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## Research Article

# Mapping the evidence-base of adolescent and adult vaccination in Africa: A slow but growing trend

## Abstract

**Background:** Historically, immunisation has largely focused on children. There is an increased realisation that optimal control of vaccine preventable diseases (VPDs) requires an extension of immunisation to adolescents and adults. Research is vital to guide the extension of adolescent and adult immunisation without interference with the childhood immunisation programmes. We therefore conducted a study assessing the types and quality of available research on adolescent and adult immunisation in Africa from 2011 to 2019.

**Methods:** A search for English articles on vaccines and immunisation targeting humans in Africa; and published between January 2011 and March 2019 was conducted. PubMed and Africa Wide databases were searched.

**Results:** The search yielded 8899 articles of which 354 met the inclusion criteria. Most immunisation research focused on adults (60.7%). Thirty-five countries contributed to immunisation research. South Africa and Nigeria had the greatest number of studies (75 and 44 respectively). Disease burden appeared to influence the type and quantity of research for HIV/AIDS, tuberculosis and malaria.

**Conclusion:** Advocacy, advances in technology and, changing epidemiology of diseases have paved the way for research targeting adolescent and adult immunisation. The quantity of research appeared to be influenced by the burden of the disease for some diseases; suggesting research priorities on VPDs in Africa could be driven by the most pressing needs. African governments should spur more intra- and inter-country collaboration for the development of research skills in adolescent and adult age groups on the continent.

## Abbreviations

AU: African Union; GVAP: Global Vaccine Action Plan; GIVS: Global Immunisation Vision and Strategy; JIF: Journal Impact Factor; LRTI: Lower Respiratory Tract Infection; MeSH: Medical Subject Headings; NIP: National Immunisation Programme; NITAG: National Immunisation Technical Advisory Group; VPD: Vaccine Preventable Diseases

## Introduction

In 2011, the World Health Organisation (WHO) together with the WHO member states launched the Global Vaccine Action Plan (GVAP) for the period 2011 to 2020 [1]. The GVAP was a follow up to the Global Immunisation Vision and Strategy (GIVS) launched in 2006 [2]. The goals of the GVAP are to: improve routine immunisation; meet vaccination coverage and equity targets; eradicate polio; eliminate measles, rubella

and maternal neonatal tetanus; introduce new and improved vaccines and, spur research and development for the next generation of vaccines and technologies [1]. Research can play a fundamental role in aiding the realization of all the GVAP goals. Therefore, it is important to understand the profile of immunisation research activities at global, regional and national levels.

Although the aims of GIVS and GVAP are to vaccinate people of all age groups, the African region has lagged behind the rest of the world in expanding the immunisation services to adolescents and adults. Nonetheless, significant efforts have been made by some African countries to introduce new vaccines such as rotavirus, Pneumococcal Conjugate Vaccines (PCVs) and, recently Human Papilloma Virus (HPV) vaccine into National Immunisation Programmes (NIPs) [3-5]. Ideally, the introduction of new vaccines at a national level should be preceded by evidence-based research [6]. Furthermore,

programme evaluations are critical following the introduction of new vaccines [7]. Both evidence-based vaccinology research and programme evaluations contribute to immunisation research outputs, in addition to clinical trials, policy research among other fields.

Since the launch of the Expanded Programme on Immunisation (EPI) in 1974, delivery of vaccination services is universally targeted to young children. In many countries, the EPI has evolved from providing the traditional six to 11 vaccines recommended for children [8]. As more vaccines become licensed and recommended at a global level, the opportunities for more immunisation research will also increase, more so at regional and national levels. The increase in immunisation research where more recommended vaccines are available is corroborated by Machingaidze et al., in study that described trends in childhood immunisation research in Africa [9].

Uptake of adolescent vaccines in Africa has been slow despite the WHO recommendations for inclusion of some booster and new vaccines targeting adolescents into the NIPs. Only a handful of African countries have adopted the WHO recommendations on adolescent vaccination [10]. Adolescent vaccination has been justified by the fact that a) some adolescents miss the infant vaccines hence, requiring catch up vaccination; b) immunity acquired by infant vaccination for some VPDs wanes with time hence booster doses are needed later in life and; c) new vaccines targeting adolescents have been developed, for example, one against HPV. Adolescent immunisation research in high income countries has been centred on vaccine uptake, financing and the acceptability of the vaccines [11,12]. In Africa, adolescent immunisation research should perhaps focus on the access and barriers to vaccination, delivery strategies, financing as well as assessment of the acceptability of the vaccines [13,14].

