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VACCINES IN ADULTS

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Abstract The proportion of adult population has increased globally and the current projections indicate that, by 2050, the group of 60 years and older will represent 21.1%. There are now vaccines exclusively designed for adults and others that are applied in early life but need to be updated later in life. Vaccines for adults are not only based on their respective age group but are also linked to risk factors like occupation, life style, health situation, among others. At the same time, longevity brings with it a weakening of the immune response to vaccines, a process known as immunosenescence representing an increasing challenge to adequately protect this age group. For some time, WHO has been promoting the term "Vaccination through the life course" allowing for an extension of the vaccination vision and taking adults as an integral part into the national vaccination programs and calendars. There are several vaccine preventable diseases affecting adults, but those associated with influenza virus and pneumococcus are the ones that affect the largest age group. Several recommendations include, additionally, others to prevent diphtheria, tetanus, whooping cough, hepatitis A and B, meningococcus, chickenpox, measles, rubella, mumps, herpes zoster, human papilloma virus and others. There are still many challenges to overcome in order to fully include adults, particularly health personnel, and to make vaccines extensively valued as a prevention tool in order to achieve a healthy life.

Key words: vaccines, preventable diseases, immunization programs, adult, elderly

Resumen ***Vacunas en adultos.*** La proporción de población de adultos se ha incrementado globalmente y las proyecciones muestran que para el año 2050 los mayores de 60 años representarán el 21.1%. Actualmente se dispone de vacunas dirigidas exclusivamente a adultos y otras que se aplican en niños pero que se deben actualizar a lo largo de la vida. Las vacunas en adultos se administran, no solo por el grupo de edad al que pertenecen, sino también por factores como ocupación, estilos de vida o estado de salud. Al mismo tiempo, la longevidad disminuye la respuesta inmune a las vacunas por el fenómeno de inmunosenescencia, lo cual representa un desafío para proteger adecuadamente a este grupo. Desde hace varios años la OMS, ha propiciado la utilización del término "Vacunación en el curso de la vida" lo cual permite extender la visión de la vacunación y considerar al adulto como una parte integral de los planes y calendarios de inmunización. Existen varias enfermedades prevenibles por vacunas en adultos, pero aquellas asociadas al virus de influenza y al neumococo, son las que comprenden el grupo más extenso. Diversas recomendaciones incluyen, además de estas vacunas, otras dirigidas a prevenir difteria, tétanos, tos convulsa, hepatitis A y B, meningococo, varicela, sarampión, rubéola, parotiditis, herpes zóster, virus del papiloma humano y otras enfermedades. Se reconocen muchos desafíos a superar para poder incorporar plenamente al adulto, incluyendo al personal de salud, y lograr que la vacunación sea una herramienta de prevención valorada ampliamente para el desarrollo de una vida saludable.

Palabras clave: vacunas, enfermedades prevenibles, programas de inmunización, adulto, adulto mayor

Adults at any age are exposed to diverse infectious diseases which are vaccine preventable. The risk of being affected by some of these diseases and the recommendations to be vaccinated to prevent them depends on several factors, like their health situation, age, life style, epidemiological considerations, risk exposure like occupational o travel related; children, on the contrary, are vaccinated, almost exclusively, based on their age[1-9].

Scientific and technological progress have made possible to produce several vaccines for adult use, a group age not considered previously as a target, defining now a more complex scenario for better prevention in these group. There is a low risk perception among those in these age group, since they are the survivors of child diseases; also, because most of deaths from vaccine preventable diseases are concentrated now in communities and countries under the poverty line. These are some of the determinants for the low global coverage of adults, including health personnel[10-13].

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However, from demographic data, the proportion of adults and older adults is the top segment of accelerated population growth. The proportion of people > 60 years increased from 9.2% in 1990 to 12.7% in 2015 and will reach 21.1% in 2050, being the growth even more accelerated in low income countries.

Longevity generates a progressive loss of natural antibodies acquired through suffering the diseases or being vaccinated[14]. Immunosenescence is a natural ageing process of the immunological system and may be aggravated by diseases, emotional stress, malnutrition, and other factors. Due to a reduced production of hematopoietic tissue in the bone marrow and the decreasing renewal potential of the mother cells, the natural, nonspecific and rapid immune response is compromised[15]. Epithelial barriers are more permissive to invasion by infectious agents, neutrophils show functional alterations and macrophages become less efficient[16, 17], creating a diminished response of older adults to vaccines.

