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Report on WHO meeting on immunization in older adults: Geneva, Switzerland, 22–23 March 2017

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12. Gregory A. Poland: Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on vaccine development to Merck & Co. Inc., Avianax, Dynavax, Novartis Vaccines and Therapeutics, Seqirus, and Adjuvance Technologies. Dr. Poland holds three patents related to vaccinia and measles peptide vaccine research. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

Abstract

Many industrialized countries have implemented routine immunization policies for older adults, but similar strategies have not been widely implemented in low- and middle-income countries (LMICs). In March 2017, the World Health Organization (WHO) convened a meeting to identify policies and activities to promote access to vaccination of older adults, specifically in LMICs. Participants included academic and industry researchers, funders, civil society organizations, implementers of global health interventions, and stakeholders from developing countries with adult immunization needs. These experts reviewed vaccine performance in older adults, the anticipated impact of adult vaccination programs, and the challenges and opportunities of building or strengthening an adult and older adult immunization platforms. Key conclusions of the meeting were that there is a need for discussion of new opportunities for vaccination of all adults as well as for vaccination of older adults, as reflected in the recent shift by WHO to a life-course approach to immunization; that immunization in adults should be viewed in the context of a much broader model based on an individual's abilities rather than chronological age; and that immunization beyond infancy is a global priority that can be successfully integrated with other interventions to promote healthy ageing. As WHO is looking ahead to a global Decade of Healthy Ageing starting in 2020, it will seek to define a roadmap for interdisciplinary collaborations to integrate immunization with improving access to preventive and other healthcare interventions for adults worldwide.

Keywords

Immunization; Global health; Ageing; Immune senescence; World Health Organization; Vaccine development

1. Introduction

Vaccination of older adults has been shown to reduce transmission and serious disease caused by vaccine-preventable diseases mainly in high income countries (HIC), but the policy of vaccinating this age group has not been widely implemented in LMICs. The World Health Organization (WHO) convened a meeting in March 2017 to review policies on immunization of adults (with a focus on older adults), to discuss vaccine performance in this group and to review the pipeline of vaccines under development that might be of benefit to adults and older adults in the future. While the meeting was relevant to HICs as well as LMICs, the focus was intentionally on the latter. The only vaccines with WHO recommendations for specific use in elderly adults are influenza vaccines [1], therefore influenza and influenza prevention represented an important case study and area of discussion in the meeting for vaccine policy and implementation needs globally. Finally, the meeting aimed to discuss the challenges and opportunities for strengthening adult immunization in LMICs and to identify activities and policies that can be pursued to this end.

This was the first WHO meeting on older adult immunization since 2011 [2]. The objectives of the meeting were the following: (1) to review policies on immunization of adults, with a focus on older adults; (2) to discuss the incidence and determinants of vaccine preventable

diseases in adults; (3) to discuss vaccine performance in older adults and the pipeline of vaccines under development that may be of benefit to adults and older adults; (4) to discuss challenges and opportunities for strengthening an adult immunization platform in low- and middle-income countries; and (5) to identify policies that could be developed and activities that can be pursued to promote access to vaccination for older adults in LMICs. Participants included academic and industry researchers, funders, civil society organizations, implementers of global health interventions, and stakeholders from developing countries with adult immunization needs. The agenda and list of participants are in the Online Supplement. The two-day meeting was organized around a series of background topic areas, followed by case studies in LMICs, and then discussion on data needs for policies and investments of vaccine programs targeting older adults. This report is based on presentations and discussion from the meeting.

2. Ageing and vaccination

2.1. Changing demographics and markets for vaccines

The world population is ageing. The number of individuals aged 60 and older is predicted to increase from 600 million to 2 billion from 2000 to 2050, with 80% of older adults living in developing regions [3], with a preponderance of women [4]. As people age, they develop increased susceptibility to many infectious diseases. As part of a broad public heath strategy the number of vaccine doses needed to target older adults is anticipated to outpace those needed by routine pediatric immunization programs.

Some countries are developing plans for this demographic change, but many countries do not have vaccination policies specifically targeting adult populations. Even in HICs, vaccination use in adults can be low [5]; for example, despite a WHO recommendation, only 45% of 115 member states with an influenza policy include programs targeting the “elderly” risk group, and most of these are HICs [6].

For the purposes of this report, older adults are defined as people in the second half of their life, i.e. over half of the life expectancy for a particular country. While examples and discussion specific to older adults are provided in this report, sometimes when the data specific to older adults are sparse or when discussion of a broader age group is warranted, the report refers to all adults.

2.2. WHO vaccine recommendations and age

Current WHO guidance on routine vaccines, summarized in WHO vaccine position papers [7], focuses heavily on pediatric immunization. There is some consideration of immunization in pregnancy, immunization in health-care workers, high-risk occupations, notes on travel vaccines or regional use, but few recommendations for vaccination to protect adults in general against infectious diseases, with the exception of a permissive recommendation for influenza vaccine use in elderly persons and persons with chronic disease. The older target group is not defined by WHO, and countries have implemented “elderly” influenza vaccine programs beginning at a variety of ages (including 50, 60, and 65 years).