Adult vaccination in Africa has mostly focused on pregnant women for whom vaccines are delivered at ante-natal clinics during routine visits. Mandatory vaccination for travellers to certain countries and mass vaccination campaigns following VPD outbreaks also serve as opportunities for adult vaccination [15-17]. Largely, most adults in Africa remain unvaccinated despite the vaccines being available. Although there are fewer recommended routine vaccines for adults in general compared to children and adolescents, the WHO has a set of recommended vaccines for healthcare workers [8], who due to the nature of their jobs, are frequently exposed to VPDs. Nevertheless, immunisation policies for adults are lacking in many African countries and more research is needed to understand how to best improve vaccine uptake in older populations.

Immunisation research has the potential to play a vital role in informing policies on vaccination. The year 2019 marks eight years since the GVAP was launched. The aim of this study is to describe the trends in adolescent and adult research outputs on immunisation and vaccines in Africa from 2011 to 2019.

## Methods

### Search strategy

Two electronic databases; PubMed and Africa Wide were

searched for English peer reviewed articles from January 1, 2011 to March 13, 2019. The two databases were chosen as this study formed part of research to update an evidence map on childhood immunisation research output already published by Machingaidze et al. [9]. Medical subject headings (MeSH) and free text terms for vaccines, immunisation, children, adolescents, adults and, Africa were searched. The full search strategy is provided in the appendix (Appendix A). Reference list of the selected articles were also searched to identify other relevant articles.

### Study selection

Studies were included if they: 1) were carried out in humans, 2) were conducted in Africa, 3) focused on vaccines, immunisation programmes or policies and, epidemiology of VPDs targeted by traditional or new EPI vaccines. Studies on VPDs in children were reported elsewhere [18]. Studies reporting the epidemiology of VPDs without any reference to a specific vaccine were excluded. Retrieved articles were screened by one reviewer (HEC) and verified by a second reviewer (BK).

### Data extraction and analysis

One reviewer (HEC) extracted data from the included articles using a pre-designed data extraction form. Extracted data was verified by a second reviewer (BMK). Data was extracted and studies were classified as clinical or operational research. Other study details extracted from all studies were the setting, period and, disease targeted. In addition, for studies conducted in South Africa only, the affiliation of the primary author was recorded. The affiliation details were used for a different review focusing on South Africa immunisation research only and therefore, the affiliation data is not reported in this study. Extracted data was imported into STATA v. 14 for analysis. Results were presented as proportions.

A proxy for accessing the quality of studies developed in a similar review [9] was used to assess the quality of the included studies. Studies published in journals with a Journal Impact Factor (JIF) greater than zero but less than two were considered to be of 'moderate' quality. 'Good' quality studies were considered to be those published in journals with JIFs of two to five. 'Very good' and 'excellent' quality was assigned to studies indexed in journals with JIFs of, six to ten and greater than 10 respectively. As the JIFs change annually, we used the latest metrics for the year 2018 [19].

## Results

### Literature search

A total of 8399 articles were retrieved from the search. The number of articles retrieved from PubMed and Africa Wide was 6502 and 2897 respectively. After removal of duplicates, the titles and abstracts of 6986 articles were screened. After the screening, 6169 articles were excluded. The full text of the remaining 817 were further screened and 354 articles met the study inclusion criteria (Figure 1).

### Quantity and quality of the adolescent and adult immunisation research

A total of 354 studies in adolescents and adults were published in 133 journals during the review study period. The JIFs ranged from 0.12 to 79.258. Over 50% of the articles were published in journals considered to be of good, very good or excellent quality. The journals with the highest number of articles are shown in Table 1.

### Contributions of adolescent and adult immunisation research by the african countries

Studies were reported from 64.8% (35 out of 54) of the African countries. South Africa (n=75) and Nigeria (n=44) generated a combined total of 33.6% (119) of all the published studies (Figure 2). Several studies (n=39) were carried out across multiple African countries, indicating there are collaborative immunisation research initiatives on the continent.

