The Efficacy, Effectiveness and Immunogenicity of Influenza Vaccines in Africa: A Systematic Review

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Abstract

The burden of influenza in Africa is significant and under-appreciated. While surveillance has increased, our understanding of seasonal influenza vaccine performance remains limited. We conducted a systematic review, using PRISMA guidelines (PROSPERO CRD42017058107), on the efficacy, effectiveness and immunogenicity of influenza vaccines in populations within Africa with the aim of identifying key data gaps to help direct future research. We searched Embase, Medline, Global Health and Web of Science for published studies from database inception to May 9th, 2018. Unpublished studies were identified by searching ClinicalTrials.gov and the Pan-African Clinical Trial Registry and by contacting experts within the field. Human studies which reported influenza vaccine immunogenicity, effectiveness and efficacy were included. The quality of each study was assessed using the GRADE framework. 1746 articles were assessed and 23 articles included: six maternal immunisation, 6 child immunisation, three elderly immunisation and 8 other articles. Only three studies were of high quality and many studies were under-powered. All studies came from only six African countries (16 from South Africa), highlighting the need for data from a broader range of African populations. The majority of studies focused on effectiveness or efficacy against laboratory confirmed influenza with limited data on severe outcomes. Several factors known to interfere with influenza immunization, such as malaria, HIV and malnutrition were under-represented in this review and require further study. Significant gaps exist in our understanding of influenza vaccine performance across all WHO high risk groups in Africa.

Introduction

The impact of influenza on African populations and health systems is under-appreciated. Influenza causes approximately 300,000-650,000 deaths per year with the highest mortality rates seen in sub-Saharan Africa.[1] The per capita influenza-associated hospitalisation rate in children <5 years is estimated to be 174 per 100,000/year in Africa compared to 53 per 100,000/year in Europe.[2] Influenza surveillance in 15 African countries (2006 – 2010) showed the overall proportion of influenza positivity was 21·7% in influenza-like illness (ILI) cases and 10·1% in severe acute respiratory infection (SARI).[3] A combination of poor nutrition and socioeconomic conditions, higher prevalence of co-infections (E.g. HIV, tuberculosis, *Streptococcus pneumoniae*) and limited access to healthcare, may contribute to seasonal influenza infections playing a greater role in respiratory disease-related morbidity and mortality in Africa than in high income countries (HIC).[4]

In 2012, the WHO Strategic Advisory Group of Experts recommended influenza vaccination programmes focusing on key high-risk groups:[5] pregnant women, children aged 6–59 months, individuals with specific chronic illnesses, the elderly and health care workers. Despite these recommendations, by 2014, only three African countries (of 47 WHO member states) had seasonal influenza vaccine policies: South Africa, Algeria and Morrocco.[6] While the reasons for this are multifactorial (including health economic), there is a lack of knowledge regarding influenza vaccine performance in African populations and no systematic review has been published. Previous examples such as rotavirus and oral polio vaccines show that efficacy and immunogenicity data from HIC are not always transferrable to low and middle-income countries (LMICs).[7] Several factors such as year-round transmission of influenza within the tropics,[8] high HIV prevalence and reduced maternal antibody transfer with malaria infection[9] could influence vaccine performance. We have carried out a systematic review of the current literature to identify key data gaps in the efficacy, effectiveness and immunogenicity of influenza vaccines in African populations and help shape future research priorities.

Methods

The study was conducted using PRISMA guidelines and registered with PROSPERO (CRD42017058107).

Search strategy and selection criteria

Published articles were identified by searching Embase, Medline, Global health and Web of Science using the following strategy: (influenza OR flu) AND (vaccin* OR immuni#ation OR Influenza Vaccines [Subject heading]) AND (effic* OR effect* OR immune* OR respons* OR protect*) AND (Africa OR Africa [Subject heading] OR each African country [defined by United Nations]). A full list of included countries is shown in the Appendix. Databases were first search on the 17th of January 2017 and an updated search carried out on the 9th of May 2018. Unpublished trials were identified by searching Clinicaltrials.gov and the Pan-African Clinical Trial Registry. Experts within the field were contacted. References within identified studies were reviewed for additional articles. All studies which assessed influenza vaccine efficacy, effectiveness or immunogenicity (definitions below) in populations within African countries, were included. No studies were excluded based on year, language or quality. Purely descriptive observational studies were excluded, as were animal immunogenicity studies.

Definitions, data extraction and quality assessment

Vaccine efficacy is defined as a relative reduction in influenza risk after vaccination determined by a randomised controlled trial (RCT). Effectiveness denotes a relative reduction in odds of influenza associated with vaccination in an observational study. Immunogenicity is used to mean the immune response to influenza vaccination. Two authors (BL and EPA) carried out the following methods independently. Titles and abstracts were screened for relevance. Full articles were reviewed against inclusion and exclusion criteria. Data from included trials were extracted: population, design/methodology, participant numbers, type of vaccine, and key findings (vaccine efficacy/effectiveness with confidence intervals and/or haemagglutination inhibition titres). Data were inputed into a table created in Microsoft Word. Vaccine efficacy or effectiveness studies were grouped and evaluated as per WHO high risk groups.[5] Immunogenicity outcomes were summarised together. The limitations and quality of each study were assessed using the GRADE framework[10] and used to identify populations lacking high quality studies. Discrepancies with data extraction and quality assessment were settled by discussion and consensus. A meta-analysis would be carried out if greater than two studies from the same WHO high risk group[5] were identified which shared similar populations, interventions, comparison and outcomes.