WHO has a mandate within the Global Vaccine Action Plan 2011–2020 to "improve health by extending by 2020 and beyond the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live" [8]. Furthermore, the WHO Initiative for Vaccine Research (IVR) has long been interested in immunization of older adults, and has held and contributed to relevant meetings on the topic over the past decade [2], which have influenced the research agenda worldwide. Of the major data gaps previously identified, most still remain [2]. These include disease burden data for many vaccine preventable diseases in older adults, duration of protection of routine childhood vaccines among older adults, performance of new vaccines targeting older adults within LMIC contexts, and how to identify the optimal time for immunization of older adults to ensure sufficient immunologic response and memory.

One goal in the WHO's Global Strategy and Action Plan on Ageing and Health [9] is to design interventions to prevent disease and to influence trajectories of individuals' intrinsic capacity (defined as a combination of one's physical and mental capacities). One of the important activities to promote healthy ageing is to "*ensure access and affordability of medical products, vaccines, and technologies*" as part of integrated care for people in the second half of life [10].

2.3. Definitions: at what age are people considered old?

Healthy ageing is defined by the WHO as "*the process of developing and maintaining the functional ability that enables wellbeing in older age*" [11]. This ability depends on both an individual's physical and mental capacities and on the environments one inhabits (for example access to transport and assistive devices) [10]. As described in the WHO's World Report on Ageing and Health [11], while intrinsic capacity tends to decline with increasing age, a primary characteristic of older ages is great diversity. Even in the poorest settings, an eighty year old may be healthy, independent, and vibrant, while a sixty year old may need significant care and support. Chronological age is thus a poor marker of health state, and there is no fixed age when someone becomes "old". Furthermore, this diversity is often a consequence of the cumulative impacts of advantage or disadvantage across a person's life. This means that those with the greatest health needs in older age may have the least access to the specific required resources.

In any population in the second half of life, three groups can be proposed: those with high and stable capacity; those with decreasing capacity; and those with substantial loss of capacity [10], although individuals can transition between these states. Rather than defining target groups for vaccination solely by their chronological age, assessing an individual's level of capacity may add important information on their need for vaccination, response to vaccination, or the functional benefits likely to arise. For example, where a vaccine is currently recommended for those above 65 years [12], some individuals may benefit from vaccination at an earlier age because of declining capacity. While implementing this approach would require development and adoption of simple and robust measures of capacity in a clinical setting, discussions of this topic may be beneficial in order to better understand optimal target groups for vaccination.

3. Reasons for vaccination of adults and older adults

Discussion in the meeting highlighted many reasons and benefits for vaccinating older adults and, indeed, any age group after infancy (see Table 1).

3.1. Examples of benefits of vaccinating older adults

Respiratory pathogens, such as *Haemophilus influenzae* type b (Hib), influenza virus, respiratory syncytial virus (RSV) [13] and *Streptococcus pneumoniae* [14–16] are key targets for vaccine development and implementation in older adults in HICs, and vaccination of adults or older adults should have an impact on the burden of these diseases in LMICs.

When studied from 2005 to 2008, influenza activity in Thailand correlated with hospital admissions and deaths in older adults. This finding led to a policy of administering domestically-manufactured influenza vaccines to high-risk older adults [17,18]. Similar studies have been conducted in Central America [19], Ghana [20], and India [21], demonstrating the burden of disease in older adults and the unrealized potential impact of vaccine programs targeting them. There are more limited data on other respiratory infections in older adults; for example, two Thai studies [16,22] found many hospitalized *Streptococcus pneumoniae* cases were in older adults and authors called for cost effectiveness data to inform future vaccine use.

In some cases, childhood vaccination can affect disease in older adults due to population (herd) immunity, providing sufficient vaccine effectiveness (VE) and coverage can be achieved. This has been observed with influenza vaccination in Japan [23] and the United States [24]. In some settings, it has been suggested that a highly effective infant influenza vaccination program might make vaccinating older adults unnecessary [25], but further data are necessary. Another vaccine example is the a substantial positive impact of pneumococcal vaccination of infants and children on mortality and morbidity of seniors which was observed in the United States [26].

Another benefit of vaccinating people of all ages is an indirect effect on the ability of microbes to resist the effects of drugs, or anti-microbial resistance (AMR). The Global Action Plan on AMR [27] states that immunization could reduce AMR in three ways: first, by using existing vaccines to prevent infectious diseases whose treatment would require antimicrobials; second, by using existing vaccines to reduce the prevalence of primary viral infections which are often inappropriately treated with antibiotics or that can lead to secondary infections that require antibiotic treatment [28]; and, third, by the development and use of new vaccines targeting pathogens difficult to treat (or untreatable) due to AMR. In addition, vaccination might selectively target resistant strains of an organism, reduce the opportunity for pathogens to exchange resistance genes, or reduce bystander selection of resistance in normal flora species [29].