Vaccine response is dependent on the antigen type: attenuated live virus and protein associated antigens induce antibodies production in high levels, as well as TCD8. Inactivated virus vaccines only induce high level of antibodies. That is why older adults produce low antibodies level to influenza, hepatitis B, diphtheria and tetanus vaccines. Several interventions have been developed to increase older adults' response: higher concentration of antigens, additional doses, use of subcutaneous injections instead of intramuscular, use of adjuvants and conjugated vaccines[18-22].

In 1989, the World Health Assembly called to eliminate neonatal tetanus by 1995, launching the pregnant women vaccination. By the end of the 90s, due to measles outbreaks in adults, adolescents and young adults were included in mass campaigns, and, at the same time, older people started to receive seasonal flu vaccines annually. Little by little, health personnel and people with comorbidities began to receive other vaccines like hepatitis B, Hib (*Haemophilus influenzae* type B) and pneumococcal polysaccharide 23 valent (PPV23). Respiratory infections, viral and bacterial linked, are more severe in the extremes of life, being pneumococcus and influenza virus the two main causes[23-28].

There are several new vaccines under development, like respiratory syncytial virus and others containing new immunogens, that are more effective or use new technologies, like the inactivated vaccine against herpes zoster. It is increasingly more important, for the scientific community as well as for the entire society, to know more about the wide spectrum of available vaccines for adults, and to use them in an optimal and rational way, in order to be able to reduce the morbimortality from these diseases, reduce health costs and improve quality of life.

There are several evidence-based recommendations at international, regional and local level for vaccines in adults[9-12]. Usually the guidelines recommend influenza, pneumococcus, diphtheria/tetanus (double-adults) or pertussis/diphtheria/tetanus (triple acellular), hepatitis A y B, meningococcus, varicella, measles/rubella/mumps (triple viral), herpes zoster, human papilloma virus and others, i.e. people in risk or endemic areas Argentinian hemorrhagic fever, yellow fever[1-3, 9, 11-14, 16, 17, 22-25].

Diphtheria

It has recently reemerged in the Americas with cases in Haiti, Dominican Republic and Venezuela; immunity declines progressively with years[21].

Tetanus

Cases are reported annually in several countries and most of them, in adults with incomplete or obsolete vaccination[17].

Pertussis (whooping cough)

Recommendations are to include acellular triple vaccine (dTpa), at least one dose during the life course, instead of double (dT), due to the burden of disease caused by *Bordetella pertussis* since this disease has usually a mild or atypical presentation in adults and is less notified in older adults over 65 years of age[17, 26, 27]. Also recommended is dTpa vaccine in the last trimester of pregnancy in order to transfer antibodies from mother to child, close to delivery, generating high impact on morbimortality of newborns and under 6 months old[28]. Health workers and caregivers in contact with newborns should also be vaccinated since they become important carriers and disseminators for pertussis.

Influenza

Influenza vaccine was introduced for older adults, pregnant women and adults with chronic diseases. Due to minor antigen changes in the virus, each year the composition of the vaccine is updated on two occasions, in February in the northern hemisphere and in September in the southern hemisphere. Inactivated trivalent vaccine is developed in embryonated eggs and contains two virus, subtypes influenza A (H1N1 y H3N2) and one lineage of virus B (Victoria or Yamagata). Vaccine effectiveness to prevent non-complicated flu in adults over 60 years is around 70%, while in adults older than 60 years, effectiveness is lower, not more than 53%. For this age group, the use of inactivated trivalent flu vaccine is associated with a decrease in pneumonia hospitalizations between 32% and 45%, in hospital mortality due to pneumonia and

flu between 31% and 65% and for respiratory diseases between 43% and 50%, while reducing mortality for all causes between 27% and 30%[18].

In pregnant women the inactivated trivalent flu vaccine reduces flu like diseases by 36% with an effectiveness of 63% reduction of flu cases in under 6 months old children[29].

For the more frequent comorbidities, like those associated with chronic pulmonary or cardiovascular diseases, as well as diabetes, the flu vaccine has been proven to reduce the risk of complications like a new acute heart attack or hospitalization rates in diabetics, during the virus circulation season[30]. One of the challenges for flu vaccine is to achieve higher efficacy in adults over 60, the group suffering the highest rate for flu related hospitalization and death. Inactivated trivalent vaccines with adjuvants or with higher doses of antigens (60 micrograms instead of current 15 micrograms) have been proven to increase efficacy and effectiveness in these age group by around 25%[19].

