous zoster episodes. Currently, re-vaccination is not recommended, considering the lack of data and the persistence of vaccine efficacy. Contraindications include previous anaphylactic reactions to any component of the zoster vaccine, pregnancy, and primary cellular or acquired immunodeficiency.[88-90] Further details on the possible use of the ZLAV in immunocompromised patients are reported below.

Tick-borne encephalitis (TBE) vaccination

The TBE vaccine is an inactivated, cell culture-derived vaccine.[47,48]

No clinical trials have been conducted to determine the efficacy of TBE vaccines, but the effectiveness and safety of current vaccines has been proven in a number of observational studies.[47-49] In Austria, high vaccination coverage has led to a significant decrease in TBE incidence.[48] The overall field effectiveness in regularly vaccinated persons is approximately 99%, with no statistically significant difference between age groups,[49] It is at least as high after the first 2 vaccinations, i.e., before the completion of the basic vaccination scheme by a third vaccination, but is significantly lower (approximately 95%) in those with a record of irregular vaccination. TBE break-through infections are reported rarely and primarily occur in older age groups.[49]

In areas where the disease is highly endemic (≥5 cases/100,000 per year), implying that there is a high individual risk of infection, the World Health Organization recommends vaccination of all age groups.[50] Where the rate of TBE is moderate or low (5-y incidence of < 5/100,000 per year), or is limited to specific areas or outdoor activities, vaccination should target individuals in the most severely affected cohorts.[50] The primary

vaccination series consists of 3 doses (day 0, 1 to 3 months after the first dose, and 5 to 12 months after the second dose), and a booster dose should be administered every 3 y.[49] If a rapid immune response is required, an accelerated schedule based on immunization on day 0, day 14 and month 5–7, or on day 0, day 7 and day 21, may be used.

In summary, experts recommend vaccination against TBE for elderly individuals (≥65 y) in risk areas. The TBE vaccine is contraindicated in persons with a history of anaphylaxis or anaphylactic hypersensitivity to any component of the vaccine or its container.[47-49]

Immunocompromised adults

The number of immunocompromised patients continues to grow at an astonishing rate, although an estimation of the total number or the prevalence of the immunosuppressive conditions is very problematic, considering the diversity of causes and the cut-off levels for immunodeficiency.[94-96]

Adults with weakened immune systems are particularly vulnerable to infection and the burden of transmissible disease is heavier than that in immunocompetent patients because infections recur, persist longer and are often more severe than usual.[94-96] Recurrent infections can place "frequent flier" patients at hospitals at greater risk of further contracting hospital-acquired infections.[97]

The list of conditions that can cause relevant immunocompromise include: primary immunodeficiencies; malignancy, particularly in patients undergoing treatment; human immunodeficiency virus (HIV) infection; iatrogenic immunosuppression for organ transplantation; rheumatologic disorders; and autoimmune diseases.

Vaccination is the most effective strategy to decrease the burden of many community-acquired infections, although the immune response to vaccines in these patients is almost consistently depressed and safety issues must be considered for live, attenuated vaccines.[96-98]

Influenza vaccination

Strong evidence exist about influenza vaccine efficacy and effectiveness in immunocompromised patients. Trivalent influenza vaccine (TIV) is effective in reducing: (i) ILI after vaccination in patients with HIV infection, those with cancer, those undergoing peritoneal dialysis and hematopoietic stem cell transplantation (HSCT) recipients; (ii) laboratory-confirmed influenza in HIV-infected patients, compared with patients receiving placebo or no vaccination; (iii) hospitalisation in adults with cancer and haematological malignancies; (iv) pneumonia in patients undergoing haemodialysis and in solid organ transplant (SOT) recipients; and (v) mortality in immunosuppressed adults with cancer, in those who are asplenic and in haemodialysis patients.[99-102] In these patients, the immune response was typically lower in comparison with that in immunocompetent controls.[99-102]

In HIV-infected patients, vaccination was generally well tolerated, although a transient increase in viremia and decrease in the percentage of CD4+ cells (not accompanied by worsening of clinical symptoms) was reported in some studies.[100,103] Inactivated influenza vaccines do not trigger rejection episodes and should not be withheld in transplant recipients for that reason.[99,103]

In summary, annual vaccination with the inactivated influenza vaccine is recommended for all immunocompromised adults. In transplant recipients, it should be administered starting 6 months after HSCT and after intensified immunosuppression in SOT recipients has been completed, including the first 2-month post-transplant period. The LAIV should not be administered to immunocompromised patients.

