# The efficacy, effectiveness, and immunogenicity of influenza vaccines in Africa: a systematic review

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**The burden of influenza in Africa is substantial and underappreciated. Although surveillance has increased, the medical community's understanding of seasonal influenza vaccine performance remains limited. We did 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 database, and Web of Science for published studies from database inception to May 9, 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 Unpublished studies were identified by searching ClinicalTrials.gov and the Pan-African Clinical Trial Registry, and by contacting experts within the field.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 that reported influenza vaccine immunogenicity, effectiveness, and efficacy were included. 1746 articles were assessed and 23 articles were included. Only three of the 23 studies were of high quality and many studies were underpowered. All 23 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 supported influenza with limited data for severe outcomes. Several factors known to interfere with influenza immunisation, such as malaria, HIV, and malnutrition were under-represented in this Review and require further study. Substantial gaps exist in our understanding of influenza vaccine performance across all WHO high-risk groups in Africa. Filling these knowledge gaps is vital to guide future influenza vaccine policies.**

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## Introduction

The impact of influenza on African populations and health systems is underappreciated. Influenza causes approximately 300 000–650 000 deaths per year globally with the highest mortality in sub-Saharan Africa.[1] The estimated number of deaths varies greatly because of the annual fluctuation of viral transmission and disease severity, as well as the difficulties accurately estimating disease burden for the world. The per-capita influenza-associated hospitalisation rate in children younger than 5 years old is estimated to be 174 per 100 000 each year in Africa, compared with 53 per 100 000 each year in Europe.[2] Influenza surveillance in 15 African countries (2006–10) showed that the overall proportion of influenza positivity was 21·7% in influenza-like illness cases and 10·1% in severe acute respiratory infection.[3] A combination of poor nutrition and socioeconomic conditions, a higher prevalence of co-infections (eg, HIV, tuberculosis, and *Streptococcus pneumoniae*), and poor access to health care could contribute to seasonal influenza infections having a greater role in respiratory disease related morbidity and mortality in Africa than in high-income countries (HICs).[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, older people (≥65 years), 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 Morocco).[6] Although the reasons for why so few countries introduced vaccine policies are multifactorial (including health economics), an absence of knowledge regarding influenza vaccine performance exists in some African populations and no systematic review has been published to our knowledge to date. Previous examples, such as rotavirus and oral polio vaccines, show that efficacy and immunogenicity data from HICs are not always transferable to low-income 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 did a systematic review of the current medical literature to identify key gaps in the data for efficacy, effectiveness, and immunogenicity of influenza vaccines in African populations, and help shape future research priorities.

## Methods

### Search strategy and selection criteria

The study was done with use of PRISMA guidelines and registered with PROSPERO (CRD42017058107). Published articles were identified by searching Embase, MEDLINE, Global Health database, and Web of Science with use of the following search 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 the UN]). A full list of included countries is shown in the appendix. Databases were first searched on Jan 17, 2017, and an updated search was done on May 9, 2018, for publications since database inception. 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 that assessed influenza vaccine efficacy, effectiveness, or immunogenicity in populations within African countries were

