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GUEST EDITORIAL

Special focus on challenges and opportunities for the development and use of vaccines in Africa

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ABSTRACT

Immunization of children against vaccine-preventable diseases is one of the most cost-effective and potentially equitable public health interventions. Nevertheless, approximately 19.9 million of the world's annual birth cohort are either under-immunized or have not been vaccinated at all. Understanding the factors contributing to under-immunization in settinsg such as sub-Saharan Africa which bears a disproportionate burden of vaccine preventable diseases is key to unlocking the full potential that vaccines offer in reducing under-5 morbidity and mortality. The series or articles in this issue of the Journal, mainly through systematic analysis of District Health Surveillance data bases from 35 countries, highlight the challenges faced in improving vaccination coverage rates in sub-Saharan Africa which has stagnated at approximately 72% for completion of the primary series of infant vaccines over the past decade. The reasons for under-immunization of children is sub-Saharan Africa is identified to be multi-factorial and may differ between and within countries. This highlights the need for country-specific, possibly at a district or sub-regional level, interrogation of factors contributing to under-immunization of children, to work toward providing Universal Health Coverage as envisioned in the Sustainable Development Goals.

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The focus on challenges and opportunities for the development and use of vaccines in Africa in this issue of the Journal, is particularly timeous as the world commits to the Sustainable Development Goals (SDG) and to Universal Health Coverage (UHC).[1] A key pillar of UHC is vaccination, which is undoubtedly one of the most cost-effective and equitable public health interventions in the public health armamentarium. Its importance is embodied in the "Decade of Vaccines" which kicked off in 2011 and which draws to a close in 2020. The vision for the "Decade of Vaccines" was articulated in the Global Vaccine Action Plan (GVAP), adopted by 194 Member States of the World Health Assembly in May 2012, which sought to deliver universal access to immunization. This was expected to avert 24.6–25.8 million vaccine-preventable deaths in this decade alone.[2] Key to this agenda is ensuring equitable access to immunization services, regardless of geographic locality, ethnic or religious beliefs or socio-economic background. Also included among the six strategic objectives of GVAP was country ownership of immunization programs.

The GVAP goals place sub-Saharan African countries under the spotlight due the disproportionate burden of vaccine preventable cases and deaths in this region. Notably, although approximately 25% of the annual global births occur in sub-Saharan Africa, these children contribute to 45–50% of severe morbidity and fatalities worldwide from leading vaccine-preventable diseases.[3] By 2030, it is estimated that one-third of all births globally will occur in sub-Saharan Africa. Furthermore, although modelling exercises indicate that global under-5 childhood deaths are likely to decrease to 4.4 million by 2030, 60% of these childhood deaths are expected to occur in sub-Saharan Africa unless there is improvement in deployment of life-saving interventions such as vaccines. To address this challenge, regional goals and ambitious targets were further elaborated in the WHO African Regional Strategic Plan for Immunization (2014–2020) and the 2016 Addis Declaration on Immunisation.[4]

While the reliability of data on immunization coverage in low-middle income countries remains a challenge, monitoring these targets nevertheless gives us insight into progress and obstacles. Encouragingly 18 countries have >90% coverage with Penta 3, yet overall 3rd dose of diphtheria-tetanus toxoid-pertussis (DTP3) coverage has plateaued at 72%, with 80% of missed children residing in 10 countries (7 of which are in sub-Saharan Africa). In 2017 only 16 out of 47 sub-Sahara African countries had achieved >90% coverage of the first dose of measles vaccine.[5] Furthermore, immunization equity analyses shows that economic disparities, place of residence and educating status continue to determine children's

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immunisation status. Vaccine supply remains a challenge with 16 countries reporting one or more stock-outs of vaccines lasting for more than one week in 2017. Although polio eradication/elimination efforts are making progress with the last case of wild poliovirus being detected in Nigeria in 2016, vaccine derived poliovirus is now posing a challenge. While steady progress is being made towards Maternal Neonatal Tetanus elimination with 38 countries having been validated as having achieved MNT elimination, another nine countries have still to achieve this goal and funds to complete this elimination target are lacking.