Pneumococcal vaccination

The body of evidence on pneumococcal vaccine efficacy and safety among patients with immunocompromising conditions is limited and focus on HIV-infected and haemodialysis patients.

Pneumococcal vaccination is recommended for: (i) patients with asplenia or sickle cell disease; (ii) patients with primary immunodeficiency disorders; (iii) HIV-infected patients; (iv) patients with solid or haematologic cancers; (v) HSCT patients; (vi) SOT candidates and recipients; (vii) end-stage heart, kidney, liver or lung disease; (viii) patients with chronic inflammatory illness who are receiving immunosuppressive therapy; and (ix) cochlear implant candidates.[104]

The pneumococcal vaccination schedule includes PPV23 administration ≥8 weeks after PCV13 and a second dose of PPV23 5 y later.[105,106] For those who were previously immunized with PPV23, PCV13 should be administered ≥1 y after the last PPV23 dose.[105]

The aforementioned schedule is recommended for cancer patients 3 months after intensive chemotherapy and for SOT patients 2–6 months after transplantation. In patients for whom a splenectomy or cochlear implant is planned, vaccination with PCV13 followed by PPV23 is recommended 2 weeks after the splenectomy or 2 weeks before surgery, respectively. In HSCT patients, 3 doses of PCV13 should be administered 3–6 months after HSCT, separated by a 2-month interval, followed by 1 dose of PPV23 12 months after transplantation. For patients with chronic graft-versus-host disease (GVHD) a fourth dose of PCV12 should replace the PPV23, because patients with GVHD are unlikely to mount protective responses to polysaccharide vaccines. The PPV23 vaccine can be given after resolution of GVHD and at least 8 weeks following PCV13.

Diphtheria, tetanus, pertussis (dTp) vaccination

The dTp is recommended for:[103,106,107] (i) all patients 6 months after HSCT (a 3-dose series of a vaccine with high tetanus and acellular pertussis content [DTaP] may be more immunogenic and should be considered for the initial vaccination, regardless of patient age, whereas dTap should be used as a booster rather than as part of the primary series); (ii) 3 months after cancer chemotherapy, patients should be vaccinated with dTap, and in regimens that include anti–B-cell antibodies, vaccination should be delayed at least 6 months; (iii) patients with chronic inflammatory illness who are in treatment with immunosuppressive drugs; (iv) HIV-infected patients, based upon their

serological status; and (v) SOT candidates or end-stage heart, kidney, liver and lung disease, based upon their serological status.

Human papillomavirus (HPV) vaccination

Persons infected with HIV are at higher risk of developing HPV-associated cancers.[108] To date, HPV vaccination is routinely recommended in a few countries (including the United States and Australia) for HIV-infected individuals and for any other person who is immunocompromised by disease or medications through age 26 y.[109,110] However, the HPV vaccination could be less effective in immunocompromised subjects. A randomized study compared the immunogenicity of the bivalent 16 and 18 HPV vaccine and the quadrivalent 6, 11, 16 and 18 in HIV-infected men and women taking antiretroviral therapy and who were virologically suppressed, and the study showed that both vaccines were immunogenic and well tolerated, but the bivalent HPV vaccine induced a better response in women compared with the tetravalent vaccine.[111] A 3-dose schedule administered at 0, 1–2 and 6 months instead of the 2-dose schedule at 0–6 months, is recommended.[109-112]

Measles, mumps, and rubella (MMR) vaccination

There is consensus about avoiding live vaccines in immunocompromised patients, due to the risk of severe vaccine-induced disseminated disease.[98,103] MMR vaccination is contraindicated in the following: (i) patients with leukocyte adhesion deficiency and defects of cytotoxic granule release such as Chediak-Higashi syndrome; (ii) patients with defects of interferon (IFN) alpha or gamma production; (iii) patients receiving chemotherapy; (iv) patients receiving ongoing anti-B-cell antibody therapy; (v) HSCT patients undergoing immunosuppression or suffering from GVHD; and (vi) HIV-infected patients with CD4 T-cell lymphocyte counts $<200/mm^3$.