Several studies illustrate how existing vaccines can reduce infections in vaccinees of all ages [30] and through population (herd) immunity [31], but very few studies have been conducted to measure vaccine effectiveness at preventing anti-microbial use or AMR. As secondary outcomes of pneumococcal conjugate vaccine (PCV) use, some studies in infants in HICs

have shown a reduction in antibiotic prescription [32], a reduction in antimicrobial purchases [33], or reduced duration of antibiotic use [34]. Modeling studies have concluded that high coverage with PCV in 75 countries not currently achieving 80% coverage could avert many millions of days of antibiotic use in young children [35].

Low-income countries (LICs) are at highest risk of AMR [36], so vaccine use in those countries could potentially yield the greatest benefits. There is, however, a significant lack of data on the impact of vaccines on AMR in LICs, especially in older adults.

3.2. Health economics of vaccination of adults and older adults

Health economic evaluations such as cost-effectiveness analysis are important tools for investigating whether the social and economic benefits of an intervention such as vaccination outweigh the opportunity costs of the intervention. However, evaluations of vaccination of adults and older adults in LMICs are severely lacking compared to similar evaluations of pediatric vaccination. For example, two reviews of cost-effectiveness studies of seasonal influenza vaccination found only five studies for older adults in LMICs [37,38].

Many economic evaluations do not capture some of the broader economic benefits of vaccination at the individual, household and society level that are particularly relevant to adult vaccination. For example, evaluations of the indirect benefits of vaccination should consider the roles older adults play in the volunteer sector and as caregivers in families and communities, looking after infants and children as part of the “informal economy” [39]. These aspects may be particularly valuable in LMICs [40]. In addition, traditional measures of health utility such as quality- or disability-adjusted life years may not capture what older adults value most about good health and maintenance of functional ability. Alternative measures of health utility for older adults have been proposed, including independence, and ability to do the things that they value [41].

The impact of population (herd) immunity adds a further level of complexity to economic evaluations. In some settings, it might be more cost-effective to protect older adults from an infection by vaccinating infants to eliminate the infant reservoir of the pathogen. Consensus guidelines for methodological approaches to estimating direct and indirect costs of vaccine-preventable diseases in LMICs are required, and are being developed by WHO for influenza [42]. Similar guidance would be of value for other vaccine preventable diseases that disproportionately affect older adults.

4. Protection of older adults

4.1. Vaccine performance in older adults

Vaccine performance can be measured by vaccine immunogenicity, efficacy, or effectiveness. Vaccines can be less immunogenic in older adults due to immunosenescence (see Section 4.2). Concomitant anti-inflammatory and immunomodulatory therapies are more likely to have significant negative interactions with vaccines in older adults [43]. Immune responses (and adverse reactions) to vaccines tend to be higher in females than males, and loss of function with age might be more frequent or of greater magnitude in males [4]. At all ages, vaccine effectiveness tends to be higher in women than in men [4].

Often vaccines have a lower vaccine effectiveness in older adults compared to younger adults, and several approaches have been used to overcome this: (a) increasing the number of doses administered, (b) increasing the dose of antigen in the formulation, and (c) incorporating adjuvants, such as MF59 in the Fluad® seasonal influenza vaccine [44]. It has been proposed that early-season use of influenza vaccines might result in antibodies that wane by the start of a late-season virus circulation [45] so the timing of vaccination could also be important.

The performance of seasonal influenza vaccines in older adults has been reviewed in several meta-analyses [46,47], and vaccine effectiveness has been observed to be suboptimal compared to other age groups. However, recent systematic reviews of the use of adjuvanted influenza vaccine formulations [44] and intradermal administration [47] have shown improved immunogenicity of seasonal influenza vaccines in the elderly. These studies have been conducted in HICs and less data are available on influenza vaccine use in adults in LMICs [48]. PCV and pneumococcal polysaccharide vaccine (PPV) effectiveness have also been reviewed; PPV effectiveness was found to be 50% [30] and PCV effectiveness was 48.5% in preventing invasive pneumococcal disease in healthy adults aged 65 years and over [49].

Analyses have shown that the high-dose influenza vaccine in older adults (Fluzone®, Sanofi Pasteur) performs better in older adults than the standard influenza vaccines [50]. It has a higher VE, and induces higher antibody responses in adults aged more than 65 years compared with the standard formulation (60 μg HA vs 15 μg HA per dose). A supplementary analysis showed the high-dose vaccine was better at preventing serious cardio-respiratory events and pneumonia than the standard vaccine [51], and a retrospective cohort study in the United States found the vaccine to be more effective than the standard dose vaccine in preventing influenza-related medical encounters, hospital admissions, and death in adults 65 years of age and older [52–54].