See Online for appendix

For the **Pan-African Clinical Trial Registry** see https://pactr.samrc.ac.za

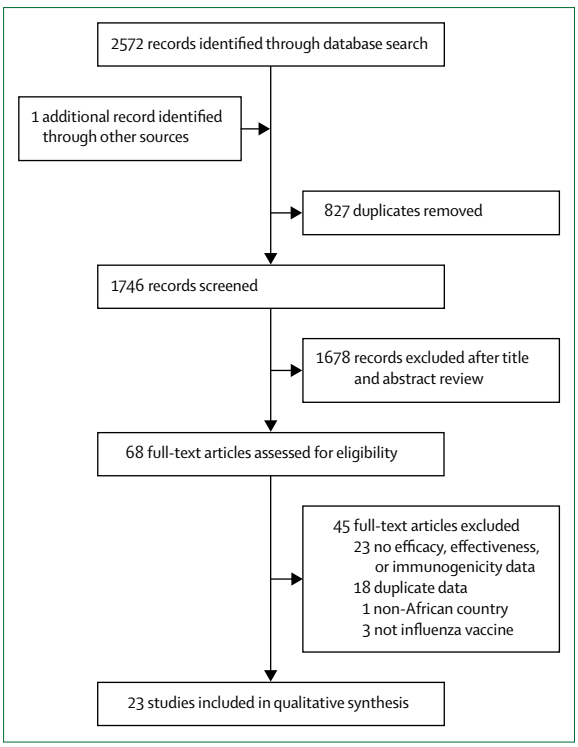


*Figure 1:* **Study selection process**

included. No studies were excluded on the basis of 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 the immune response to influenza vaccination. BBL and EPA did all of the following tasks independently: (1) titles and abstracts were screened for relevance; (2) full-text articles were reviewed against inclusion and exclusion criteria; (3) data from included trials were extracted (ie, population, design or methods, participant numbers, type of vaccine, and key findings [vaccine efficacy or effectiveness with CIs, or haemagglutination inhibition titres, or both); (4) data were inputed into a table created in Microsoft Word; (5) vaccine efficacy or effectiveness studies were grouped and evaluated as per WHO high-risk groups;[5] and (6) immunogenicity outcomes were summarised. We assessed the limitations and quality of each study using the Grading of Recommendations, Assessment, Development and Evaluations framework.[10] Discrepancies with data extraction and quality assessment were settled by discussion and consensus reached between all authors. A meta-analysis was to be done if more than two studies from the same WHO high-risk group[5] were identified sharing similar populations, interventions, comparisons, and outcomes. However, a meta-analysis was deemed unsuitable because of the low number of studies sharing the designated features.

## 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, 23 studies were excluded because of no efficacy, effectiveness, or immunogenicity data, 18 because of duplicate data, one because data was from a non-African country, and three because of no influenza vaccine usage. 23 studies were included (appendix).[11–33]

Studies varied by study design, vaccine type (trivalent inactivated influenza vaccine [IIV3]; live attenuated influenza vaccine, [LAIV]), and study population (panel). 16 of 23 studies were from South Africa,[11–14,16–19,23,25,27–32] two studies were from Gabon,[21,22] two studies were from Kenya,[20,26] and one study was included each from Mali,[15] Senegal,[24] and The Gambia.[33] The study populations identified in the 23 studies included six in pregnant women, six in children, three in older people, one in adults who are HIV-positive, one in health-care workers, and six in all age groups. Study designs included 12 RCTs, six case-control studies, and one cohort study. 17 studies used IIV3, three used LAIV, two used both IIV3 and LAIV, and one used a monovalent inactivated pandemic H1N1 vaccine. 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.

### 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 African RCT[12–14] and one study reporting a secondary analysis from both RCTs (appendix).[31] A single centre, randomised, double-blind, placebo-controlled trial including pregnant women with and without HIV (60% on highly active antiretroviral therapy at enrolment, median CD4 count 393·5 cells per μL) was done in South Africa.[11] The attack rate of influenza in placebo recipients with HIV was higher than in placebo recipients without HIV (17·0% *vs* 3·5%). The per protocol vaccine efficacy against all RT-PCR-confirmed symptomatic influenza was 54·4% (95% CI 19·5–74·2; p=0·005) for women not infected with HIV and 70·6% (23·0–88·8; p=0·02) for women infected with HIV. Infants born to women not infected with HIV had a per protocol vaccine efficacy against RT-PCR-confirmed symptomatic infection of 45·6% (95% CI 2·4 to 69·7; p=0·04) at 6 months of age compared with 42·3% (–96·9 to 83·1, p=0·52) in infants exposed to HIV. No effect of vaccination on birthweight, clinical febrile illness, or influenza-like illness was seen, although the study was not powered for these outcomes.

An extended follow-up study[12] of women not infected with HIV did not show 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 infants not exposed to HIV showed that vaccine efficacy against RT-PCR-confirmed symptomatic influenza was 53·9% (95% CI 10·4–77·4; p=0·02) at less than and up to 16 weeks of age, with no significant protection at 16–24 weeks.[13] A further analysis of the infants not exposed to HIV showed that maternal immunisation reduced hospital admissions for all-cause acute lower respiratory infection 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% (0–67; p=0·05).[31]

Results from a multicentre, active-controlled, observer-blind RCT in pregnant women not infected with HIV done 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% (28·0–89·1) in the 6 month postpartum 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 4 months, decreasing to 37·3% (7·6–57·8) by 6 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 to 19; p=0·39).[31]