Results

Study selection and characteristics

Titles and abstracts of 1746 published articles were screened (Figure 1) and 68 full-text articles were assessed for eligibility. Of these, studies were excluded due to a lack of efficacy, effectiveness or immunogenicity data (23), presence of duplicate data (18), data from a non-African country (1) and lack of influenza vaccine usage (3). 23 studies were included (Supplementary table 1).[11-33] Studies varied by study design, vaccine type (inactivated influenza vaccine, IIV3; live attenuated influenza vaccine, LAIV) and study population (Table 1). 16 were from South Africa,[11-14,16-19,23,25,27-32] two each from Gabon[21,22] and Kenya,[20,26] and one study each from Mali[15,33] Senegal[24] and The Gambia.[33] The following study populations were identified: pregnant women (6 studies), children (6), elderly (3), HIV-Positive adults (1), healthcare workers (1) and all age groups (6). Study design included RCTs (12 studies), case-control studies (6), and cohort studies (1). Vaccines used included IIV3 (17 studies), LAIV (3), both IIV3 and LAIV (2) and a monovalent inactivated pandemic H1N1 vaccine (1). Articles were evaluated in detail after grouping by WHO high-risk population.[5] A summary of vaccine efficacy and effectiveness from each study is shown in figure 2. A meta-analysis was deemed unsuitable due to the low number of studies sharing a similar population, intervention, comparison and outcome.

Influenza vaccination in pregnant women

One RCT from South Africa[11] and one from Mali[15] evaluated influenza vaccination in pregnant women, with three studies reporting secondary analyses from the South Africa RCT[12-14] and one study reporting a secondary analysis from both RCTs (Supplementary table 1).[31] A single centre, randomised, double-blind placebo-controlled trial including HIV-uninfected and HIV-infected pregnant women (60% on HAART at enrolment, median CD4 count 393·5 cells/mm^3) was conducted in South Africa.[11] The influenza attack rate in HIV-infected placebo recipients was higher than in HIV-uninfected placebo recipients (17·0% vs to 3·5%). The per-protocol vaccine efficacy against all reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed symptomatic influenza was 54.4% (95% CI 19·5, 74·2, P=0.005) for HIV-uninfected women and 70·6% (95% CI 23·0, 88·8, P=0·02) for HIV-infected women. Infants born to HIV-uninfected women had a per-protocol vaccine efficacy against RT-PCR-confirmed symptomatic infection of 45·6% (95% CI 2·4, 69·7, P = 0·04) at six months of age compared to 42·3% (95% CI -96·9, 83·1, P=0·52) in HIV-exposed-uninfected infants. No impact of vaccination on birthweight, clinical febrile illness or ILI was seen, although the study was not powered for these outcomes.

An extended follow up study[12] of the HIV-uninfected women failed to show statistically significant protective efficacy against RT-PCR-confirmed symptomatic influenza during the following season. No power calculation for vaccine efficacy in the extended period was reported, which included only a subset of participants. A secondary analysis of the HIV-unexposed infants showed that vaccine efficacy against RT-PCR-confirmed symptomatic influenza was 53·9% (95% CI 10·4, 77·4, P=0·02) at ≤16 weeks of age, with no statistically significant protection at >16–24 weeks.[13] A further analysis of the HIV-unexposed infants demonstrated that maternal immunisation reduced hospitalisation for all-cause acute lower respiratory infection (ALRI) by 57·5% (95% CI 7·0, 81·0, P=0·032) during the first 90 days of life.[14] The vaccine efficacy against severe infant pneumonia over the first 180 days of life was 43% (95% CI 0, 67, p=0·05).[31]

Results from a multicentre, active-controlled, observer-blind RCT in HIV-uninfected pregnant women conducted in Mali[15] showed similar results. The vaccine efficacy against all RT-PCR-confirmed symptomatic influenza was 76·6% (95% CI 28·4, 94·8) for women during pregnancy and 70·1% (95% CI 28·0, 89·1) in the six-month post-partum period. Cumulative per-protocol vaccine efficacy against all RT-PCR-confirmed symptomatic influenza in infants was 70·2% (95% CI 11·3, 91·1) during the first four months, decreasing to 37·3% (95% CI 7·6, 57·8) by six months of age. No difference was seen in the birthweights between vaccine groups, although the study was not powered for this outcome. A secondary analysis of this trial reported a vaccine efficacy against all-cause severe infant pneumonia in the first 180 days of life of -17% (95% CI -67, 19, P=0.39).[31]

Influenza vaccination in children

Four studies were identified which reported vaccine efficacy (3) or effectiveness (1) of influenza vaccination in children (Supplementary table 1).[19,20,23,24] A multicentre, double-blind, placebo-controlled RCT in healthy children aged 6 to <36 months from South Africa, Brazil, and Argentina[23] investigated the efficacy of LAIV (Ann-Arbor backbone, Medimmune). Data from the South African participants (n=277) was obtained via personal communication with authors of a meta-analysis analysing country-stratified data (Christopher Ambrose, personal communication).[34] This data generated an efficacy estimate for two LAIV doses of 87% (95% CI 64, 95) for prevention of culture-confirmed symptomatic influenza in South Africa. There are no country-stratified demographic data available on factors such as nutritional status or ethnicity, which may be important to assess the generalisability of these findings to other African populations.