4.2. Immunosenescence and biomarkers

Studies of immunosenescence in preclinical models and humans have identified many aspects of adaptive and innate immune responses that decline or change with age [55]. Biomarkers for these changes have the potential to inform more rapid vaccine development for older adults. The number of naïve T lymphocytes declines with age, following involution of the thymus after puberty, compromising the ability to respond to new vaccinations (or infections). It has also been suggested that the expanded T cell responses required to keep persistent infections controlled, such as Epstein Barr virus and human cytomegalovirus (HCMV), reduces “space” for new T cells, particularly CD8+ T cells [55]; however, the effect of HCMV infection on immune function, including the response to influenza vaccine, appears to be heterogeneous, and is seen only in older individuals who might have had persistent HCMV infection for decades [56]. Recently, older adults were shown to have increased senescent and exhausted varicella zoster virus (VZV)-specific T cells which may contribute to their inability to prevent VZV reactivation and the subsequent development of herpes zoster [57].

The number and function of B lymphocytes also decreases with age, with an increase in the number of late/exhausted B cells that are terminally differentiated, non-proliferating and with poor effector function [58,59]. Many immune cell types express a senescence-associated secretory phenotype, defined as the secretion of several pro-inflammatory cytokines including tumor necrosis factor alpha, interleukin 6 and interleukin 8 [55,58], which promotes chronic low-grade inflammation. Numbers of dendritic cells (DCs) and Langerhans cells decline [60], and DCs exhibit reduced phagocytosis and class 1 human leucocyte antigen expression [55].

These changes in immune function have been shown to impair primary responses to yellow fever (YF) vaccine in travelers, even though protective levels were still achieved [60]. Memory immune responses, such as to seasonal influenza vaccine, have also been shown to be affected [58].

Despite immunosenescence, it is still possible to induce immune responses in older adults that are protective or equivalent to those seen in younger age groups; examples include: (a) phase III trials of the two-dose HZ/Su subunit vaccine branded as “Shingrix” against herpes zoster that showed similar vaccine efficacy in ages 50 years and older [61] and 70 years and older (~90%) [62]; (b) phase I/II trial of a candidate *Staphylococcus aureus* single dose, non-adjuvanted, inactivated vaccine in healthy adults aged 65 –85 years showed that functional antibody responses which met pre-defined thresholds in the older adults [63]; and (c) two trials with different *Clostridium difficile* vaccines that showed similar responses across different age groups [64,65].

Identification of biomarkers of immunosenescence might inform rational design of vaccines, for example those that include novel adjuvants, to enhance immune responses in older adults, or could be used to identify individuals who are unlikely to respond to a given vaccine. Systems approaches in biology research are being used to identify such markers [66]. Data obtained to date suggest that the changes observed in immunosenescence are also found in many fundamental biological pathways such as cell proliferation and hormone regulation as well as lymphocyte activation and differentiation [66].

Although most of the data on ageing and immunosenescence have been collected in HICs, a pilot study conducted in Pakistan found similar changes in immune cell phenotypes in young (aged 18–28 years) and older (aged 50–85 years) men, to those seen in HICs [67].

5. Vaccines that are or could be of benefit to older adults

Multiple licensed vaccines are currently used in adults, although they remain underused in the general adult population and in some target groups. In addition, there are new vaccines for adults in the development pipelines of many vaccine manufacturers (Table 2).

Some of the vaccines in Table 2 are of interest for people of any age with low intrinsic capacity, such as *Staphylococcus aureus* [68]; extraintestinal pathogenic *Escherichia coli*, because of its role in urinary tract infections [69]; and *C. difficile*, because of its high morbidity and mortality, especially in older adults. These three pathogens are also important targets from the perspective of reducing AMR.

6. Considerations for vaccination of adults and older adults in LMICs

As stated above, much of the data on the need for, and use of, vaccines for adults comes from studies in HICs. There are, however, important differences between HIC and LMICs that need to be taken into consideration, including specifics related to adult immunization in terms of disease epidemiology, health infrastructure, opportunities for life-course immunization, and policymaking in this age group.

6.1. Disease epidemiology and comorbidities

The epidemiology and timing of infectious diseases can be very different in LMICs, based on factors such as differential exposure due to climate, geography and hygiene and an earlier risk of exposure to a diverse and larger number of pathogens. In addition, co-infections such as tuberculosis or human immunodeficiency virus (HIV) can affect the risk of severe outcomes from vaccine preventable diseases as well as the immune response to vaccines [70]. Immune responsiveness can also be affected by differences in nutrition, such as vitamin A deficiency [71], and obesity [72]. There is also evidence, albeit in infants, that diet, exposure to microorganisms and parasites, and anti-microbial (and anti-helminthic) use can affect the immune system [73]. In general, there may be a myriad of environmental conditions that result in a different picture of co-morbidities of infectious diseases and other non-communicable diseases (NCDs) and conditions in LMICs compared with HICs. Reduced access to healthcare and social services in LMICs can also affect an individual's functional capacity at any age, and can limit access to vaccination.