### Influenza vaccination in children

Four studies were identified, including three that reported efficacy and one that reported effectiveness of influenza vaccination in children (appendix).[19,20,23,24] A multicentre, double-blind, placebo-controlled RCT in healthy children aged from 6 to 36 months from South Africa, Brazil, and Argentina[23] investigated the efficacy of LAIV (Ann-Arbor backbone; MedImmune, Gaithersburg, MD, USA). Data from the South African participants (n=277) was obtained via personal communication with authors of a meta-analysis assessing country-stratified data (Ambrose C, AstraZeneca, Washington DC, USA, personal communication).[34] These data generated an efficacy estimate for two LAIV doses of 87% (95% CI 64–95) for prevention of culture-supported symptomatic influenza in South Africa. No country-stratified demographic data are available on factors such as nutritional status or ethnicity, which might 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, Pune, India) among healthy children in Senegal aged 2–5 years was reported in 2016.[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 to 20·9) for all influenza strains and –6·1% (–50·0 to 25·0) for all vaccine-matched strains (78·2% were pdm09H1N1) against RT-PCR-confirmed symptomatic influenza. The overall attack rate was 18% and the vaccine-matched strain attack rate was 8–9%. Most vaccine-unmatched isolates were influenza B (Victoria lineage) viruses. The absence of immunogenicity measurements to investigate the absence of efficacy observed was a major limitation of this study.

Madhi and colleagues[19] did a randomised, double-blind trial comparing two doses of IIV3 with placebo in children with HIV aged from 6 to 59 months in South Africa. The per protocol vaccine efficacy (culture or RT-PCR-confirmed or both symptomatic influenza) was not significantly different from placebo at 24·7% (95% CI –64·7 to 66·4). This absence of significant difference could, in part, be explained by the antigenic drift observed in the dominant circulating H3N2 strain. Although the absence of efficacy could be explained by poor IIV3 immunogenicity in a population with HIV, the study was also underpowered. The required sample size of 420 to detect a 50% or more 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

***Panel*: Characteristics of included studies**

**Country**
- South Africa: 16
- Mali: 1
- Kenya: 2
- Gabon: 2
- Senegal: 1
- The Gambia: 1

**Study design**
- Randomised trial: 12
- Case-control: 6
- Cohort: 1
- Other: 4

**Study population**
- Maternal immunisation: 6
- Older people: 3
- Children: 6
- Other: 8

**Vaccines**
- Trivalent inactivated influenza vaccine: 17
- Live attenuated influenza vaccine: 3
- Trivalent inactivated influenza vaccine and live attenuated influenza vaccine: 2
- Monovalent inactivated: 1