The efficacy of one dose of Russian-backbone LAIV (Nasovac-S®, Serum Institute of India Pvt Ltd) among healthy children in Senegal aged 2 to 5 years was reported recently.[24] This single centre, randomised, double-blind, placebo-controlled study was designed assuming a 6% influenza incidence. Per-protocol vaccine efficacy was 0.0% (95% CI -26·4, 20·9) for all influenza strains and -6.1% (95% CI -50.0, 25.0) for all vaccine-matched strains (78·2% were pdm09H1N1) against RT-PCR-confirmed symptomatic influenza. The overall attack rate was 18% and vaccine-matched strain attack rate 8–9%. Most vaccine-unmatched isolates were influenza B (Victoria lineage) viruses. The absence of immunogenicity measurements to investigate the lack of efficacy observed was a major limitation of this study.

Madhi *et al.* (2013)[19] conducted a randomised, double-blind trial comparing two doses of IIV3 with placebo in HIV-infected children aged 6 to 59 months in South Africa. The per-protocol vaccine efficacy (culture and/or RT-PCR-confirmed symptomatic influenza) was not significantly different from placebo at 24·7% (95% CI -64·7, 66·4). This may, in part, be explained by the antigenic drift observed in the dominant circulating H3N2 strain. Although the lack of efficacy could be explained by poor IIV3 immunogenicity in an HIV-infected population, the study was also underpowered. The required sample size of 420 to detect ≥50% reduction in influenza was based on an assumed attack rate of 20%, whereas the observed attack rate in placebo recipients was only 10%.

Vaccine effectiveness (against RT-PCR-confirmed symptomatic influenza) of IIV3 in children aged 6 months to 10 years was estimated from a test negative case-control study in Kenya.[20] The study was undertaken during a 3-year period where the Kenya Medical Research Institute/Centers for Disease Control-Kenya and Kenyan Ministry of Health offered free influenza vaccine to children in two low-income rural and urban settings. Approximately 35% of all eligible children were vaccinated (2 doses IIV3 if aged <9 years). Patients attending with symptoms meeting pre-defined ALRI/ILI criteria were tested for influenza using RT-PCR. Controls were matched for age, date of sample and study site. Effectiveness estimates were controlled for the interval between symptom onset to sample collection. The combined results for the 3-year study found a vaccine effectiveness of 48·4% (95% CI 31·5, 61·2). The overall effectiveness was 50·2% (95% CI 24·9, 66·9) in 6 months to <5-year olds and 46·2% (95% CI 19·2, 64·2) in 5 to <10-year olds. The main limitations of the study are those inherent in the test-negative case control design, which include possible

differences between those seeking health care for ALRI/ILI and the general population. HIV testing was not routinely performed. 1% of subjects were known to be HIV-infected, with overall adult HIV prevalence 17% and 14% in the rural and urban setting respectively. Only medically-attended cases of ALRI/ILI were included, thereby missing community-managed cases. Nevertheless, this study provides the most robust IIV3 vaccine effectiveness estimates to date in African children and includes data from two diverse and economically deprived settings.

Influenza vaccination in elderly adults

Three studies have assessed the efficacy or effectiveness of influenza vaccines in elderly adults, all conducted in South Africa (Supplementary table 1).[16-18] The two randomised trials[16,17] were conducted in community-dwelling ambulatory adults ≥60 years, where approximately 70% of participants were white. Both trials included the use of LAIV, which is unlicensed for adults >49 years in the USA, and thought to be less effective than IIV3 among elderly adults based on observational data.[16] A randomised, double-blind, placebo-controlled study[16] showed LAIV efficacy against culture-confirmed symptomatic influenza of 42·3% (95% CI 21·6, 57·8), with 52.5% (95% CI 32·1, 67·2) efficacy against A/H3N2 strains and no efficacy against influenza B strains (-10·1%, 95% CI -113·0, 42·7). Although the reason for the poor performance against vaccine-matched influenza B strains is not clear, seroconversion to the influenza B vaccine component was lower than to A/H3N2 (figure 3). Vaccine efficacy was not significantly different between participants aged 60–69 years and those >70 years old.

A randomised, open-label trial compared the relative efficacy of IIV3 and LAIV in adults ≥60 years[17] against culture-confirmed symptomatic influenza. The study was powered on an assumed influenza attack rate of 8%, with non-inferiority between the two arms. The incidence of influenza was much lower than expected at 0·9% in LAIV and 1·5% in IIV3 arms. As such, the study was significantly underpowered and no robust conclusions were possible.

Finally, a retrospective nested case-control study in adults ≥65 years registered in a private medical funding organisation assessed influenza vaccine effectiveness against hospitalisation for acute respiratory conditions, non-elective cardiovascular disease, or all-cause death.[18] Although not explicitly stated, participants presumably received IIV3, as to our knowledge LAIV was not available for routine clinical care in South Africa. Each case presenting with any of the primary endpoints

were matched (by case identification date) to four randomly chosen controls from the same cohort and vaccination status ascertained from health records to calculate vaccine effectiveness. After adjustment for a number of confounders (e.g. comorbidities, age, gender), influenza vaccination was associated with a statistically significant reduction in the combined primary outcome measures by 19·3% (95% CI 3·1, 32·9) and all-cause mortality alone by 23·6% (95% CI 1·0, 41·0). However, a *post hoc* sensitivity analysis suggested that a healthy user bias in the likelihood of receiving influenza vaccine could potentially explain the vaccine effectiveness estimates seen.