Three months after chemotherapy and 6 months after anti-B-cell antibody therapy, patients should be vaccinated using the schedule routinely indicated for immunocompetent individuals.[103] In HSCT patients, MMR is recommended for seronegative individuals at least 2 y after transplant, if they have no GVHD, and do not receive any immunosuppressive drugs.[103] In an outbreak situation and based upon the experience in Brazil, vaccination should be considered on an individual basis in HSCT patients at $\geq$1 y after transplant.[112] In HIV-infected patients, MMR is recommended for those with CD4 T-lymphocyte counts $\geq$200 cells/mm^3.[103]

When administered, the 2 MMR doses should be separated by $\geq$3 months. In immunocompromised patients, MMR vaccine should not be administered in combination with the V vaccine.

Varicella (V) and zoster vaccination

The V and zoster vaccines are not licensed for use in immunocompromised patients due to their potential risk of severe disease in patients who lack a sufficient T-cell-mediated immune response, and they should not be administered to highly immunocompromised patients.[98,103,113]

However, the V vaccine is recommended for immunocompromised patients without a history of V, prior vaccination or serological evidence of VZV infection, if affected by HIV infection without severe immunosuppression or a primary immune deficiency disorder without defective T-cell-mediated immunity, such as primary complement component deficiency disorder or chronic granulomatous disease.[98,103] A 2-dose schedule separated by a 3-month interval is recommended.

In the case of immunosuppressive therapy administration, the V vaccine should be administered 4 weeks before treatment with a 2-dose schedule separated by a 4-week interval.[114]

The V vaccine should not be administered in combination with the MMR vaccine.

The recommendations on vaccination against zoster in immunocompromised patients are more stringent than those against V due to the higher live attenuated virus content and probable residual VZV-specific immunity.[113] The ZLAV vaccine should be considered for persons aged 50 y and older with a history of V or zoster infection, 4 weeks prior to immunosuppressive therapy.[113] In immunosuppressed elderly persons with leukaemia, lymphoma and HIV, or during and for 6 months after a prescription for an immunosuppressive drug, including oral corticosteroids, as well as in patients with rheumatoid arthritis, psoriatic arthritis, psoriasis, spondylitis and inflammatory bowel disease, the ZLAV vaccine has been shown to be safe and effective in reducing the incidence of zoster, whereas in patients with haematological malignancies, ZLAV was safe and compared to no vaccination, may reduce herpes zoster, but without a statistically significant difference.[115] However, ZLAV is actually contraindicated in immunocompromised persons and only those with leukaemia in remission and those who have not received chemotherapy or radiation for at least 3 months may receive ZLAV.[113] The adjuvanted VZV gE subunit vaccine will be the vaccine of choice for immunocompromised persons.[93]

Haemophilus influenzae *type b (Hib) vaccination*

The Hib vaccine has been administered in the last 20 y in the pentavalent and hexavalent vaccines in infants and toddlers. However, in immunocompromised adult patients, Hib vaccine should be administered: [116] (i) in asplenic patients or those who have sickle cell disease; and (ii) in HSCT patients.

There are no data on the timing the Hib vaccination based upon the serologic response in patients undergoing splenectomy. In HSCT patients, 3 doses of vaccine should be administered 6–12 months after transplantation.

Meningococcal vaccination

Conjugated meningococcal vaccine should be administered to the following:[117] (i) patients with primary complement deficiencies; and (ii) asplenic patients or those who have sickle cell disease.

The meningococcal vaccine should be given at least 2 weeks before splenectomy.[117] The primary series with quadrivalent conjugated vaccine and quadrivalent polysaccharide vaccine should be administered for individuals aged $\leq$ 65 y and >65 y, respectively.[117] Re-vaccination with the quadrivalent

conjugated vaccine every 5 y is recommended; for adults >55 y old who have not previously received the conjugated vaccine, re-vaccination with the quadrivalent polysaccharide vaccine is recommended.[117]

A reduced antibody response to some pneumococcal serotypes has been reported when both the conjugated meningococcal vaccine and PCV13 are administered simultaneously.[118]

Hepatitis A virus (HAV) vaccination

Administration of the HAV vaccine is indicated for immunocompromised, seronegative adults if they fulfil the following criteria:[119] (i) HIV-infected patients; (ii) patients with solid or haematologic cancer; (iii) HSCT patients (in these cases, 2 doses of vaccine should be administered pre-transplantation or 6 months after transplantation); (iv) SOT recipients (in these cases, 2 doses of vaccine should be administered pre-transplantation or 6 months after transplantation); (v) patients asplenic or who have a sickle cell disease; (vi) persons with chronic inflammatory diseases on immunosuppressive medications; (vii) patients with liver disease.