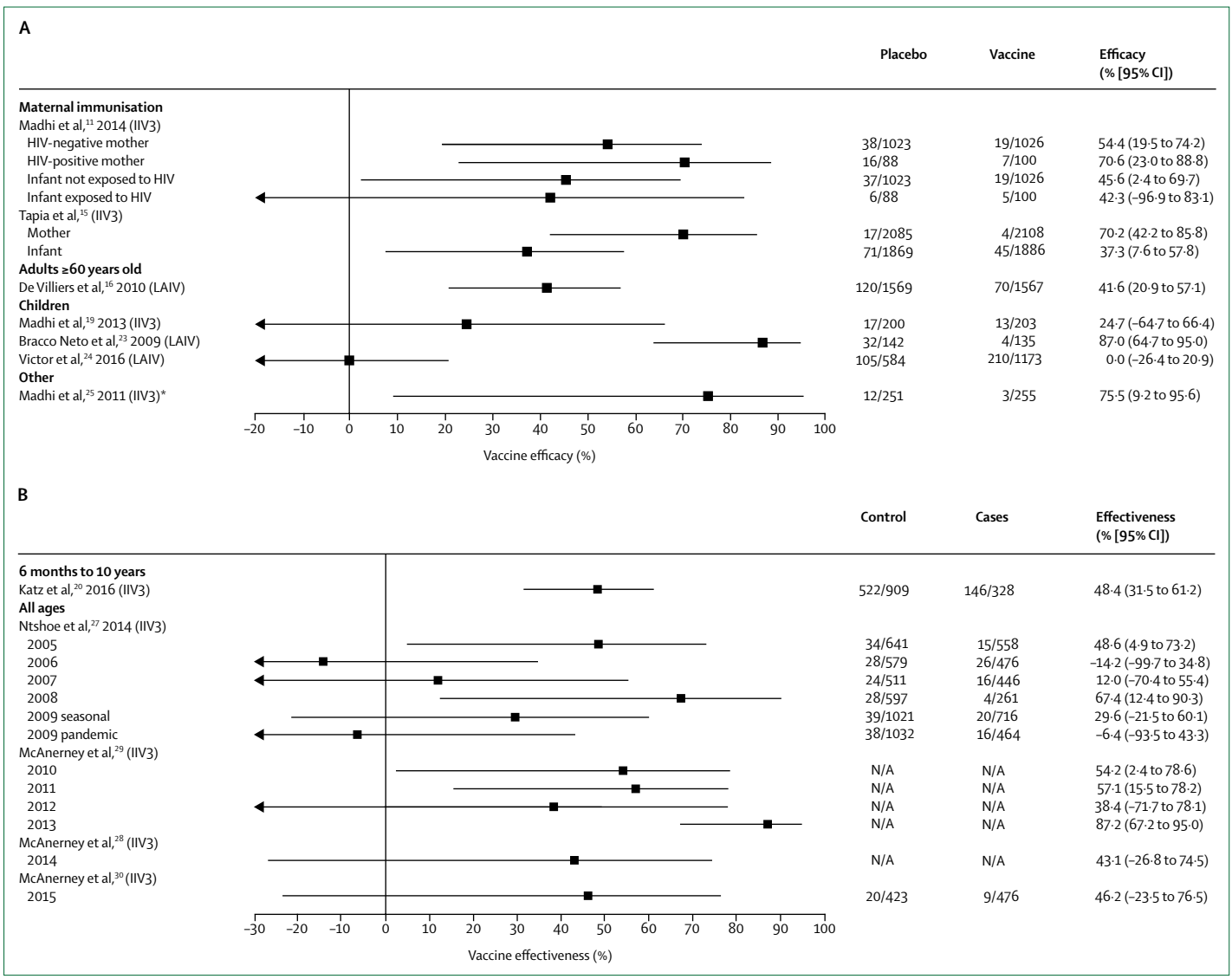


***Figure 2*: Forest plot of influenza vaccine efficacy (A) and effectiveness (B)**
Data are n/N. IIV3=trivalent inactivated influenza vaccine. LAIV=live attenuated influenza vaccine. N/A=not available. *Vaccine efficacy estimates are per protocol with the exception of Madhi and colleagues,[25] which reports intention to treat.

case-control study in Kenya.[20] The study was undertaken during a 3-year period in which the Kenya Medical Research Institute, Centers for Disease Control-Kenya, and the Kenyan Ministry of Health offered free influenza vaccines to children in two low-income rural and urban settings. Approximately 35% of all eligible children were vaccinated (two doses of IIV3 if aged less than 9 years). Patients attending with symptoms meeting predefined acute lower respiratory infection or influenza-like illness criteria were tested for influenza with use of 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% (24·9–66·9) in children aged from 6 months to up to 5 years and 46·2% (19·2–64·2) in children aged from 5 years to up to 10 years. The main limitations of the study are those inherent in the test-negative case-control design, which include possible differences between individuals seeking health care for acute lower respiratory infection or influenza-like illness and the general population. HIV testing was not routinely done. 11 (1%) of 1237 participants were known to have HIV, with overall adult HIV prevalence at 17% in the rural setting and 14% in the urban setting. Only medically attended cases of acute lower respiratory infection or influenza-like illness 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 older people

Three studies have assessed the efficacy or effectiveness of influenza vaccines in older adults, all done in South Africa (appendix).[16–18] The two randomised trials[16,17] were done in community-dwelling ambulatory adults aged 60 years and over, in which approximately 70% of participants were white. Both trials included the use of LAIV, which is unlicensed for adults aged over 49 years in the USA, and thought to be less effective than IIV3 among older adults based on observational data.[16] A randomised, double-blind, placebo-controlled study[16] showed LAIV efficacy against culture-confirmed symp-tomatic influenza of 42·3% (95% CI 21·6–57·8), with 52·5% (32·1–67·2) efficacy against influenza A virus subtype H3N2 strains, and no efficacy against influenza B strains (–10·1%, –113·0 to 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 influenza A virus subtype H3N2 (figure 3). Vaccine efficacy was not significantly different between participants aged 60–69 years and those over 70 years old.