Influenza vaccination in other populations

HIV-infected adults:

In addition to the studies above including HIV-infected subjects, a double-blind, randomised, single centre, placebo-controlled trial of IIV3 in HIV-infected adults aged 18–55 years was performed in South Africa (Supplementary table 1).[25] Participants had either been on first-line antiretroviral therapy (ART) for ≥3 months or were ART-naïve with a CD4+ count >100 cells/µl. Vaccine efficacy (against culture and/or RT-PCR-confirmed symptomatic influenza) was 75·5% (95% CI 9·2, 95·6) for all strains and a non-significant 73·3% (95% CI -1·2, 95·2) for vaccine-matched strains. No significant reductions in ILI or ARI was seen. The study was underpowered as 312 participants per study group were required to detect a 30% reduction in influenza, assuming an attack rate of 40% in the placebo arm. Only 255 and 251 participants were recruited to the IIV3 and placebo arms respectively and only 4·7% of placebo recipients developed influenza.

Healthcare personnel:

A prospective cohort study was carried out in healthcare personnel across five Kenyan hospitals (Supplementary table 1).[26] Participants were asked about vaccination status during a monovalent pdm09H1N1 influenza vaccination campaign. The study controlled for month of follow up, gender, age, hospital location and contact with patients. The study failed to find an association between vaccination and reduced incidence of acute respiratory illness, work days missed, or RT-PCR-confirmed influenza. As only 2/531 specimens tested detected pdm09H1N1, low circulating levels of pdm09H1N1 may explain the negative findings.

Miscellaneous populations:

Four test-negative case-control studies were identified from South Africa which estimate vaccine effectiveness across all age groups (Supplementary table 1).[27-30] All originated from the same research team, using a network of general practitioners based in all provinces of South Africa (~90% within private healthcare centres). Patients presenting with an ILI had a throat and/or nasal swab tested for influenza by viral culture or RT-PCR. Influenza positive patients were classified as cases and influenza negative patients as unmatched controls. The first study estimated vaccine effectiveness between 2005 and 2009.[27] Age-adjusted effectiveness was 48·6% (95% CI 4·9, 73·2) in 2005, -14·2% (95% CI -9·7, 34·8) in 2006, 12·0% (95% CI -70·4, 55·4) in 2007, 67·4% (95% CI 12·4, 90·3) in 2008, and 29·6% (95% CI -21·5, 60·1) in 2009. Details of vaccine and circulating strain match are shown in supplementary table 1. The authors adjusted for age but no additional confounders. During 2009, the number of samples which each sentinel site could send was limited to five per week due to limited laboratory testing capacity. Sample selection was at the practitioner's discretion, which could have introduced selection bias. McAnerney *et al*.[29] estimated vaccine effectiveness between 2010 and 2013 and adjusted for age, underlying medical conditions and seasonality. Adjusted vaccine effectiveness was 54·2% (95% CI 2·4, 78·6) in 2010, 57·1% (95% CI 15·5, 78·2) in 2011, 38·4% (95% CI -71·7, 78·1) in 2012 and 87·2% (95% CI 67·2, 95·0) in 2013. The vaccine effectiveness in 2014[28] and 2015,[30] adjusting for age, underlying medical conditions and seasonality, was 43·1% (95% CI -26·8, 74·5) and 46·2% (95% CI -23·5, 76·5) respectively.

The years of poor vaccine effectiveness were mainly related to antigenic drift resulting in vaccine and circulating strain mismatch, although small sample size in some years may also have contributed. As the data are from primary care settings, vaccine effectiveness against severe influenza is not included. Finally, as sentinel sites are private health care facilities where <20% of the South African population seek healthcare, the generalisability of these findings may be limited.

Studies assessing immunogenicity of influenza vaccines

Twelve studies were identified that evaluated influenza vaccine immunogenicity,[11-13,15-17,19,21,22,25,32,33] the majority of which focused on haemagglutination inhibition (HAI) titres, considered at present to be the gold standard immune correlate of protection following immunisation.[35] This is, however, primarily true following IIV3 and not LAIV (which does not induce potent serum HAI responses), and where a clear correlate of protection is not yet established.

Figure 3 shows Geometric Mean Fold Rise (GMFR) following vaccination for studies where this is reported or can be calculated .

Two studies evaluated IIV3 immunogenicity in pregnancy.[11,15] Pregnant women in South Africa mounted robust HAI titres following vaccination to all strains (Figure 3). In Mali, only HAI responses to pdm09H1N1 (HIV-negative women) are reported, which were higher than those seen to pdm09H1N1 in South African HIV-negative women (GMFR 14·9 vs 6·9). The mean age at enrolment was similar in the two studies (24·7 vs 26·2 years), but gestational age at enrolment was higher in Mali than in South Africa (32·6 vs 26·8 weeks). Pre-vaccination geometric mean titres (GMT) to pdm09H1N1 were 30·0 in South Africa and 20·9 in Mali. The reasons for this GMFR difference is unclear, but highlights the potential for variable responses in different African populations.

Transfer of influenza-specific antibodies to infants following maternal immunisation and durability of this immunity was explored.[11,13,15] In South Africa, HIV-unexposed children had higher HAI geometric mean titres (GMT) than HIV-exposed uninfected children to pdm09H1N1 (87·2 vs 48·2), H3N2 (41·4 vs 32·4) and influenza B (86·7 vs 50·0) at ≤7 days after birth. Both groups had significantly higher titres than placebo recipients. Follow up of the HIV-unexposed children in the first 6 months[13] showed rapid waning of HAI GMTs to all antigens, with the proportion of children with HAI ≥1:40 dropping from 78·3% (pdm09H1N1), 56·6% (H3N2) and 81·1% (influenza B) at birth to 39·5%, 19·1% and 40% respectively by 16 weeks. Similar observations were found in Mali,[15] where HIV-unexposed children had HAI GMT to pdm09H1N1 of 141·6 at birth, 39·0 at 2-3 months and 33·7 at 4-5 months of age.