Hepatitis B virus (HBV) vaccination

Administration of HBV vaccine is indicated for immunocompromised seronegative adults if:[120] (i) patients with solid or haematologic cancer (in these cases, the 3-dose series should be completed 2 or more weeks prior to chemotherapy; if the vaccine was administered post to initiation of chemotherapy, vaccination should start ≥3 months post-chemotherapy and ≥6 month post anti-B-cell antibodies); (ii) HIV-infected patients (in these cases, high-dose hepatitis B vaccine [40 μg] should be considered); (iii) HSCT patients (in these cases, 3 doses of vaccine should be administered pre-transplantation or 6 months after transplantation); (iv) SOT patients (in these cases, 3 doses of vaccine should be administered pre-transplantation or 6 months after transplantation); (v) asplenic patients or those who have sickle cell disease; (vi) persons with chronic inflammatory disease on immunosuppressive medications; and (vii) patients with liver disease.

Yellow fever vaccination

The yellow fever vaccine is not licensed for use in immunocompromised individuals.[121]

If travel to an endemic area cannot be avoided, yellow fever vaccination can be considered in asymptomatic HIV-infected individuals with CD4 T-cell lymphocyte counts ≥200 cells/mm^3.[121]

Recommendations for households of immunocompromised adults

Household contacts of immunocompromised adults should receive:[122] (i) the MMR vaccine; (ii) the V vaccine and ZLAV vaccines; (iii) the rotavirus vaccine if infants 2–7 months old (for 4 weeks after vaccination, immunocompromised patients should avoid handling the diapers of infants who have been vaccinated with rotavirus vaccine); and (iv) annually, the inactivated influenza vaccine (LAIV should be avoided, particularly in individuals who live in a house with an HSCT recipient within 2 months after transplant, or who has GVHD, or with a patient with severe immune deficiency).

Household contacts can safely receive for travel the following:[122] (i) the yellow fever vaccine and (ii) the oral typhoid vaccine.

Administration of the oral polio vaccine (OPV) is contraindicated.[122]

Adults at risk

This section focuses on pregnant women and health care workers (HCWs), whereas travelers are not considered due to the heterogeneous characteristics of this category of subjects.

Vaccination of pregnant women

The immunization of pregnant women provides important health benefits for these women and their infants.[123] Multiple vaccines were examined with regards to their appropriateness for maternal vaccination, including the influenza, pneumococcal, dTp, HPV, MMR, V, meningococcal, HAV and HBV vaccines. Of these vaccines, LAIV, MMR, and V are contraindicated for pregnant women, whereas HPV is not recommended for pregnant women.[124] Accordingly, these 4 vaccines are not considered part of the recommendations but MMR, V, and HPV vaccines should be assessed and administered, if appropriate, to the woman prior to becoming pregnant. However, an analysis of available data suggests that administration of the V and HPV vaccines during pregnancy thus far has not negatively impacted pregnancy outcomes, such as increasing the rates of miscarriage and birth defects.[124,125] Additionally, data indicate that inadvertent administration of the rubella vaccine to pregnant women does not appear to result in vaccine-related congenital rubella syndrome, and while administration of LAIV during pregnancy occurs rarely, there is no evidence of significant maternal adverse outcomes after receipt of LAIV.[124]

Due to the risk of complications associated with influenza during pregnancy, the benefits in terms of reduction of influenza cases because of the placental transfer of antibodies to the newborn, and the safety of inactivated vaccines, all women who will become pregnant, or who will be pregnant, during the influenza season are advised to receive the inactivated trivalent or quadrivalent influenza vaccine at any time during the pregnancy.

According to recent data on the utility and safety of maternal immunization to protect neonates and young infants against pertussis,[126] all pregnant women are advised to receive a dose of the dTap vaccine. While dTap can be given at any time during the pregnancy, in order to maximize the maternal antibody response and passive antibody transfer to the neonate, the best time to administer the vaccine is between 27 and 36 weeks of gestation. If the woman has not previously received dTap, and if dTap is not administered during the pregnancy, dTap should be administered immediately post-partum.