### Adolescent and adult immunisation research by %GDP spent on health

Broadly, African countries all fall under 3 categories: low-; lower-middle-; and, upper-middle income countries. We looked at the %GDP spent on health [20]. The rationale behind evaluation of %GDP spent on health was to investigate if there could be an association with increased immunisation research outputs (Table 2).

%GDP spent on health did not appear to influence the research outputs. As an example, Liberia had the highest %GDP spent on health and only one study from the country was included in our study. The same can be argued for Nigeria with less %GDP spending but with many studies included in the review.

Table 1: Top 10 journals with their journal impact factors.

Journal	Number of studies	2018 JIF	Quality of the journal
Vaccine	48	3.285	Good
Plos One	46	2.766	Good
BMC Public Health	16	2.420	Good
Lancet Infectious Diseases	11	25.148	Excellent
Clinical Infectious Diseases	10	9.117	Very Good
Journal of Infectious Diseases	9	5.186	Very Good
Malaria Journal	7	2.845	Good
New England Journal of Medicine	7	79.258	Excellent
South African Medical Journal	6	1.5	Moderate
American Journal of Tropical Medicine and Hygiene	5	2.564	Good

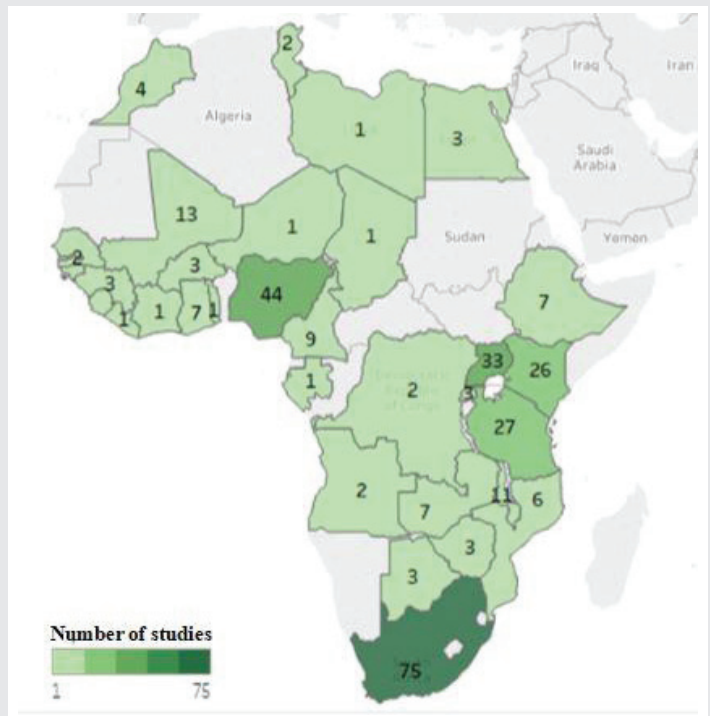


Figure 2: Country specific research output.

Table 2: Classification of countries in relation to number of studies compared to %GDP spent on health in 2016.

Country	Number of studies	% GDP on health
<b>Top 5</b>		
South Africa	75	8.11
Nigeria	44	3.65
Uganda	33	6.17
Tanzania	27	4.14
Kenya	26	4.55
<b>Bottom 5</b>		
Libya	1	6.15
Niger	1	6.23
Chad	1	4.54
Benin	1	3.86
Liberia	1	9.62