6.2. Health infrastructure for adult vaccination

The implementation in 1974 of the Expanded Programme on Immunization (EPI) has meant that routine immunization infrastructure has focused on neonates, infants (e.g. immunization visits at ages 6, 10 and 14 weeks, and 9 months) and pregnant women. Achieving high vaccination coverage in target groups outside the traditional program can be difficult. Countries considering strengthening immunization platforms for older adults would benefit from strategies and lessons learned from similar efforts in other age groups [74]. Currently, more than 80 countries have introduced human papillomavirus (HPV) vaccine into their national immunization programs, usually with school-based vaccination; 33 of these are LMICs, and an additional 25 LMICs are undertaking pilot programs prior to full scale introduction [75]. Lessons learned from HPV programs [76], including the usefulness of pilots or demonstration projects [77], could be valuable for establishing new platforms for adult vaccines, especially ones where multi-dose regimens are required [78]. For example, adults taking infants to a pediatric vaccination clinic could also be offered immunizations or other services.

6.3. Opportunities within life-course immunization in LMICs

A major barrier in many LMICs is that there is often not a comprehensive health system to reach all adults, including older adults, for preventive healthcare. If one could be established, it could have many benefits for all kinds of health interventions, including screening, diagnostics and treatments.

There is interest within the vaccine community, and those whose primary focus is the health of older adults in general, on new opportunities to build preventive and other healthcare services around or including immunization. Life-course immunization may include the following healthcare points and systems: well-baby, school-entry, school-leaving, general practice, community pharmacies [79], community nurses, adolescent health, universities and colleges, ante-natal care, outpatient clinics for the chronically sick, nursing homes, military services, services for new migrants, and travel vaccination clinics.

Many healthcare systems may benefit from increasing attention on disease prevention, particularly in LMICs. Increasingly, there is anticipated to be a shift to self-management of and prevention of medical conditions, with individuals taking more responsibility for their health, which could include demanding vaccines for themselves or their parents or other family members.

6.4. Mandates and policymaking

Although adults and older adults are not often explicitly identified as target groups for vaccination, they are included in global strategies and policies. The stated vision of the Decade of Vaccines (2011–2020) is for "*a world in which all individuals and communities enjoy lives free from vaccine-preventable disease*" [8]. In addition, Goal 3 of the United Nations Sustainable Development Goals [80] is to "*ensure healthy lives and promote well-being for all* ***at all ages***", and includes a target of "*access to safe, effective, quality and affordable essential medicines and vaccines for all*".

Despite broad, bold policy statements, however, there is often delayed uptake of new vaccines for some target groups and ages for a variety of reasons [81], some of which are especially applicable to adult vaccination. For example, successful introduction of any new vaccine requires engagement and alignment of multiple stakeholders. Governments must see the value in a new vaccine before they are willing to introduce it and this requires recognition of the burden of disease and the fact that an affordable, deliverable vaccine is available. Purchasers (donors, governments or private health providers) are unlikely to pay for the vaccine unless they think it will be seen as a priority by end users, and vaccine developers and manufacturers will not produce the vaccine unless they believe it will be purchased. Other reasons relate to the general lack of awareness by adults that vaccine-preventable diseases such as pneumococcal pneumonia, influenza and shingles can have devastating effects on the health, function and socioeconomic contributions of a normal healthy older person, let alone those who may have a chronic condition such as diabetes.

To promote influenza vaccination of older adults, for example, it might be important to recognize that seasonal influenza infections do not just result in a short-term increase in accelerated mortality, but also result in low-quality of life and morbidity that can extend for several months after the influenza season [82]. The costs of the social and economic burden need to be quantified for the stakeholders in question. In some situations, to stimulate uptake of vaccines for an ageing population, it might be preferable to re-frame the narrative to one that reflects the contributions that older adults across society make with advancing age in good health or simply their higher quality of life.

7. Barriers to adult vaccination

Adult vaccine coverage is low, even in HICs, for a variety of reasons [83]. Perceived and actual barriers can be categorized at the level of the individual and community demand for vaccines, or with the vaccination process and system (Table 3). This list of barriers has been modified from a prior publication [79], with additional information based on presentations and discussion at the meeting. Some of the barriers apply to vaccination of all age groups; others are specific or more relevant to vaccination of adults.

Despite the barriers to vaccination after infancy, some which are listed in Table 3, many countries are gaining experiences that should be useful in the future and to other countries [84]. The International Federation on Ageing's World Coalition on Adult Vaccination [85] is one of several global and regional projects aiming to help improve uptake rates of adult vaccination through building an understanding of the community and systemic barriers and then working across sectors and disciplines to create solutions.