Data on protection against maternal and neonatal tetanus have shown that pregnant women who have never been

vaccinated against tetanus should receive 3 vaccinations containing tetanus and reduced diphtheria toxoids in either the form of dT or dTap.[127] However, dTap should replace one dose of dT, preferably between 27 and 36 weeks' gestation.[127]

Ideally, the pneumococcal vaccine should be given before pregnancy, but there are inadequate data to provide a specific recommendation for the use of these vaccines in pregnant women. However, data that are available suggest that the administration of PPV23 during the second or third trimester is safe (there are no data on the administration of PPV23 during the first trimester).[128] Thus, PPV23 is recommended if some other risk factor is present. There are currently limited data regarding the use of PCV during pregnancy.

Regarding meningococcal vaccination, the data indicate that the administration of meningococcal vaccine (both the conjugate and the polysaccharide vaccine) is not correlated with any concerning patterns in maternal, infant, or fetal outcomes.[129] Consequently, vaccination of pregnant women with meningococcal vaccines is recommended, if indicated.

HAV can cause severe illness in pregnant women and can be passed to the fetus, but it does not carrier any known risk to the developing fetus.[130] Thus, HAV vaccine is recommended for pregnant women if another high-risk condition or other indication is present.

Like HAV vaccine, HBV vaccine carries no known risk to the developing fetus.[131] Thus, HBV vaccine is recommended for pregnant women who are identified as being at risk for HBV infection.

Vaccination of health care workers (HCWs)

HCWs have a responsibility to protect the patients they serve by adopting all reasonable interventions, including vaccination, to reduce the transmission of infectious diseases. Multiple vaccines for HCWs are safe and efficacious, and high vaccination coverage among these important personnel reduces the risk of transmission of disease among them and to their patients.[132] Vaccines examined with regards to their appropriateness for HCW vaccination included influenza, pertussis, V, MMR, HBV, and meningococcal containing vaccines.

As recommended by health authorities for the reduction of influenza transmission to patients potentially at risk of complications, as well as for a decrease in influenza-related costs associated with the loss of HCWs' working days,[133] it is recommended that all HCWs receive the influenza vaccine every influenza season. The LAIV may be administered only to non-pregnant, healthy HCWs aged 49 y and younger. The inactivated injectable influenza vaccine (trivalent or quadrivalent) is preferred over the LAIV for HCWs who are in close contact with severely immunosuppressed patients when they require protective isolation.

All HCWs who have not, or are unsure if they have, previously received a dose of dTap are advised to receive a dose of dTap immediately, without regard to when the previous dose of dT was given.[134] All HCWs are then recommended to receive dT boosters every 10 y.

Several V outbreaks involving HCWs have been reported in hospitals and consequently, HCWs are recommended to receive 2 doses of varicella vaccine, 4 weeks apart, if there is no knowledge of prior chickenpox (or herpes zoster) infection, there is no documentation of prior varicella vaccination, or when there is no serologic evidence of immunity.[135]

HCWs with no serologic evidence of immunity to MMR or documentation of prior vaccination are recommended to receive 2 doses of MMR vaccine at least 28 d apart.[136]

HCWs who are routinely exposed to isolates of *Neisseria meningitidis* are recommended to receive vaccination with the tetravalent conjugated meningococcal vaccine.[137]

Moreover, HCWs are recommended to receive 3 doses of HBV vaccine at 0, 1, and 6 months if there is no documentation of prior HBV vaccination (complete 3-dose vaccine series) or if there is no serologic evidence of immunity.[138] HCWs should be tested for HBV surface antibody (anti-HBs) 1–2 months after the third dose to document immunity.[138] HCWs whose anti-HBs are less than 10 mIU/mL should be re-vaccinated with a second 3-dose series. Non-responders (i.e., those in whom anti-HBs remains less than 10 mIU/mL after the second 3-dose series) should be considered susceptible to HBV and should be counselled regarding precautions to prevent HBV infection and the need to obtain HBV immunoglobulin prophylaxis for any known or probable parenteral exposure to HBs antigen (HBsAg-positive blood or blood from an individual with an unknown HBsAg status).

While no specific recommendations have been made for HCWs for the other vaccines, recommendations do exist for the vaccination of adults. All HCWs should be assessed for their own adult immunizations and provided all appropriate adult vaccines, as recommended.