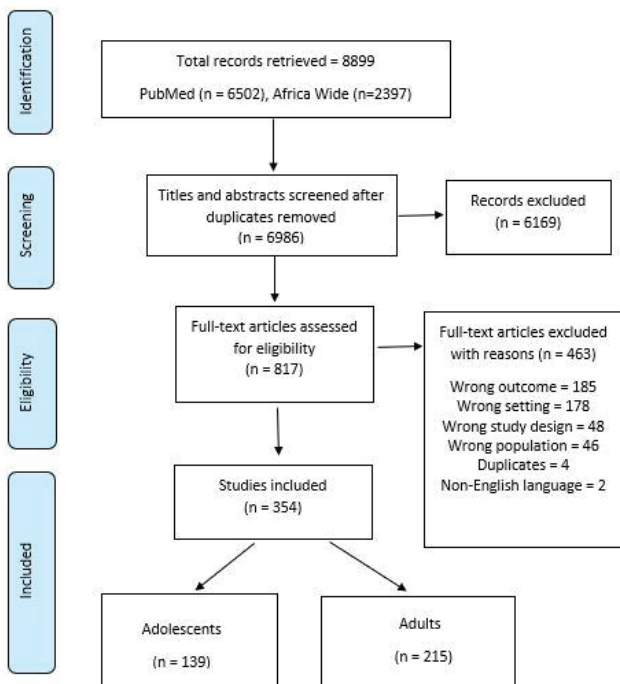


Figure 1: Flowchart for selection of studies.

## Immunisation research outputs for diseases with the highest burden in africa

Immunisation research outputs for the five major infectious diseases (HIV/AIDS, tuberculosis (TB), lower respiratory tract infections, diarrheal disease and, malaria) affecting adolescents and adults in Africa [21], were assessed. The rationale for the assessment was to establish if the immunisation research outputs mirrored the burden and setting of the diseases known to exist in the North, West, Central, East and Southern regions of Africa.

**HIV/AIDS:** Of all the studies, 11.5% were on HIV/AIDS. Research on the disease emanated from nine countries (Guinea-Bissau, Nigeria, Tanzania, Uganda, Zambia, Togo, Mozambique and, South Africa). South Africa contributed most (48.7%) of the studies on HIV/AIDS.

**Tuberculosis:** Tuberculosis accounted for 7% of the studies. Six countries (Kenya, Senegal, Tanzania, Uganda, South Africa and Zambia) contributed to research on this disease with South Africa contributing 52% of the studies.

**Malaria:** Malaria accounted for 8% of the studies. Research on malaria came from eleven countries mainly in West and East Africa with Kenya reporting the highest proportion of studies (17.2%).

**Diarrhoeal and Pneumococcal diseases:** Very few studies were carried out on these diseases (2%) and a majority were from Southern Africa.

### Classification of the immunisation research outputs

**Type:** The number of clinical (phase I-IV trials, epidemiology of VPDs, mortality, immunological and, adverse events following immunisation) was lower than operational (policy, finance, advocacy and, programme management) studies. The proportions of clinical and operational studies were 43.5% and 56.5% respectively. The highest number of clinical studies were carried out on HIV/AIDS while the highest number of operational studies were carried out on anogenital cancers mostly cervical cancer (Table 3).

**Study populations:** We assessed the different groups (adolescents and adults, including pregnant women) that the immunisation research was conducted on, from 2011 to 2019. Most (n=175; 49.4%) of the immunisation research outputs reported adults only, as the study population (Table 4). The top three diseases that the immunisation research was most frequently directed towards are also shown in Table 4.

**Trends in research outputs:** Looking at the absolute numbers, there was a substantial increase in the immunisation research outputs on adolescents (more than double), adults and pregnant women in 2011 compared to 2017 (Figure 3). There was a threefold increase in the overall (all population groups) numbers of research outputs in 2011 compared to 2017 (Figure 3). The low numbers observed in 2019 is due to the shorter period (January to March) than the other past years where we retrieved data for full calendar year. Nevertheless, the decline observed in 2018 is worrying and warrants further investigation

**Table 3:** Classification of studies with respect to disease.

Disease	Clinical	Operational	Total	% of 354
Anogenital cancer	28	109	137	38.7
HIV/AIDS	30	11	41	11.6
Malaria	19	11	30	8.5
Tuberculosis	20	5	25	7.1
Hepatitis B	7	19	26	7.3
Influenza	10	13	23	6.5
Ebola	8	7	15	4.2
Tetanus	5	5	10	2.8
Meningitis	3	3	6	1.7
Cholera	5	2	7	1.9
Whole cluster of EPI diseases**	1	4	5	1.4
Rubella	4	0	4	1.1
Shigella	1	0	1	0.2
Pneumococcal disease	5	1	6	1.7
Diarrhoeal disease	1	1	2	0.5
Yellow fever	4	1	5	1.4
Polio	0	1	1	0.3
Non-infectious causes	0	1	1	0.3
Typhoid	1	3	4	1.1
Pertussis	1	2	3	0.8
Streptococcal disease	0	1	1	0.3
Hepatitis C	1	0	1	0.3
Total	154	200	354	100

\*Country specific; \*\*Tuberculosis, polio, diphtheria, tetanus, pertussis, hepatitis, haemophilus influenza disease, measles, diarrhoea, cervical cancer, yellow fever.