8. Gaps in knowledge

One of the objectives of the meeting was to identify challenges and opportunities for strengthening adult immunization in LMICs. Significant gaps in knowledge regarding vaccination of adults and older adults, particularly in LMICs, were identified (Table 4). Most of the existing data that are available come from HICs, or a limited number of MICs (Brazil, China, India, Mexico, Thailand). Some MICs have parts of their population with some characteristics of HIC and other parts that are under-developed. They could represent good settings to compare interventions in different subpopulations of the same country exposed to different conditions.

9. Conclusions

There are global mandates to expand and strengthen immunization in older adults, however critical data to inform policy making and public health practice in LMICs remain limited. More data are needed on vaccine-preventable disease burden in older adults in LMICs and the estimated impact vaccines would have on this burden. Further, new ways to look at impact of vaccine programs, that take into account the contributions of healthy older adults and the consequences of their declining intrinsic capacities to society, are needed. Two clear conclusions from the meeting were that immunization of adults should be viewed as a key component of a comprehensive approach to health, and that protecting older adults from vaccine-preventable diseases might mean achieving high vaccine coverage in all age groups (including infants), and not simply older adults. Additionally, the need for vaccine research and development related to immunosenescence was identified, given the remarkable increase in the population of older adults.

To achieve significant increases in adult vaccination coverage, the knowledge gaps listed in Table 4 should be addressed. Equally important will be the need for a shift in overall thinking about providing protection against vaccine-preventable diseases, which has to date focused nearly exclusively on vaccination of infants [86]. Activities to improve coverage with infant vaccines should not diminish, but an increasing emphasis needs to be placed on

life-course approach to immunization schedules to protect adults and older adults, especially given the significant and changing demographics of the global population. There is already some evidence from HICs of the benefits of using existing vaccines in older adults [49,82]. Although the efficacy of some vaccines might be lower in older adults than is usually seen with infant vaccines, these data need to be viewed in the context of the increased risks from disease and broader social and economic benefits of prevention in older populations. Misconceptions about the benefits of vaccination of older adults should not prevent its use.

Decreasing adult preventable disease through improved uptake of appropriate vaccines will require strong champions, both individual and institutional [87], at a time when there are many competing priorities for health spending. Obtaining data is critical to gaining a deeper understanding of the impact of adult vaccination on problems such as AMR, as well as the growing need to guard against preventable illnesses in an ageing global population with co-morbidities and concomitant conditions. The “business case,” that is, the direct and indirect associated health-care and broader societal costs and benefits, is critical to justify a life-course approach to vaccination. Raising awareness of the importance of vaccination of adults and older adults is just the beginning of truly cementing the intervention within a broader public health strategy.

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Abbreviations

AMR	anti-microbial resistance
DC	dendritic cell
EPI	Expanded Program on Immunization
HAV	hepatitis A virus
HBV	hepatitis B virus
HCMV	human cytomegalovirus
Hib	*Haemophilus influenzae* type b
HICs	high income countries
HIV	human immunodeficiency virus
HPV	human papillomavirus

LMICs	low- and middle-income countries
MICs	middle-income countries
MMR	measles, mumps and rubella vaccine
Mtb	mycobacterium tuberculosis
NCDs	non-communicable diseases
NITAG	national immunization technical advisory group
PCV	pneumococcal conjugate vaccine
PPV	pneumococcal polysaccharide vaccine
RSV	respiratory syncytial virus
VZV	varicella zoster virus
WHO	World Health Organization

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Table 1

Reasons for vaccinating after infancy.