Conclusions

Extending the benefits of vaccination to all age groups including the older population is a healthcare priority. Notably, in contrast, adult vaccination decreases mortality and morbidity linked to vaccine-preventable diseases[139] as well as is associated with reduced use of antibiotics and a decrease in antibiotic-resistant infections.[140,141]

Table 2 summarizes recommendations on vaccination for adults and the elderly. However, although immunization is considered one of the most impactful and cost-effective public health measures, vaccination coverage rates are largely lower than the stated goal of ≥95% among adults,[142] and strong efforts are required to increase the coverage in this population, considering the patient's risk on the basis of the age-related immune-senescence, the high frequency of an underlying chronic disease, or the pregnancy status and work activities. It is also interesting to note that there is increasing scientific evidence indicating that the strategy of vaccinating the direct contacts of those who are most vulnerable to certain infectious diseases may be an effective additional measure to reduce their incidence.

However, the evidence is limited in a number of areas and further studies are required to show the proof of clinical protection in some groups and the timing of immunization. Active surveillance toward vaccine-preventable diseases, the evaluation of efficacy of the vaccines launched in the market in the last 5 y, efficacy and safety of vaccines in immunocompromised

Table 2. Recommendations on vaccination for adults and the elderly.

Category	Type of vaccination	Recommendation
Adults	Influenza	Influenza vaccination of healthy adults both for individual protection and for the overall reduction of disease burden and virus circulation, which is demonstrated in the presence of a good match between the vaccine and circulating strains
	Pneumococcal	No pneumococcal vaccines are routinely recommended for adults <65 y with no underlying risk factors. PCV13 vaccination (with the possible addition of PPV23 at least 1 y later) may be recommended for the individual protection against IPD and all-cause pneumonia.
	dTp	An effective boosting policy every 10 y with dTp in young adults
	HPV	All adolescent women and men before becoming sexual active up to 20 y of age. Vaccination of older women up to 45 y of age is advised as an individual protective measure not reimbursed by public health programmes
	MMR and V	All adults lacking evidence of immunity (whether natural or acquired, due to prior vaccination) against any of measles, mumps or rubella should receive 2 doses of the MMR vaccine with a minimum interval of 4 weeks. Similarly, healthy adults lacking anamnestic recall of experiencing varicella should receive 2 doses of the V vaccine with a minimum interval of 4 weeks
	TBE	In areas where the disease is highly endemic, TBE vaccination is recommended in all age groups
Old adults	Influenza vaccination	Routine annual influenza vaccination for all individuals 65 y of age and older
	Pneumococcal vaccination	In the 65 y and older population: • without previous PPV23 vaccination, the use of the PCV13 vaccine first and a second vaccination with PPV23 8 weeks to 6 months after the PCV13 shot; • with previous PPV23 vaccination, a new vaccination with PCV13 at least 12 months after the PPV23 vaccination; • PPV23 or PCV13 may be co-administered with the influenza vaccine; • the use of PPV23 together with or before PCV13 is not recommended.If PCV13 is not available, experts recommend the use of PPV23 for any patients 75 y or older and a risk-based strategy for population between 65 and 75 y
	dTp	Vaccination with • dT for all elderly individuals (≥ 65 y) every 10 y; • dTap, according to the extent of the outbreak in each country
	Herpes zoster	ZLAV for individuals aged 50 y and older, even in the absence of a previous zoster episode. Re-vaccination is not recommended
	TBE	Vaccination against TBE for older people (≥ 65 y) in areas at risk
Immuno-compromised adults	Influenza	Annual vaccination with inactivated influenza vaccine
	Pneumococcal	Pneumococcal vaccination for patients with asplenia or sickle cell disease, those with primary immunodeficiency disorders, those HIV-infected, those with solid or haematologic cancer, HSCT patients, SOT candidates and recipients, those with end-stage heart, kidney, liver or lung disease, those patients with chronic inflammatory illness in treatment with immunosuppressive drugs, and cochlear implant candidates. Pneumococcal vaccination schedule includes PPV23 administration ≥ 8 weeks after PCV13, and a second dose of PPV23 5 y later. For those who were previously immunized with PPV23, PCV13 should be administered ≥ 1 y after the last PPV23 dose
	dTp	dTap is recommended for all patients 6 months after HSCT, 3 months after cancer chemotherapy, in those with chronic inflammatory illness in treatment with immunosuppressive drugs, in the HIV-infected, in SOT candidates or those with end-stage heart, kidney, liver and lung disease
	HPV	HIV-infected individuals and for any other person immunocompromised due to disease or medication through age 26 y, of both genders, with a 3-dose schedule
	MMR	MMR vaccine 3 months after chemotherapy and 6 months after anti-B-cell antibody therapy, in HSCT, seronegative individuals 2 y after transplant if they have no GVHD and do not receive any immunosuppressive drug, in HIV-infected patients with CD4 T-lymphocyte counts ≥ 200 cells/mm.[3] In these patients, the MMR vaccine should not be administered in combination with the V vaccine
	V and herpes zoster	The V vaccine for patients without a history of varicella, prior vaccination or serological evidence of VZV infection, if HIV-infected without severe immunosuppression or with a primary immune deficiency disorder without defective T-cell-mediated immunity. In the case of immunosuppressive therapy, the V vaccine should be administered 4 weeks before treatment with a 2-dose schedule separated by a 4-week interval. The V vaccine should not be administered in combination with the MMR vaccine. ZLAV is actually contra-indicated in immunocompromised persons and only those with leukemia in remission and who have not received chemotherapy or radiation for at least 3 months can receive ZLAV
	Hib	Hib vaccination in asplenic patients or those who have sickle cell disease and in HSCT patients
	Meningococcal	Conjugated meningococcal vaccine should be administered to patients with primary complement deficiencies and to those who are asplenic or who have sickle cell disease
	HAV	The HAV vaccine is indicated for immunocompromised, seronegative adults if HIV-infected, patients with solid or haematologic cancer, HSCT patients, SOT recipients, those who are asplenic or who have sickle cell disease, persons with chronic inflammatory diseases on immunosuppressive medications, and patients with liver disease.
	HBV	The HBV vaccine is indicated for immunocompromised, seronegative adults with solid or haematologic cancer, HIV-infected patients, HSCT patients, SOT patients, those who are asplenic or who have sickle cell disease, persons with chronic inflammatory disease on immunosuppressive medications and patients with liver disease
	Yellow fever	