Since 2013, and due to antigenic differences in the two circulating virus B lineages and the virus impact on flu disease, WHO recommended the development of quadrivalent vaccines containing the two lineages[31]. Quadrivalent vaccines, compared with trivalent, have demonstrated a superior immunogenicity for B components and similar for the other strains, in children as well as in adolescents, young and older adults with higher effectiveness in children and young adults[32-37].

Other vaccines available for adults are the one produced with recombinant DNA technology and those cellular line-based. The first one avoids mutations or adaptative changes suffered by the virus during replication in embryonated eggs and is faster to produce. This vaccine was first developed as trivalent, but now is available as quadrivalent, contains 45 micrograms of each one of the antigens, and is already approved by the regulatory agencies in several countries for adult use[38, 39]. Cellular line-based vaccines are not dependent on eggs availability allowing for more volume and faster production. Some are already approved in Europe and the USA for use in adults[40].

Pneumonia

Invasive pneumococcal disease, seen as bacteremia, meningitis or other severe locations, is more frequent in older adults or adults with comorbidities, particularly immunocompromised persons, or with consumption of tobacco or alcohol. *Streptococcus pneumoniae* is the most commonly identified agent for community acquired pneumonia (CAP), the most frequent infection in adults. Since the 80s the antipneumococcic vaccine with 23 polysaccharides (PPSV23) containing serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F,18C, 19A, 19F, 20, 22F, 23F and 33F, protecting against more than 85% of serotypes responsible for invasive modalities, is available. The vaccine is developed from capsular polysaccharides and produces a response independent of T cells, therefore, not immunogenic in under 2 years old. Several studies in adults have shown that it prevents invasive forms, while for community acquired pneumonia its effect is to attenuate the severity, but without evidence yet that it serves to prevent occurrence[16, 41]. The most recent development of a conjugated pneumococci vaccine with a transporter protein, initially 7 valent and later on 11 and 13 valent, has allowed for a T cell dependent immune response with efficacy in under 2 years old for the prevention of invasive forms, pneumonia and middle otitis due to *S. pneumoniae*. Conjugated vaccines also reduce nasopharynx carriers, with a herd effect documented through the observed reduction on invasive disease due to *S. pneumoniae* in unvaccinated older adults. The conjugated 13 valent vaccine (PCV13) contains serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F shared with vaccine PPSV23 and one own serotype 6A. Studies comparing vaccine PCV13 in adults with PPSV23, have shown a better immunogenic response for most of the serotypes they both share, better response when PCV13 is administered first if they are both administered. This vaccine has shown efficacy close to 50% to prevent CAP due to serotypes included in the vaccine, in a randomized double-blind study compared with placebo in older adults. In spite of the burden of disease in older adults and adults with comorbidities due to *S. pneumoniae*, of data about effectiveness of PPSV23 and PCV13 in adults, as well as the herd impact due to pediatric vaccination, there is no yet consensus or uniformity in the recommendations about use of antipneumococcal vaccines in adults at international level. As an example, the PAHO TAG Vaccines (Technical Advisory Group on Vaccines) stressed the importance of the herd impact through pediatric vaccination and calls the countries to expand the coverage in order to protect older adults. ACIP (Advisory Committee on Immunization Practices) from CDC-USA recommends for older adults and adults with comorbidities the use of a sequential scheme including both vaccines PCV13 y PPSV23[42]. The Ministry of Health of Argentina has adopted this same scheme in 2017 and, in both cases, evaluate the impact of pediatric vaccination on the incidence of invasive forms and CAP through herd effect. In Germany, the STIKO, national committee for vaccines recommendations, has advised to use only PPSV23 in adults over 60 and revaccination every 6 years[41].

There are new conjugated vaccines under development with 15 and 20 serotypes to allow for an extension of protection. Hopefully there will be more and better data to establish more clearly the best alternative to protect against invasive forms in older adults and those with comorbidities and from CAP which is the most frequent in these population groups (Table 1).