The last decade has also witnessed many successes and innovations from which lessons can be learned. The Global Alliance for Vaccines and Immunisation (Gavi) has supported new vaccine introduction in the poorest African countries by subsidising vaccine procurement and programmes. As a result, the timelines by which pneumococcal conjugate vaccine (PCV) and rotavirus vaccine were introduced into public immunization programs have been drastically reduced. In contrast to the quarter-century time lag before *Haemophius influenzae* type b conjugate vaccine (HibCV) was introduced into public immunization programs of the majority of LMIC compared to high-income countries, the scaling-up of PCV and rotavirus vaccine introduction in LIC was more than halved relative to its deployment in high-income countries.[6] Shah et al estimated that 134,714 hospitalizations and 20,986 deaths were prevented in 2016 among the 29 African countries which introduced rotavirus vaccination prior to end of 2014. Furthermore, it is estimate that if all African countries had introduced rotavirus vaccines at benchmark immunization coverage, 47% of all-cause diarrhea hospitalizations and 39% of deaths would have been prevented.[7] The introduction of HibCV and PCV into many public immunization programs has been temporally associated with 51% and 90% reduction in pneumococcal and Hib disease, respectively between 2000 (pre-vaccination for most African countries) and 2015 (PCV-era). Nevertheless, in 2015 there were still an estimated 294 000 pneumococcal in HIV-uninfected children aged 1–-59 months in 2015,[8] with approximately 60% of the annual birth cohort globally still not being immunized with PCV.

Further successes have also been observed with other new vaccines that were introduced targeting endemic diseases and emerging epidemic pathogens. Twenty out of 25 countries within the meningitis belt have introduced the conjugate vaccine MenAfriVAC© through campaigns and four through routine immunization, eliminating the feared meningitis A outbreaks of the past.[9] In 2015, the unprecedented West African epidemic of Ebola virus haemorrhagic disease resulted in the expedited evaluation of several Ebola candidate vaccines, with the rVSV Ebola vaccine demonstrating efficacy allowing its ongoing use in outbreaks through a ring study protocol.[10] Challenges, however, remain in the development of vaccines targeting malaria, HIV and tuberculosis- which remain leading causes of death in Africa. Although the RTS-S malaria vaccine was demonstrated to have 45% efficacy during the first 18 months of life[11] this was followed by subsequent waning of immunity by seven years of age; including an excess of cases among vaccine recipients in some high-burden settings.[12]

Despite the progress and success in immunization contributing to reducing childhood deaths, it is estimated that approximately 19.9 million (15%) of the annual birth cohort of 132 million are either not vaccinated or under immunized. Approximately 10 million of these un-vaccinated or under-immunized children live in sub-Saharan Africa, primarily due to low immunization coverage rates. Understanding the mediators contributing to under-immunization and non-vaccination of children in sub-Saharan Africa is, therefore, fundamental to derive the full benefits that vaccines stand to offer at an individual and societal level. This includes the potential for immunization of young children in advancing socio-economic development, with an estimated 44-fold return on the initial cost of investment in immunization; which includes avoiding treatment costs and loss of productivity averted over the lifespan.[13]

The medium and long-term public health impact of vaccines and the sustainability of programmes is, however, dependent on government political commitment. For Gavi-graduating countries and non-Gavi eligible middle-income countries where an increasing percentage of the annual birth cohort occur and where great wealth disparities exist, governments need to take over long term funding of immunisation programme financing. While Gavi's purchasing power allows market shaping and significant cost reductions for the poorest countries, the pricing of vaccines such as PCV and rotavirus in middle-income countries is almost 3–6 fold greater than offered to Gavi. Consequently, for many African countries, local country ownership of the entire immunization program needs to be prioritized to enable informed-decision making. Yet in 2017 less than one-third of countries were supporting > 50% of expenditure on vaccines using government funds, a figure that has changed little in five years. Furthermore, as we contemplate what the world will look like by 2030, additional new challenges are confronting the African region. The rapid growth in Africa's population is shifting towards urban living often in poor housing conditions. Numerous cities across the continent are heading for populations of 5–10 million people, and at least two mega-cities of more than 10 million people by 2030