The impact of helminths on IIV3 immunogenicity was evaluated in Gabon, in children aged 7 to 12 years[21] from rural and semi-urban settings. Although exact HAI titres are not provided, children from semi-urban settings had significantly higher HAI responses (H1N1 and influenza B) than those from rural areas. The presence of helminths was associated with poorer immunogenicity. A follow up study[22] failed to show a significant effect of albendazole on HAI response to IIV3, although the study was powered for a much higher helminth burden than observed.

Serum HAI increases following LAIV in elderly adults from South Africa were low, in keeping with previous studies of LAIV (Figure 3).[16,17] HAI responses to IIV3 were lower in individuals aged ≥70

years compared to those aged 60 – 69 years.[17] The impact of HIV infection on IIV3 immunogenicity in both adults and children in South Africa is explored in three studies.[11,19,25] HAI titre GMFR in HIV+ve pregnant women was <50% of the GMFR seen in HIV-ve pregnant women (2.9 vs 6.9, 2.4 vs 6.0 and 3.2 vs 10.0 for pdm09H1N1, H3N2 and influenza B respectively, figure 3). Adults on ART had significantly higher seroconversion rates than ART-naïve patients to all antigens (Figure 3). HIV-infected children aged 6 – 35 months had significantly lower seroconversion rates than those aged 36 – 59 months to H3N2 (34·8% vs 70·6%), with similar trends for H1N1 (39·1% vs 58·8%) and influenza B (34·8% vs 47·1%).

Two immunogenicity studies focused on antibody responses other than HAI.[32,33] A study of healthy white South African students investigated anti-haemagglutinin and anti-neuraminidase antibody rises (single radial disc diffusion) following inactivated and live vaccines.[32] Anti-haemagglutinin responses were observed in >60% of individuals and were similar in all vaccine groups. Anti-neuraminidase responses were identified in a greater proportion of inactivated vaccine recipients ($p<0.05$). The second study focused on Natural Killer cell responses to IIV3 in The Gambia.[33] Anti-IIV3 IgG concentrations were significantly boosted by vaccination in children (2-6 years old) and young adults (20-30 years old) but not in older adults (60-70 years old).

Conclusions and future directions

Our systematic review identified only 23 published studies evaluating efficacy, effectiveness or immunogenicity of influenza vaccines in Africa. As such, we did not exclude studies based on limitations in methodological design, to provide a complete picture of the available data. Due to the heterogeneity in study design, age group and vaccine type, a meta-analysis of these data are not possible. Several RCTs were underpowered, due to over-estimates of influenza attack rates, highlighting the importance of robust influenza incidence data to inform study design and sample size calculations. Improved influenza surveillance systems would help provide this, as well as a means to calculate vaccine effectiveness following influenza vaccine rollout.

Other reasons why several studies failed to produce conclusive results include antigenic drift and unpredictability of dominant circulating strains each year. Estimating required sample sizes based on individual strain attack rates could avoid a loss of power due to antigenic drift, as it is unusual

for all strains to drift significantly in one season. Quadrivalent vaccines containing both B-Yamagata and B-Victoria lineages should ideally be used to further minimise vaccine mismatch.

No studies specifically addressed the impact of time of vaccination and influenza seasonality on vaccine performance. In contrast to temperate climates, countries in Africa experience year-round transmission or exhibit several peaks of transmission (some coinciding with rainy seasons).[8,36,37] Vaccine strategies such as biannual influenza vaccination need further consideration.[38] As the timing of vaccine availability is currently dictated by requirements for temperate countries, more data are required on the suitability of these vaccine formulations for contemporaneous strains in the tropics.

Several other factors likely to effect influenza vaccine performance were under-represented. Placental malaria infection and maternal hypergammaglobulinaemia are known to effect placental antibody transfer[9] and the impact of these conditions on maternal immunisation strategies should be studied. The impact of factors such as HIV, malnutrition and TB also require further study to understand the effect on influenza vaccination. While it is difficult to draw firm conclusions about the relative effectiveness of influenza vaccines in HIC and LMIC from the data currently available, the most comprehensive effectiveness data (from South Africa)[27-30] shows a similar range when compared with USA effectiveness data from the same years (Appendix).[39]

Our review also highlights the need to obtain data from a broader range of African populations, with 16 of the 23 studies performed in South Africa. Even within these studies, several were performed in groups that may not be representative of the wider socioeconomic makeup in the country. Given the genetic and environmental heterogeneity across Africa, further studies to explore any regional variation in vaccine efficacy are important. Studies should include immunogenicity measures to provide insight into any findings observed. While some studies we identified measured serum HAI to assess IIV3 immunogenicity, LAIV studies should include measures of mucosal antibody and systemic T-cell responses as LAIV likely protects via multiple mechanisms. Our own ongoing study of LAIV in Gambian children (NCT02972957) hopes to shed light on the reasons for the poor LAIV efficacy in Senegal.[24]

The majority of studies used laboratory-confirmed influenza illness as a primary outcome and no strong conclusions could be drawn for severe outcomes such as hospitalisation, medically-attended pneumonia or mortality. These outcomes are important for policy decisions on the implementation of future influenza vaccine programmes[40] and demonstration of mortality benefit following vaccination is a criterion for GAVI investment.[41] The reduction in all-cause ALRI and severe infant pneumonia following maternal immunization in South Africa is encouraging but clearly more data are required.[14,31]