Reason	Notes and examples
Improving population (herd) immunity and disease control	
Catch-up - coverage with the complete schedule of infant vaccines is not 100%, leaving some of the population unprotected	Global burden of disease data for tetanus mortality, showing that most cases are in LMICs and deaths are at all ages [88]
The vaccine(s) in question might not have been in use while the adult population were infants	Applies to recent vaccine introductions, such as measles, mumps and rubella (MMR), hepatitis B virus, varicella zoster virus, and pneumococcal conjugate vaccine
Protection against pathogens with changing strains or serotype prevalence that might differ in different age groups	Examples include: influenza and *Streptococcus pneumoniae* (pneumococcus)
Protecting at-risk populations after childhood	
Protection against occupation-associated exposure to specific pathogens	Especially healthcare workers, food handlers, laboratory workers, but also those with close contact with animals
Prevention of infections in hospitalized patients	Examples include: Methicillin-resistant *Staphylococcus aureus*; *C. difficile*; norovirus
Respiratory diseases can have serious impacts in adults/ older adults. Higher rates of morbidity or mortality with older onset of other infections	There is a link between seasonal influenza and functional decline in activities of daily living in people living in nursing homes in the USA, [89]. Varicella case fatality rate in older adults is 25–174-fold higher, compared with children [55]
Risk of infection increases, or has higher morbidity, with chronic conditions	An example includes, Hepatitis B and diabetes due to cross-infection in healthcare settings [90]
Protection through the life-course	
Vaccination of women before or during pregnancy to protect themselves and their infants	Examples include: diphtheria, influenza, pertussis, polio, MMR, varicella, tetanus [91]
Vaccination to prevent unnecessary antibiotic use given the growing concerns about antimicrobial resistance	The following pathogens have developed significant drug-resistance: *Acinetobacter baumannii*, candida sp., *C. difficile*, diphtheria, *Enterobacter* sp., *Enterococcus faecium*, *Escherichia coli*, gonococcus, *Haemophilus influenzae* type B, HIV, *Klebsiella pneumoniae*, malaria, meningococcus, *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, typhoidal and non-typhoidal *Salmonella*, *Shigella* sp., *Staphylococcus aureus*, tetanus
Vaccination of travelers	Examples include: hepatitis A virus, polio, typhoid, yellow fever, and others
Prevention of chronic and latent infections	Examples include: *Mycobacterium tuberculosis*, herpes simplex virus, varicella zoster virus, hepatitis B virus [92]
Secondary prevention of non-communicable diseases (NCDs)	Some infections are being linked to causality of NCDs. Influenza vaccination could reduce cardiovascular events in at-risk people, including the middle aged [93,94]. Influenza vaccine reduced major cause-specific mortality (stroke, renal disease, diabetes, pneumonia, chronic-obstructive pulmonary disease, malignancy and heart disease) in Taiwanese older adults [95]
Deterioration of the immune system with age could compromise the homeostatic equilibrium between microbiota and host	Reduced bacterial diversity in the gastrointestinal tract is correlated with *C. difficile*-associated diarrhea [55]
Vaccines needed for protection against emerging diseases, outbreaks and pandemics	Examples include chikungunya, cholera, Ebola, Middle East respiratory syndrome, severe acute respiratory syndrome, pandemic influenza, tick-borne encephalitis and Zika

Note: Gathered from presentations and discussion at the WHO meeting.

Table 2

Examples of licensed vaccines, or vaccines in development, for use in adults– by stage of development, as of 2017.

Stage	Vaccines
Preclinical	**Influenza, Respiratory syncytial virus**
Phase I	***Clostridium difficile***, **HIV, Respiratory syncytial virus**
Phase II	Ebola, **Enterotoxigenic *Escherichia coli***, Extra-intestinal pathogenic Escherichia coli, **HIV, Norovirus**, **Respiratory syncytial virus**, ***Staphylococcus aureus***, *Streptococcus pneumoniae* (pneumococcus),
Phase III	***Clostridium difficile***, Varicella zoster virus
Licensed	Diphtheria tetanus pertussis, Hepatitis A virus, Hepatitis B virus, influenza, meningococcal meningitis, pneumococcus, Varicella zoster virus, *Haemophilus influenzae* type b
Not publicly known	**Group B streptococcus**, **Zika virus**

Notes: Vaccines exclusively for maternal immunization to protect newborns and cancer immunotherapies have not been included. Vaccines for pathogens in bold were discussed at the WHO Product Development for Vaccines Advisory Committee 2016 meeting; references are on the meeting website [96] See also the WHO Vaccine Pipeline Tracker [97] for references for dengue, Ebola, enteric diseases, HIV, malaria, *Mycobacterium tuberculosis*, Respiratory syncytial virus, Zika virus and other priority emerging pathogen and WHO information on vaccines and diseases for landscape analyses [98].

Table 3

Barriers to vaccination – including barriers specific to adult vaccination, WHO meeting on immunization in older adults, March 2017.