It is in the above context, that this special issue of the journal interrogates some of the key challenges faced in sub-Saharan African countries, the majority of which have been unsuccessful in meeting the target of at least 90% of children being fully vaccinated.[5] The reasons for under-immunization of children is multi-factorial and may differ between and within countries. Observations from Ethiopia, despite having one of the most comprehensive portfolio of vaccines available in its public immunization program in sub-Saharan Africa, illustrate the need to focus on implementation science to benefit from progressive policy. As pointed out by Master et al. in this issue, despite an array of vaccines purportedly being available at no-cost to the parents, the country has the second largest number of unvaccinated children globally; with only 38.5% of children 12–23 months of age being fully vaccinated in 2016. This is further compounded by the timeliness of vaccination, which could undermine the full benefit of vaccination, being affected by parental hesitancy in Addis Ababa where vaccine coverage is much higher than elsewhere

in the country.[14] It is in this context that studies such as undertaken by Tesfaye et al. is important. Although the immunization coverage rates observed in Northwest Ethiopia was higher (58.4%) than the national average; large percentages of children remained partially vaccinated (17%) or not vaccinated at all (24.6%). Factors identified to contribute to under-immunization included rural residence, absence of antenatal care during pregnancy and lack of maternal knowledge on vaccination. Surprisingly, however, children of women who were ever married and whose travel time was ≤30 minutes to the vaccination clinic also had lower rates of being completely vaccinated. Local information such as this is essential to inform immunization program managers of identifying and addressing these mainly remediable factors that are contributing to under-immunization in this and other similar settings.[15]

The importance of addressing vaccine hesitancy and interrogating factors contributing to missed opportunities for vaccination was recognised by the Scientific Advisory Group of Experts (SAGE) to WHO.[16] Whilst innovations are underway to address barriers to vaccine access and supply, addressing the mediators of vaccine hesitancy requires a complex approach addressing structural, social, religious and psychological factors that likely differ between and possibly even within countries. As such, the commentary by Cooper et al. correctly point out that whilst the primary mediators around vaccine hesitancy in industrialized countries are likely influenced by confidence, complacency, convenience, risk calculation, and collective responsibility ("5C model"); the knowledge gap surrounding the reasons for vaccine hesitancy in LMIC settings require more focus.[17] This is in support with the WHO recommendation for National Governments to incorporate plans to measure vaccine hesitancy into national immunization programs. As indicated by Cooper et al, this would require a multi-sectorial approach, including social-scientist working in tandem with medical experts and program managers.

The complexity of addressing vaccine hesitancy and other mediators of under-immunization is further illustrated by a number of multi-country analyses involving District Health Surveillance databases from 35 sub-Sahara African countries. Ndwandwe et al. report that although missed opportunities for vaccination were more common in children from poor households in nineteen countries; the opposite was observed in five countries where children of mothers from higher wealth quintile backgrounds paradoxically had more missed opportunities for vaccination.[18] Further analyses of the same dataset by Sambala et al. which interrogated maternal education level as a predictor for missed opportunities for vaccination, similarly reported conflicting findings.[19] Hereto, although children of educationally-disadvantaged mothers were more likely to have had missed vaccine opportunities in the majority of countries (n = 19); again in 5 countries the opposite association was observed. These analyses further conclude that in addition to maternal-education, other factors influencing vaccination include neighbourhood socioeconomic status, other children under-5 years of age, media access and household wealth index – with wide geographic and even inter-country variability.

Although addressing factors that contribute to missed opportunities for vaccination at a local or country level, is estimated to have the potential of increasing immunization coverage rates by up to 30% in some settings; much work remains to be done to understand the reasons for under-immunization, which might need to be interrogated at an inter-country level.[20] As an example, although some reports suggest that children born to HIV-infected women are more likely to be under-immunized, meta-analysis of data from 27 sub-Saharan African countries did not identify maternal HIV-infection to be associated with DTP3 under-immunization. Furthermore, no association was observed between DTP3 coverage and other country characteristics such as HIV prevalence among women, antiretroviral therapy coverage, gross domestic product per capita, human development index, adult literacy rate and sub-region.[21] Nevertheless, the study found wide variability in immunization coverage rates in the different settings (26%–94%);[21] and identified factors that contributed to under-immunization. This led to proposals for interventions that are focussed on young HIV-infected, unemployed women, those without formal education, individuals living in communities with high illiteracy rate and in countries with low adult literacy rate.[22]