The only two studies of LAIV efficacy in African children have provided dramatically contrasting results.[23,24] It is possible that the recent lack of efficacy in Senegal seen is unique to the pdm09H1N1 strain and simply mirrors the poor effectiveness of LAIV against pdm09H1N1 observed in the USA.[42] If ongoing efforts to improve this LAIV component are successful, further RCTs would be warranted in African populations given the greater efficacy of LAIV seen in children when compared to IIV3 in previous studies.[43,44] Furthermore, lower manufacturing costs compared to IIV3 (partly as less antigen is required therefore allowing more doses per egg) and less need for trained healthcare personnel to deliver an intranasal vaccine make LAIV particularly suitable in Africa. The potential for successful LAIV rollout to provide indirect benefit by reducing transmission to unvaccinated vulnerable populations (shown recently in the UK)[45] should also be assessed. Data are also not available on how best to immunise 6 months – 2-year old children, an age group that responds poorly to IIV3 and are outside the licence for LAIV use. The results are awaited of a safety and immunogenicity study comparing MF59^{TM}-adjuvanted IIV3 with standard IIV3 (NCT01819155) in Senegalese children aged 6 to 71 months.

The lack of any robust IIV3 efficacy data in the elderly is striking. Even in HIC, standard IIV3 are only modestly immunogenic due to immunosenescence.[46] The use of MF59-adjuvanted IIV3 and high dose IIV3 have emerged as two strategies to enhance the immunogenicity and efficacy of influenza vaccines in this high-risk group.[47,48] To our knowledge, there are no ongoing studies of these vaccines in Africa and should be the focus of future studies in elderly populations. With the increasing burden of cardiovascular disease in LMIC, the potential for influenza vaccination to prevent stroke and heart disease is also important to consider. An ongoing multicentre RCT of influenza vaccine to prevent adverse vascular events (RCT-IVVE, NCT02762851) aims to include adults aged ≥18 years from several African sites with study completion estimated in 2020. Another

benefit of influenza vaccination may be reduction of pneumococcal pneumonia. The importance of influenza in the pathogenesis of pneumococcal pneumonia was demonstrated by the reduction of virus-associated pneumonia in an RCT of Pneumococcal Conjugate Vaccine (PCV) in South African children.[49] Furthermore, the reduction in all-cause infant ALRI following maternal immunization, despite negligible influenza detection in placebo recipients, supports an impact of influenza vaccination on reducing bacterial pneumonia.[14] An RCT of combined influenza vaccine and PCV in several high risk groups would be valuable, especially in the context of increasing pneumococcal disease due to non-vaccine serotypes.

The lower immunogenicity of IIV3 in HIV-infected patients in HIC is also reflected in the few studies from Africa, although due to the increased susceptibility to influenza in these individuals, the benefits of vaccination are greater. As ART-treated individuals mount higher immune responses to IIV3 than ART-naïve patients, increasing ART rollout could improve vaccine performance. With the high burden of HIV infection in many African countries, new vaccine strategies to enhance immunogenicity are required, for example, the use of high-dose or adjuvanted vaccines. Results are awaited from a systems vaccinology study of IIV3 in HIV-infected individuals in Uganda (NCT01916759) that may provide mechanistic insight into how best to do this. Such studies are important in informing rational design of new vaccines suited to the population in need.

The most robust data available at present to guide influenza vaccination programmes is in pregnant women. Two RCTs[11,15] have demonstrated the efficacy of IIV3 in reducing influenza in pregnant women and their infants, although for the latter group, vaccine efficacy was only significant in HIV-unexposed infants. Protection for infants via maternal immunisation is especially important given the high influenza-related morbidity and mortality in infants <6 months[50] and the lack of a licensed vaccine in this age group. Nevertheless, both serum HAI and efficacy waned rapidly by four months of age, so alternative strategies are required to increase titres in pregnant women and durability of infant protection. Future studies will additionally need to focus on the cost-effectiveness, feasibility and acceptability of maternal immunisation in line with the deliberations for other vaccines applicable in pregnancy. A recent analysis in Mali showed that such a programme would be cost-effective in most settings if vaccine can be obtained, managed and administered for ≤$1·00 per pregnant woman.[51] Ideally health economic analyses should take into account a wider range of potential benefits: impact on bacterial pneumonia, indirect benefits due

to reduced transmission, impact on antibiotic use,[52] although more data are required to inform these aspects. Furthermore, as the burden of influenza is high in Africa, even imperfect vaccine effectiveness can lead to a greater number of absolute cases prevented and significant public health benefit. Finally, as countries in Africa establish influenza immunisation programmes, it is vital that this is done alongside increased capacity for influenza surveillance, so ongoing vaccine effectiveness can be monitored over time.

Contributors

TdS proposed the study concept. BL and TdS generated the protocol and search strategy. BL carried out the search. BL, EPA and TdS did the study selection. BL and EPA extracted data and carried out the quality assessment. BL, EPA, TdS and BK carried out the data interpretation and synthesis. BK and TdS supervised the study. All authors wrote the manuscript and approved the final version for submission.

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Declaration of interests

We declare that we have no conflicts of interest.