**Table 4:** Distribution of studies and top 3 diseases across the two age groups and pregnant women

Target population	Total number of studies N (% of 354)	Top 3 diseases N		
		Anogenital cancer	Tuberculosis	HIV
Adolescents only	139 (39.3)	120	7	4
Adults only*	175 (49.4)	HIV 34	Malaria 29	Hepatitis B 24
Pregnant women	24 (6.8)	Influenza 8	Tetanus 4	Cholera 3
Adolescents + Adults	16 (4.5)	Anogenital cancer 7	HIV 3	Meningitis 1

\*Excluding pregnant women

## Discussion

**The main findings of our evidence map are:** Between 2011 and 2019, over half of the African countries (64%) contributed to immunisation research outputs in adults and adolescents; South Africa and Nigeria had the greatest number of research outputs; disease burden appeared to influence the type and quantity of research outputs; and research outputs on adolescents and adults increased gradually with a sudden drop in the number of studies published recorded in 2015.

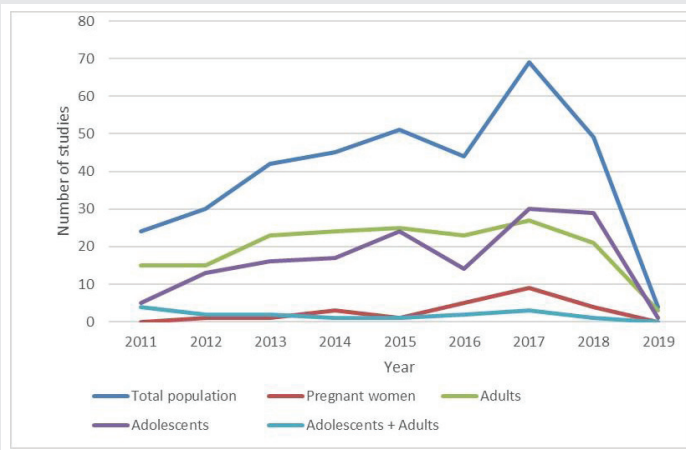


Figure 3: Distribution of publications over time.

**The 20 countries with no research contribution were from all the regions of the continent:** North, West, Central, East and, Southern Africa. One possible explanation is that studies conducted in the 20 countries may not have been indexed in the two databases we searched from. For the past decades, country-specific research on the continent has been dominated by South Africa and Nigeria [9]. The presence of multiple medical schools, health research institutions, availability of resources to conduct research and implement findings have been stated as reasons for the high research productivity by the two countries [9,22]. It was impressive to note that, multi-African collaborative research outputs almost matched country-specific research. Collaborative research is more likely to attract funding and to improve research capacity in Africa. In 2014, African governments agreed to spend 1% of the national gross domestic product on research but this has not been implemented by all countries as a result of multiple reasons such as competing national budget expenses [23]. %GDP spending on health is related to the country's level of income [20]. High-income countries spend more on health while low-income countries spend less %GDP on health. For outputs in immunisation research, our results did not show a relationship with %GDP spent on health. The critical role of research in addressing society challenges is well recognized. Prevention of communicable diseases is one of the priority areas earmarked for research by the African Union [23], and the majority of these diseases can be prevented through vaccination. Therefore, willingness and commitment to improve both research capacity and outputs are needed to reduce the burden of VPDs in Africa, more so in the adolescent and adult populations.

Historically, vaccine and immunisation research has mainly focused on children [9]. As vaccine development for diseases like cervical cancer, HIV/AIDS and malaria evolves, our results indicate a notable increase in adolescent and adult immunisation research in Africa. Most of the adolescent immunisation research in the past seven years has been centred around the acceptability of the HPV vaccine and demonstration projects for possible introduction of the vaccine into NIPs. As at 2017, only six African countries had included the HPV vaccine into their NIPs although demonstration projects have been carried out in 23 other countries [10]. All the African countries

have opted for school-based HPV vaccination strategy to immunize adolescents. One challenge to this HPV vaccination delivery strategy is a substantial proportion of adolescents in Africa may not be school going hence missing the opportunity to get the immunized. Further research is needed to quantify the potential number of girls missed using this strategy.