A randomised, open-label trial compared the relative efficacy of IIV3 and LAIV in adults aged 60 years and over[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 of the study. The incidence of influenza was much lower than expected at 0·9% in the LAIV group and 1·5% in the IIV3 group. As such, the study was substantially underpowered and no robust conclusions were possible.

Finally, a retrospective, nested, case-control study in adults aged 65 years and over 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 individual presenting with any of the primary endpoints was matched (by case of influenza identification date) to four randomly chosen controls from the same cohort, and vaccination status was ascertained from health records to calculate vaccine effectiveness. After adjustment for various confounders (eg, comorbidities, age, sex), influenza vaccination was associated with a 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% (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.

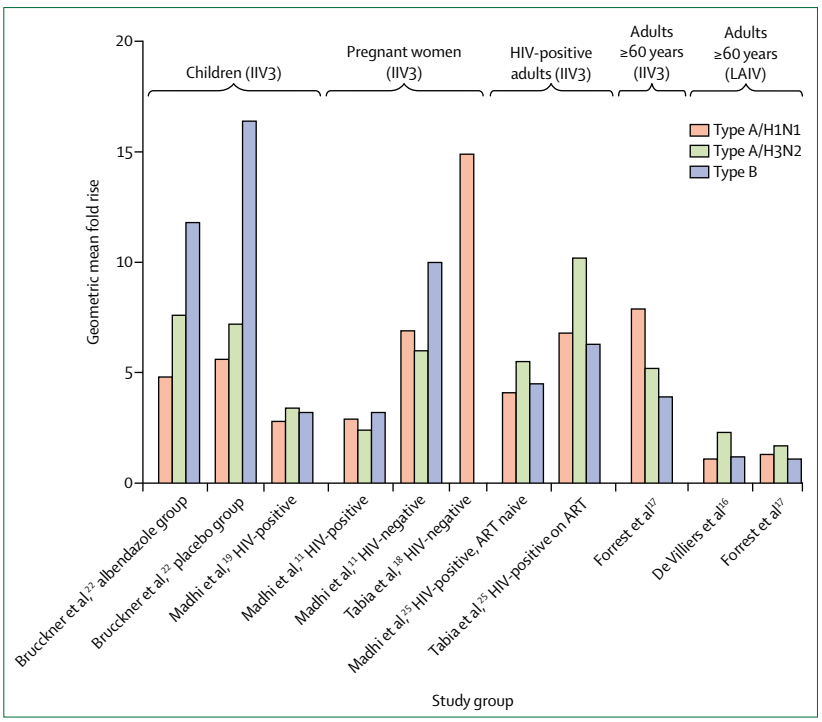


***Figure 3:*** **Summary of serum haemagglutination inhibition assay geometric mean fold rise following influenza vaccination in African populations**
ART=antiretroviral therapy. IIV3=trivalent inactivated influenza vaccine. LAIV=live attenuated influenza vaccine.

### Influenza vaccination in other populations

#### *Adults with HIV*

In addition to the studies above including people with HIV, a double-blind, randomised, single centre, placebo-controlled trial of IIV3 in adults with HIV aged 18–55 years was done in South Africa (appendix).[25] Participants had either been on first-line antiretroviral therapy for 3 months or more or were antiretroviral therapy-naive with a CD4 count of more than 100 cells per µL. Vaccine efficacy (against culture or RT-PCR-confirmed symptomatic influenza) was 75·5% (95% CI 9·2 to 95·6) for all strains and a non-significant 73·3% (–1·2 to 95·2) for vaccine-matched strains. No significant reductions in influenza-like illness or acute respiratory infection were 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 group. Only 255 participants were recruited to the IIV3 group and 251 participants were recruited to the placebo group, with only 5% of placebo recipients developing influenza.