(*Continued on next page*)

Table 2. (*Continued*)

Category	Type of vaccination	Recommendation
		If travel to an endemic area cannot be avoided, yellow fever vaccination can be considered only in asymptomatic HIV-infected individuals with CD4 T-cell lymphocyte counts $\geq$ 200 cells/mm^3
	Household contacts	They should receive the MMR, V, ZLAV, rotavirus, and inactivated influenza vaccine. They can safety receive the yellow fever vaccine and oral typhoid vaccine. Oral polio vaccine (OPV) administration is contraindicated
Adults at risk	Pregnant women	The LAIV, MMR, and V are contraindicated for pregnant women, whereas HPV is not recommended to be administered to pregnant women. They should receive the inactivated trivalent or quadrivalent influenza vaccine, dTap, PPV23 if some other risk factor is present, meningococcal vaccination, if indicated, HAV vaccine if another high-risk condition or other indication is present, HBV vaccine for pregnant women who are at risk for HBV infection
	HCWs	Annual inactivated influenza vaccine, dT boosters every 10 y, 2 doses of varicella vaccine 4 weeks apart, 2 doses of MMR vaccine at least 28 d apart, and the tetravalent conjugated meningococcal vaccine in those who are routinely exposed to isolates of *Neisseria meningitidis*.

dTap: diphtheria, tetanus, acellular pertussis; dT: diphtheria, tetanus; dTp: diphtheria, tetanus, pertussis; GVHD : graft versus host disease; HAV: hepatitis A virus; HBV: hepatitis B virus; HCWs : health care workers; Hib: *Haemophilus influenzae* type b; HIV : human immunodeficiency virus; HPV: human papillomavirus; HSCT : haematological stem cell transplantation; IPD : invasive pneumococcal disease; MMR: measles, mumps, rubella; PCV13 : 13-valent pneumococcal conjugated vaccine; PPV23 : 23-valent pneumococcal polysaccharide vaccine; SOT : solid organ transplant; TBE: tick-borne encephalitis; V: varicella; ZLAV : live attenuated vaccine against herpes zoster.

patients, as well as in pregnant women, represent the priority for future research.

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