Category	Barrier	Response
Evidence for action	Lack of burden of disease and economic data and/or policy recommendations; weak value proposition	Generate burden of disease data, evidence of VE; strong statement(s) from trusted source (e.g. WHO); promote evidence to national immunization technical advisory groups (NITAGs) and medical associations
Individual factors and information	Vaccine hesitancy or lack of awareness and action due to insufficient information, knowledge, skill, or time; or too-complex information	Improve communication methods, inform and motivate communities. Increase access to vaccine information, preferably with tailored information
Vaccination process	Adult vaccine schedules (or information) can be highly complex. Pathways to access vaccination can be complex, vaccinees might need to make several visits to get prescription, supplies and then vaccination itself. Infant programs are often prioritized by communities and governments	Simplify schedules or explain better. Integrate vaccination history with electronic medical records. Simplify and bring services closer to where adults live, work, study or currently seek medical care (e.g. ante-natal clinics). Self-administration of vaccines could overcome some immunization logistics obstacles
Vaccination system	Limitations in vaccination infrastructure are widespread and include: • Lack of advice for National Immunization Technical Advisory Groups from experts in adult vaccination • Lack of public sector support for adult vaccines and limited promotion of adult vaccination • Limited resources to purchase and deliver adult vaccines. In many countries adults ‘‘self-pay” for vaccines. • Few providers stocking adult vaccines, e.g. for fear of wastage [99]. • Low healthcare practitioner awareness and leadership, in part due to lack of training. • Territorial limitations. In some settings, only some healthcare professions can vaccinate. • Financial constraints and/or inconsistent reimbursement schemes	Improve vaccination infrastructure, as was done in Nigeria [100]. Obtain political commitment for vaccination. Implement fair reimbursement systems. Establish vaccination advocates and champions. Change in the focus of healthcare, in general, to reflect ageing populations. Promote benefits to funders so no economic barriers to end-user. Programs must be fully funded, to cover all doses in schedule. Change workflows to incorporate adult vaccination; establish new infrastructure for accessing vaccines, including out-of-school. Education and training of healthcare workers and encouragement to be fully vaccinated themselves; promote adult vaccination as a professional norm
Community perception	In some settings, society places a lower value on the health of older people than that of children [101,102]	Promote change in societal values to recognize intergenerational connections

Notes. The list is modified from [79]. The focus on barriers and responses for adult vaccination was gathered from presentations and discussion at the meeting.

Table 4

Gaps in knowledge supporting decision-making for adult and older adult immunization in developing countries.

Gap in Knowledge	Comments
Burden of disease	
What is the true burden of disease for infections that might be preventable in adults and older adults, especially in low- and middle-income countries (LMICs)?	Encourage gathering and sharing of data on broad measures of health (not just deaths due to disease); consider exacerbation of co-morbidities such as cardiovascular disease and chronic obstructive pulmonary disease
What are the broader impacts of vaccine-preventable diseases in older adults?	Large, long-term cohort studies are required to evaluate the impact of vaccine preventable diseases (and of vaccination) on frailty and relevant measures of quality of life, health care expenditure and wider social costs
Benefits of immunization for adults and older adults	
Are there associations or causal links between infectious disease and non-communicable diseases (NCDs), and what is the impact of vaccination including in older adults?	NCD endpoints (including frailty) could be incorporated in vaccine trials, using measures appropriate for LMICs. Observational studies could also be informative
What are the broader economic benefits of vaccination in older adults?	As well as standard measures, there is a need to determine how to measure the economic value of adults at different ages, including in informal economy (e.g. as caregivers).
	It is important to assess indirect economic value by preventing disease and disability, as well as by preventing exacerbation of existing co-morbidities. Patient and household surveys can help to identity the socioeconomic contribution of older adults
What data are available the impact of adult vaccines on anti-microbial use in LMICs?	With sufficient baseline data, reduction in antibiotic use could be used as an endpoint in clinical studies of vaccines
Immune responses in adults and older adults	
How does immune function change with ageing? Is the process of immunological ageing the same in HICs and LMICs?	Systems approaches could be applied to studying the biology of immunosenescence [103]
What are the impacts of obesity and other age-related or life-style conditions (nutrition, social isolation, emotional distress, physical activity) on immune function?	Different populations in high-income countries (HICs) and LMICs and with different co-morbidities should be compared
To what extent do commonly used (adult) medications have an impact on immune responses to infection and vaccination?	As an example, the response to influenza vaccines in people taking statins is altered and may be lower [104,105]
Can we measure frailty, intrinsic capacity and environmental factors? Do we have the necessary tools and are they validated?	Observational and interventional studies with vaccines could examine the potential links between these factors and prevention of disease or decline?
Interrelationships between pediatric and adult vaccination programs	
Should the need for and frequency of booster doses for infant vaccines during adulthood be revisited?	Examples include long-term immunogenicity and efficacy data for acellular pertussis [106] and tetanus vaccines
What is the potential impact of population (herd) immunity from vaccination of children on the need to vaccinate older adults?	In HICs, the value of infant/childhood conjugate vaccination (Pneumococcal conjugate vaccines, Haemophilus influenzae type b vaccines) has resulted in decreased disease burden in adults. More studies on population effects of seasonal influenza and pneumococcal vaccination of infants and young children are needed, especially in LMICs
What is the potential impact of pediatric varicella vaccination on herpes zoster in adults?	There have been suggestions that exposure to varicella may boost immunity to herpes zoster but the strength of this effect and its implications for vaccination are still being debated [107]
Program implementation	
What are the major hurdles in communication to create awareness of the benefits of adult immunization?	Training of health care personnel and appropriate communication at all levels (policy makers, health care personnel, and patients/society will be required
What vaccine delivery platforms are best for achieving high coverage?	Reaching target vaccination groups outside the traditional infant vaccination requires new strategies, delivery locations, and effective communication to promote community demand