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Figure legends

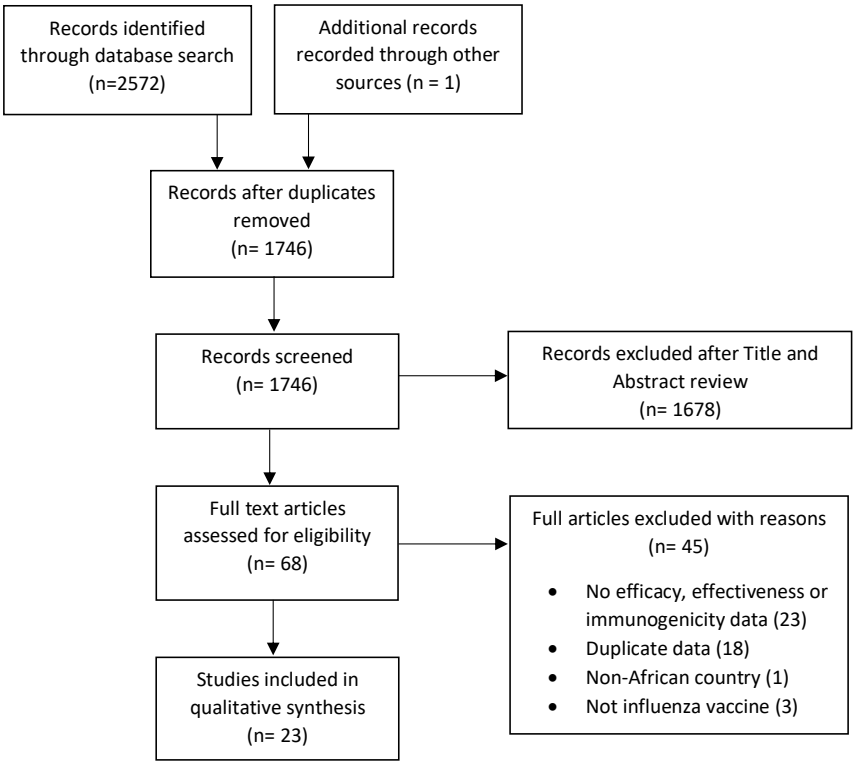
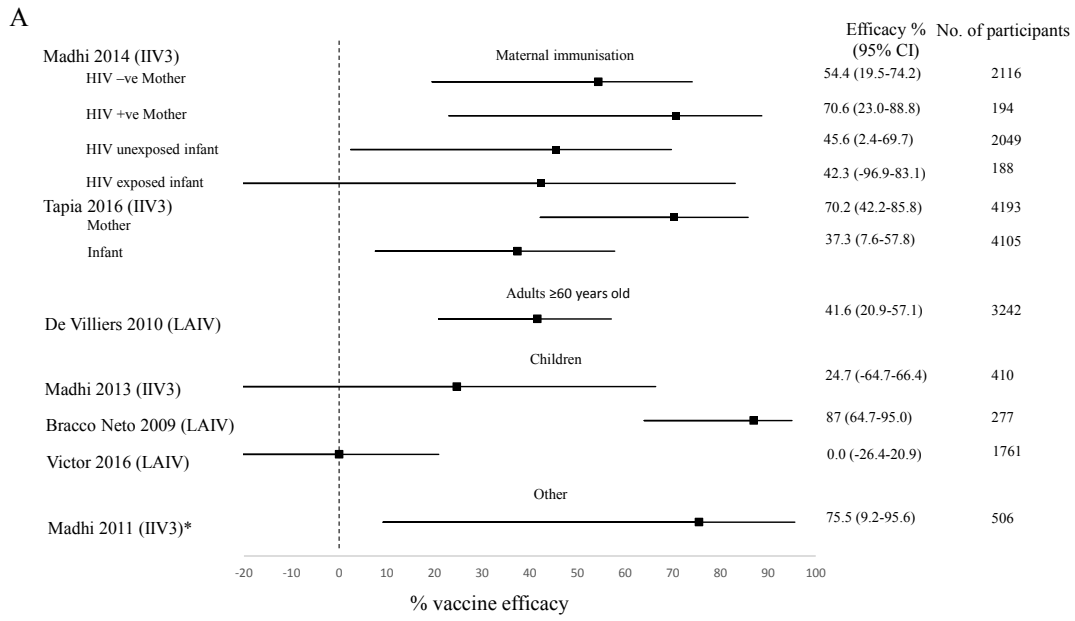