#### *Health-care personnel*

A prospective cohort study was done in health-care personnel across five Kenyan hospitals (appendix).[26]

Participants were asked about vaccination status during a monovalent pdm09H1N1 influenza vaccination campaign. The study controlled for month of follow-up, sex, age, hospital location, and number of patient contacts per day. The study did not find an association between vaccination and reduced incidence of acute respiratory illness, work days missed, or RT-PCR-confirmed influenza. As only two of 531 specimens tested detected pdm09H1N1, low circulating amounts of pdm09H1N1 could 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 (appendix).[27–30] All studies originated from the same research team, using a network of general practitioners based in all provinces of South Africa (around 90% within private health-care centres). Patients presenting with an influenza-like illness had a throat or nasal swab, or both, tested for influenza by viral culture or RT-PCR. Patients who were influenza-positive were classified as cases and patients who were influenza-negative were classified as unmatched controls. The first study estimated vaccine effectiveness between 2005 and 2009.[27] Age-adjusted effectiveness was 48·6% (95% CI 4·9 to 73·2) in 2005, –14·2% (–9·7 to 34·8) in 2006, 12·0% (–70·4 to 55·4) in 2007, 67·4% (12·4–90·3) in 2008, and 29·6% (–21·5 to 60·1) in 2009. Details of vaccine and circulating strain match are shown in the appendix. The authors adjusted for age but no additional confounders. During 2009, the number of samples that each sentinel site could send was limited to five per week because of limited laboratory testing capacity. Sample selection was at the practitioner's discretion, which could have introduced selection bias. McAnerney and colleagues[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 to 78·6) in 2010, 57·1% (15·5 to 78·2) in 2011, 38·4% (–71·7 to 78·1) in 2012, and 87·2% (67·2 to 95·0) in 2013. The vaccine effectiveness adjusting for age, underlying medical conditions, and seasonality was 43·1% (95% CI –26·8 to 74·5) in 2014[28] and 46·2% (–23·5 to 76·5) in 2015.[30]

The years of poor vaccine effectiveness were mainly related to antigenic drift resulting in vaccine and circulating strain mismatch, although the small sample size in some years might 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 in which less than 20% of the South African population seek health care, the generalisability of these findings might be limited.

## Studies assessing immunogenicity of influenza vaccines

12 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] That HAI titres are considered a gold standard is, however, primarily true following IIV3 and not LAIV (which does not induce potent serum HAI responses), and when a clear correlate of protection is not yet established. Figure 3 shows geometric mean fold rise following vaccination for studies where this was reported or could be calculated.

Two studies evaluated IIV3 immunogenicity during pregnancy.[11,15] Pregnant women in South Africa mounted robust HAI titres following vaccination to all strains (see appendix; figure 3). In Mali, only HAI responses to pdm09H1N1 (in women who are HIV-negative) were reported, which were higher than the responses seen to pdm09H1N1 in South African women who are HIV-negative (geometric mean fold rise: 14·9 *vs* 6·9). The mean age at enrolment was similar in the two studies (24·7 years *vs* 26·2 years), but gestational age at enrolment was higher in Mali than in South Africa (32·6 weeks *vs* 26·8 weeks). Prevaccination geometric mean titres to pdm09H1N1 were 30·0 in South Africa and 20·9 in Mali. The reasons for this difference are 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, children not exposed to HIV had higher HAI geometric mean titres than children exposed to HIV to pdm09H1N1 (87·2 *vs* 48·2), H3N2 (41·4 *vs* 32·4), and influenza B (86·7 *vs* 50·0) at 7 days or more after birth. Both groups had significantly higher titres than placebo recipients. Follow-up of the children not exposed to HIV in the first 6 months of life[13] showed rapid waning of HAI geometric mean titres to all antigens, with the proportion of children with HAI of 1/40 or more dropping from 78·3% to 39·5% (pdm09H1N1), 56·6% to 19·1% (H3N2), and 40·0% to 81·1% (influenza B) from birth to 16 weeks. Similar observations were found in Mali,[15] where children not exposed to HIV had HAI geometric mean titres to pdm09H1N1 of 141·6 at birth, 39·0 at 2–3 months, and 33·7 at 4–5 months of age.