Adult immunisation research has focused mostly on HIV/AIDS and malaria. For HIV/AIDS, research focused on clinical trials of candidate vaccines. After the Thailand trial in 2009 which showed a vaccine could reduce the risk of HIV, research on HIV vaccines has been gaining momentum [24]. Several phase III trials have been set up in Africa to test the safety and efficacy of a modified version of the Thai vaccine and other novel candidates [24]. The high burden of HIV in Africa, relative to other continents, makes the African region an ideal setting for early and late phase vaccine trials site.

Few studies reported research among pregnant women. Generally, pregnant women fall under vulnerable study population and therefore routinely excluded from vaccine research due to the unknown dangers to the foetus. However, vaccines against pertussis, influenza as well as maternal and neonatal tetanus (MNT) target this group [8]. Although maternal and neonatal tetanus has been marked for elimination, it is still a public health problem in 9 African countries (Angola, Central African Republic, Democratic Republic of Congo, Guinea, Mali, Nigeria, Somalia, Sudan, South Sudan) [25]. Priority should be given to MNT research to aid the disease elimination efforts.

According to the WHO 2016 statistics on mortality, lower respiratory tract infections (LRTIs), HIV/AIDS, diarrheal disease, TB and, malaria were the five top ranking causes of mortality in the African region [21]. The focus areas of the immunisation research output from Africa in the past seven years reflected the WHO 2016 statistics for HIV/AIDS, TB and, malaria in the region. Among the five top ranking diseases, only pneumococcal infections, diarrhoea and, TB have licensed vaccines and two of these (pneumococcal conjugate and rotavirus vaccines for diarrhoea) are considered new and underutilized vaccines.

Looking at HIV/AIDS and TB, Southern and Eastern African countries accounted for most of the burden of HIV/AIDS in 2017 [26]. Four Southern African countries (Angola, Zimbabwe, South Africa and Mozambique) out of 8 African countries were among the top 20 countries with the highest burden of TB [27]. It is therefore not surprising that South Africa generated the highest number of research outputs on HIV/AIDS and TB. Several HIV and TB vaccine candidates are undergoing trial thus justifying the high number of clinical studies published by South Africa on these dual epidemics.

Malaria is endemic to the tropics and the immunisation research output mirrored the burden of the disease in the tropics (East and West Africa). Several malaria vaccine candidates have undergone clinical trials [28,29]. For example RTS,S malaria vaccine candidate has been approved for use in the general public (pilot implementation) [30]. Kenya provided the highest number of studies on malaria vaccines and is one of the three

African countries alongside Ghana and Malawi selected for roll out of this first malaria vaccine targeted to at risk populations in 2018 [30].

The LRTIs are a major cause of mortality among adolescents and adults, although research on pneumococcal disease, (the leading cause of LRTIs) was low. Research on this disease is mainly carried out in children. The introduction of pneumococcal conjugate vaccines (PCV) 7, 10 and 13 among children into NIPs has led to a reduction of invasive pneumococcal disease in both children and adults in several countries [31–33]. The indirect benefits observed in adults following introduction of PCV to children shows an important link between childhood immunisation and adolescents' or adults' health.

Our review had several limitations. Firstly, only two databases were searched thus other studies not published in these databases as well as grey literature were missed. Secondly, only studies published in English were included so several studies from Central, West and, North Africa which are the French speaking regions were not included. Thirdly, journal impact factors were used as a proxy to assess the quality of individual studies. This is not ideal because journal impact factors are awarded based on the how often the journal is cited. Despite these limitations, our results serve as a foundation to guide a design of more focused reviews to understand vaccine and immunisation research trends across Africa. Our findings of the slow but growing trend of immunisation research in adolescent and adult groups in Africa is encouraging.

## Declarations

### Author's contributions

GH, SM and CW conceived the study. EH conducted the search, data extraction and analysis with supervision from BK and GH. EH wrote the first draft of the manuscript together with BK. All authors reviewed the various drafts of the manuscript. All authors reviewed and approved the final manuscript.

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