TABLE 1.– *Vaccines in adults*

Vaccine	17-64 years	≥ 65 years
Tetanus/diphteria (Td)	1 dose every 10 years in all adults	
Td+acellular pertussis (Tdap)	1 dose to replace one dose of Td once during adult lifetime, also 1 dose in each pregnancy	
Influenza	1 dose every year (seasonal vaccine) in adults with risk conditions, pregnant women and health care workers	1 dose every year in all adults ≥ 65 years
PPSV23	1 or 2 doses in adults with risk conditions	1 dose in all adults ≥ 65 years
PCV13	1 dose in adults with risk conditions	1 dose in all adults ≥ 65 years
HPV	3 doses in transplant and HIV infected men and women up to 26 years In women, based on individualized indication, can be administered without age limit	
Hepatitis B	3 doses (0, 1 and 6 m) for all susceptible adults	
Hepatitis A	2 doses (0, 6 to 12 m) in susceptible adults, particularly in those with occupational risk or based on life style	
MenACWY and MenB	1 or 2 doses (revaccinate with 1 MenACWY dose every 5 years if the risk remains) in adults with risk of severe diseases or increased risk of exposure (i.e., travelers, microbiology laboratory personnel, closed communities)	
Yellow fever	1 dose in travelers or those who live in risk areas	Assess risk/benefit (≥ 60 years)
Argentinean Hemorragic Fever	1 dose for those aged 15 to 65 years who live in risk areas	
Herpes zoster	No available for ≤ 50 years	1 dose (live zoster vaccine) 2 doses (recombinant zoster vaccine). Both in ≥ 50 years
MMR	1 or 2 doses	Those adults born before 1965 are considered immune (this varies based on country of origin)
Varicella	2 doses in susceptible young adults, particularly non-pregnant women in childbearing age, health care workers, individuals under high risk of exposure and within 72 h after contact with a varicella patient	Those adults ≥ 50 years are considered immune
Typhoid fever	1 dose if there is risk of exposure (revaccinate every 3 years if the risk remains)	
Haemophilus influenzae type B	1 dose (anatomic of functional asplenia), 3 doses after HSCT	

PPSV23: 23-valente polysaccaride pneumococcal vaccine; PCV13: 13-serotype pneumococcal conjugate vaccine; HPV: human papillomavirus vaccine; MenACWY: meningococcal group

Herpes zoster

Herpes zoster vaccine prevents a disease with an almost exclusive presentation in adults, particularly in the 5th and 6th decade of life, producing very frequently post herpetic neuralgia not easy to handle and with high impact on quality of life. The first vaccine was composed of live attenuated virus, with the same strain as varicella, but in higher concentration. This is administered in one only subcutaneous dose in adults over 50, with a demonstrated efficacy of 51.3% to prevent occurrence of herpes zoster and of 66.5% to prevent post-herpetic neuralgia. More recently, the vaccine with recombinant viral subunits (HZ/su) using glycoprotein E and adjuvant AS01B, to be administered in two intramuscular doses in space of 2 months, has demonstrated an over 90% efficacy to prevent herpes zoster and over 88% to prevent post-herpetic neuralgia[43].

Other vaccines for adults to be considered, include yellow fever[44], hepatitis B and A[45], measles/rubella/mumps (triple viral), Argentinian hemorrhagic fever[46], meningitis due to meningococci[47], typhoid fever[48], Japan encephalitis, and tick born encephalitis[49].

Conclusions

Starting with a WHO initiative, the use of "Vaccination though the life course" has expanded the use of vaccines from the beginning to the end of life. This strategy allows to expand the vision of vaccination and to include the adults as an integral part of vaccinations plans and programs and into immunization calendars. There are still many challenges to overcome in order to fully include adults and to be able to make vaccination a highly valued prevention tool to achieve a healthy life. Among these challenges are: insufficient information and medical knowledge on prevention through immunization, the huge amount of preventive recommendations that leave vaccines out, the lack of acknowledgement of adults on this matter, the fear of adverse reactions, myths against vaccines and uncertainty about their real efficacy, barriers to access since most of vaccination services and centers are only prepared for pediatric care, lack of opportunities for vaccination in the health systems and in the resource allocation. These are some of the obstacles to overcome. Well vaccinated adults protect children, protect other adults and older adults and very importantly, are an example influencing the society, demonstrating they trust, appreciate and demand vaccines on time and schedule.

Conflict of interest: None to declare

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Así nace el círculo vicioso. Si se oye repetir muchas veces que se es un sabio, cualquiera que no tenga una buena autocrítica, termina creyéndoselo. Después son los discípulos que llegados con pocos conocimientos científicos ratifican el concepto de "maestro" y cuando en el transcurso de los años entrevén un poco la falacia del juicio, los intereses creados y un poco de self-defense *contribuyen a que ellos sigan engrosando el coro de alabanzas. De ahí a afirmar que estamos en el mejor de los ambientes científicos, no hay más que un paso. Después llegan las apoteosis.*

Alfredo Lanari (1910-1985)

De los homenajes (1940). El Día Médico Vol. XII, No. 38, 1940. En: Vocación y convicción. Fundación Alfredo Lanari; Buenos Aires, 1995, p 23