The effect 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 children from rural areas. The presence of helminths was associated with poorer immunogenicity. A follow-up study[22] did not 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 older adults from South Africa were low, in keeping with previous

studies (figure 3).[16,17] HAI responses to IIV3 were lower in individuals aged 70 years or over compared with individuals aged 60–69 years.[17] The effect of HIV infection on IIV3 immunogenicity in both adults and children in South Africa has been explored in three studies.[11,19,25] HAI titre geometric mean fold rise in pregnant women who are HIV-positive was less than 50% of the geometric mean fold rise seen in pregnant women who are HIV-negative (2·9 *vs* 6·9 for pdm09H1N1, 2·4 *vs* 6·0 for H3N2, and 3·2 *vs* 10·0 for influenza B; figure 3). Adults on antiretroviral therapy had significantly higher seroconversion rates to all antigens than patients who are antiretroviral therapy-naive (figure 3). Children with HIV aged 6–35 months had significantly lower seroconversion rates than children with HIV 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 more than 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).

## Discussion

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 on the basis of limitations in methodological design to provide a complete picture of the available data. Because of the heterogeneity in study design, age group, and vaccine type, a meta-analysis of these data is not possible. Several RCTs were underpowered, because of 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 prevent underpowered studies based on inaccurate influenza attack rates, as well as a means to calculate vaccine effectiveness following influenza vaccine roll-out.

Other reasons why several studies did not 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 because of 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 effect of time of vaccination and influenza seasonality on vaccine performance. By contrast with temperate climates, countries in Africa have year-round transmission or show 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 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 affect influenza vaccine performance were under-represented. Placental malaria infection and maternal hypergammaglobulinaemia are known to affect placental antibody transfer[9] and the effect of these conditions on maternal immunisation strategies should be studied. Factors such as HIV, malnutrition, and tuberculosis also require further study to understand their effects on influenza vaccination. Although it is difficult to draw firm conclusions about the relative effectiveness of influenza vaccines in HICs and LMICs from the data currently available, the most comprehensive effectiveness data from South Africa[27–30] shows a similar range when compared with effectiveness data from the USA 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 done in South Africa. Even within these studies, several were done in groups that might 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. Although some studies that we identified measured serum HAI to assess IIV3 immunogenicity, LAIV studies should include measures of mucosal antibody and systemic T-cell responses as LAIV is likely to protect 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-supported 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 investment by Gavi, the Vaccine Alliance.[41] The reduction in all-cause acute lower respiratory infection and severe infant pneumonia following maternal immunisation 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 strikingly contrasting results.[23,24]

It is possible that the 2016 absence of efficacy seen in Senegal 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 with IIV3 in previous studies.[43,44] Furthermore, lower manufacturing costs compared with IIV3 (partly as less antigen is required therefore allowing more doses per egg), and less need for trained health-care personnel to deliver an intranasal vaccine make LAIV particularly suitable in Africa. The potential for successful LAIV roll-out to provide indirect benefit by reducing transmission to unvaccinated susceptible populations (shown recently in the 2013–14 season in the UK)[45] should also be assessed. Data are also not available for how best to immunise children aged from 6 months to 2 years, an age group that responds poorly to IIV3 and is not licensed for LAIV use. The results are awaited of a safety and immunogenicity study comparing MF59-adjuvanted IIV3 with standard IIV3 in Senegalese children aged from 6 months to 71 months (NCT01819155).

The absence of any robust IIV3 efficacy data in older people is striking. Even in HICs, standard IIV3s are only modestly immunogenic because of immunosenescence.[46] Immunosenescense refers to a reduction in immune responses to new antigens in older individuals relative to younger adults. 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 therefore, they should be the focus of future studies in older populations. With the increasing burden of cardiovascular disease in LMICs, 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 (NCT02762851) aims to include adults aged 18 years or over from several African sites with study completion estimated in 2020. Another benefit of influenza vaccination could be a reduction of pneumococcal pneumonia. The importance of influenza in the pathogenesis of pneumococcal pneumonia was shown by the reduction of virus-associated pneumonia in an RCT of pneumococcal conjugate vaccine in South African children.[49] Furthermore, the reduction in all-cause infant acute lower respiratory infection following maternal immunisation, despite negligible influenza detection in placebo recipients, supports the effect of influenza vaccination for reducing bacterial pneumonia.[14] An RCT of combined influenza vaccine and pneumococcal conjugate vaccine in several high-risk groups would be valuable, especially in the context of an increase in pneumoccocal disease from serotypes (strains) not included in pneumoccal vaccines. If influenza vaccination reduced pneumoccocal disease, it would be of added benefit to tackle the burden that current pneumococcal vaccines do not.