Figure 1: Study selection process



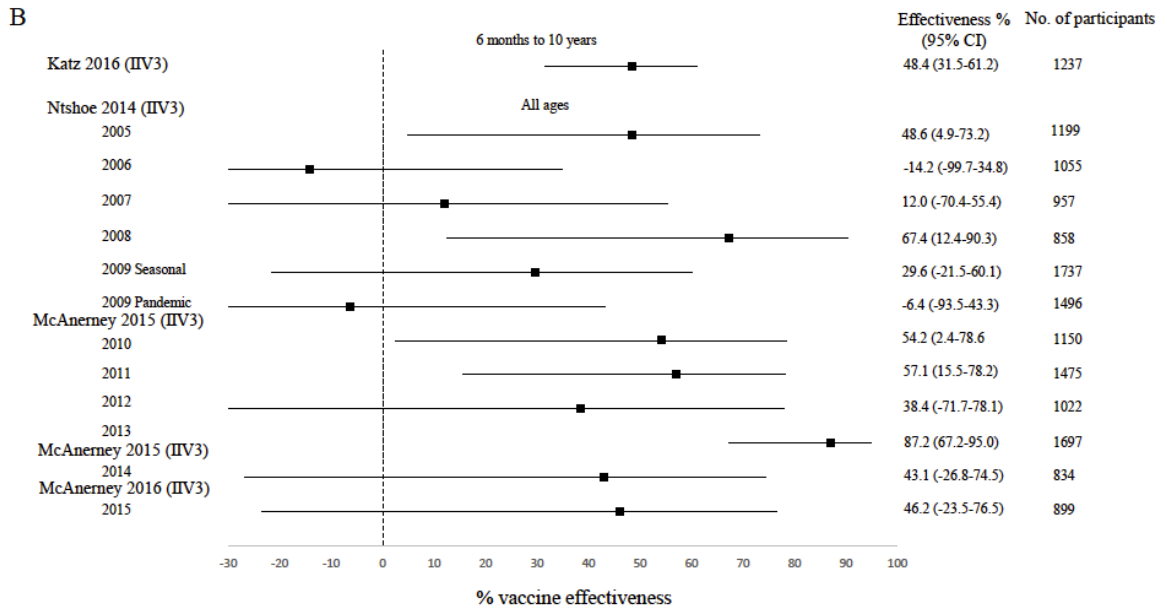


Figure 2: Forest plot of influenza vaccine efficacy (a) and effectiveness (b). *Vaccine efficacy estimates are per-protocol with the exception of Madhi *et al* 2011 which reports intention to treat. CI: Confidence interval; IIV3: Trivalent inactivated influenza vaccine. LAIV: Live attenuated influenza vaccine; HIV: Human immunodeficiency virus

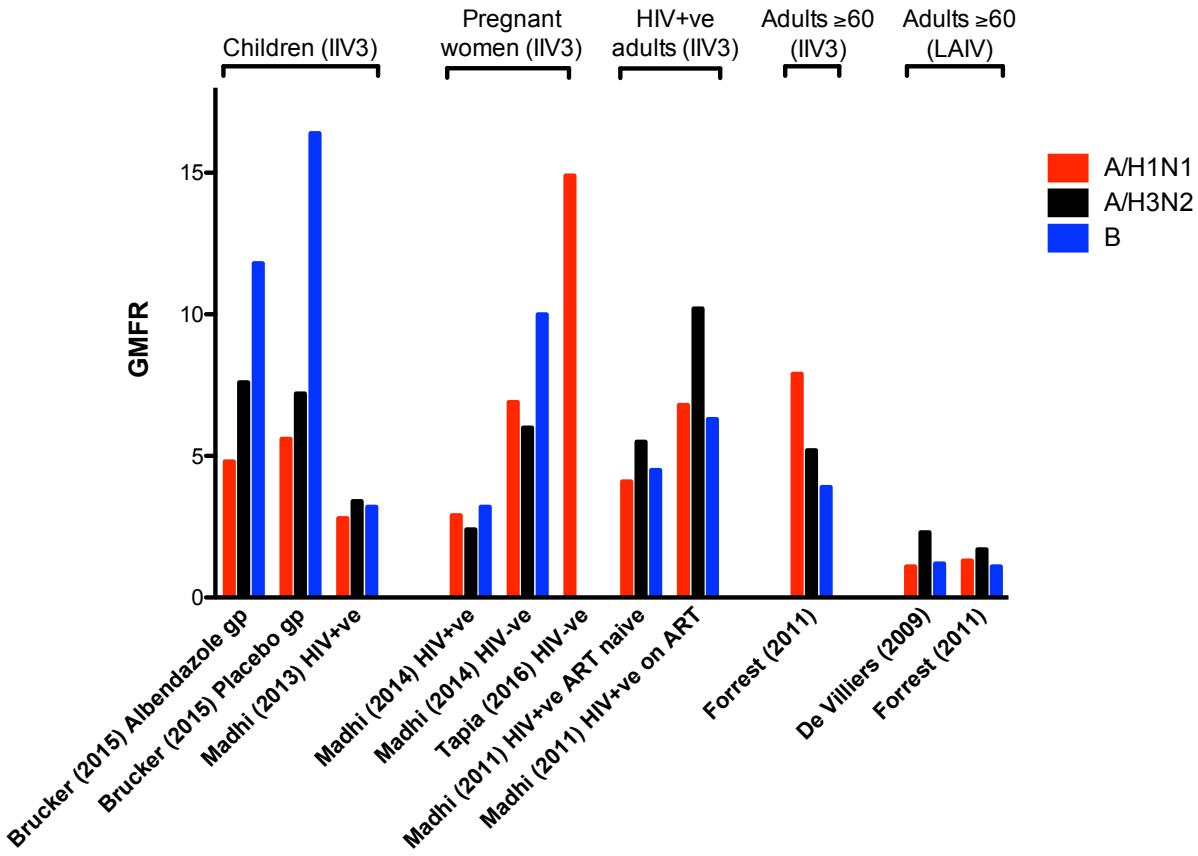


Figure 3: Summary of serum Haemagglutination Inhibition assay geometric mean fold rise following influenza vaccination in African populations. ART: Antiretroviral therapy. IIV3: Trivalent inactivated influenza vaccine. LAIV: Live attenuated influ-enza vaccine; HIV: Human immunodeficiency virus; GMFR: Geometric fold rise; gp: Group.

Country	South Africa: 16 Mali: 1 Kenya: 2 Gabon: 2 Senegal: 1 Gambia: 1
Study design	Randomised trial: 12 Case-control: 6 Cohort: 1 Other: 4
Study population	Maternal immunisation: 6 Elderly: 3 Children: 6 Other: 8
Vaccines	IIV3: 17 LAIV: 3 IIV3 & LAIV: 2 Monovalent inactivated: 1

Table 1 – Characteristics of included studies. IIV3: Trivalent inactivated influenza vaccine; LAIV: Live attenuated influenza vaccine