The need for community-engagement and a bottom-up approach that is cognisant of societal, cultural and religious considerations to address the barriers contributing to under-immunization of children was clearly also evident with the experience around polio eradication efforts in countries such as Nigeria, Pakistan and Afghanistan. A further example of this is the experience shared by Kpanake et al. in this journal, on the hypothetical willingness of Guineans to be vaccinated against Ebola; with 25% of respondents not supporting vaccination, and a further 19% demonstrating hesitancy toward vaccination.[23] These findings were not dissimilar to 34% refusal rate of individuals offered the investigational Ebola vaccine during the ring-vaccination, effectiveness study undertaken in Guinea in 2016; which was attributed to mistrust of the Ebola surveillance team. Lessons learnt from this experience, need to be expanded upon for future epidemic and pandemic threats to ensure countries are adequately informed on how best to roll-out vaccines under such emergency situations.[10] Furthermore, Uthman et al. using the richness of the District Health Surveillance databases identified that under-immunization in sub-Saharan Africa is influenced by not only individual factors but also compositional factors such as family's financial capacity, place of birth and upbringing; with increased odds of under-immunization observed based on high birth order, high number of under-five children in the house, poorest household, lack of maternal education, lack of media access, and living in poorer neighbourhoods. They estimated that 18.4% and 37.4% of the variance in odds of under-immunization could be attributed to the country and neighbourhood level factors, respectively.[24]

Other articles in this issue of the Journal, whilst not directly addressing issues of under-immunization, nevertheless, highlight additional consideration to ensure optimising the potential that vaccines have in reducing morbidity and mortality from vaccine preventable diseases. Included among these is the analysis that highlights the 1.15-fold increased

susceptibility for developing acute respiratory infections among children living in communities with high unemployment rate; and increased susceptibility for diarrhoea in children of young mothers (15–24 years). This understanding, further identifies which groups warrant particular focus within communities, in the effort to prevent disease from these vaccine-preventable diseases.[25] Interestingly, under-immunization with DTP3 coverage as a proxy for complete vaccination with the primary series of early-infancy childhood vaccines, whilst associated with 1.09-fold increased risk for acute respiratory infection symptoms with low heterogeneity across the countries; was paradoxically associated with a 17% increased risk of diarrhoea episodes, albeit with substantial heterogeneity across the countries. This illustrates the need for local understanding of the epidemiology of vaccine preventable diseases; and the need for critical appraisal of available data.[26] In other studies, Teshome et al. address the issue of mass-vaccination and demonstrate that through social-mobilisation, coupled with micro-planning of logistics, that mass vaccination against cholera was acceptable to the community and deliverable through existing health systems and at an affordable cost. This study, particularly illustrates the obvious, but frequently under-recognised importance, of community participation coupled with logistical planning for the success of immunization activities.[27] Examining alternate strategies to estimate vaccination status against Tuberculosis, although suggesting that BCG scar formation might be better measure of vaccine coverage, being independent of nutritional or socio-economic status; nevertheless re-iterate the limitations thereof with those receiving the Russian BCG strain being 2.9-fold less likely to have a scar than children vaccinated with the Danish BCGs strain.[28]

It is in the above context, coupled with the recognition that vaccine coverage rates have plateaued over the past decade in Africa, that the article by Adamu et al., calling upon National immunization programs to review current strategies and incorporate new, evidence-based innovations in an integrated manner warrants attention.[29] The integrated approach includes involvement of stakeholders involved in evidence synthesis (e.g. National and/or Regional Immunization Technical Advisory Groups), program managers and those involved in vaccine delivery, as well as end-users (parents). There has been some headway in addressing some components of this approach, however, gaps remain in many countries, including the absence or non-functionality of NationaI Immunization Technical Advisory Groups as reported by Wiyeh et al.[30] Although the number of countries with NITAGs has increased over the past decade, in 2016 only 43% of 47 African countries had an established NITAGS, of which only two-thirds were assessed as functional. The pivotal role that NITAG could play in fostering country-ownership of the immunization program, including tailoring of recommendations suited to the locality, being country-advocates, and assist in monitoring and advising on immunization matters warrants ongoing investment. Ensuring that adequate capabilities exist within country to deliver on these NITAG functions, guided by the Regional Immunization Technical Group, will contribute to the GVAP goals of country ownership and universal vaccine coverage that is free of inequity to optimise the promise which existing and future vaccines hold for the well-being of African children.

Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the authors.

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