The lower immunogenicity of IIV3 in patients with HIV in HICs is also reflected in the few studies from Africa; although, because of the increased susceptibility to influenza in these individuals, the benefits of vaccination are greater. Because individuals treated with antiretroviral therapy mount higher immune responses to IIV3 than patients who are not taking antiretroviral therapy, increasing roll-out of this therapy 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 individuals with HIV in Uganda (NCT01916759) that could provide mechanistic insight into how best to enhance immunogenicity. 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 shown the efficacy of IIV3 in reducing influenza in pregnant women and their infants, although for the infant group, vaccine efficacy was only significant in infants not exposed to HIV. Protection for infants via maternal immunisation is especially important given the high influenza-related morbidity and mortality in infants younger than 6 months,[50] and the absence of a licensed vaccine in this age group. Nevertheless, both serum HAI and efficacy waned rapidly by 4 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 2017 analysis in Mali showed that such a programme would be cost-effective in most settings if vaccine can be obtained, managed, and administered for US$1·00 or less per pregnant woman.[51] Ideally, health economic analyses should take into account a wider range of potential benefits, including effect on bacterial pneumonia, indirect benefits due to reduced transmission, and effect 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 striking public health benefit. Finally, as countries in Africa establish influenza immunisation programmes, it is essential that this is done alongside increased capacity for influenza surveillance, so ongoing vaccine effectiveness can be monitored over time.

**Contributors**

TIdS proposed the study concept. BBL and TIdS generated the protocol and search strategy. BBL did the search. BBL, EPA, and TIdS did the study selection. BBL and EPA extracted data and did the quality

assessment. BBL, EPA, TIdS, and BK did the data interpretation and synthesis. BK and TIdS supervised the study. All authors wrote the manuscript and approved the final version for submission.

#### Declaration of interests

We declare no competing interests.

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#### References

1 Iuliano AD, Roguski KM, Chang HH, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2018; **391:** 1285–300.

2 Lafond KE, Nair H, Rasooly MH, et al. Global role and burden of influenza in pediatric respiratory hospitalizations, 1982–2012: a systematic analysis. *PLoS Med* 2016; **13:** e1001977.

3 Radin JM, Katz MA, Tempia S, et al. Influenza surveillance in 15 countries in Africa, 2006–2010. *J Infect Dis* 2012; **206** (suppl 1)**:** S14–21.

4 Schoub BD, Gessner BD, Ampofo W, Cohen AL, Steffen CA. Afriflu2—second international workshop on influenza vaccination in the African continent—8 November 2012, Cape Town (South Africa). *Vaccine* 2013; **31:** 3461–66.

5 Meeting of the Strategic Advisory Group of Experts on immunization, April 2012—conclusions and recommendations. *Wkly Epidemiol Rec* 2012; **87:** 201–16.

6 Ortiz JR, Perut M, Dumolard L, et al. A global review of national influenza immunization policies: analysis of the 2014 WHO/UNICEF Joint Reporting Form on immunization. *Vaccine* 2016; **34:** 5400–05.

7 Kirkpatrick BD, Colgate ER, Mychaleckyj JC, et al. The "Performance of Rotavirus and Oral Polio Vaccines in Developing Countries" (PROVIDE) study: description of methods of an interventional study designed to explore complex biologic problems. *Am J Trop Med Hyg* 2015; **92:** 744–51.

8 Bloom-Feshbach K, Alonso WJ, Charu V, et al. Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. *PLoS One* 2013; **8:** e54445.

9 Okoko BJ, Wesumperuma LH, Ota MO, et al. The influence of placental malaria infection and maternal hypergammaglobulinemia on transplacental transfer of antibodies and IgG subclasses in a rural West African population. *J Infect Dis* 2001; **184:** 627–32.

10 Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; **64:** 383–94.

11 Madhi SA, Cutland CL, Kuwanda L, et al. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med* 2014; **371:** 918–31.

12 Mutsaerts E, Madhi SA, Cutland CL, et al. Influenza vaccination of pregnant women protects them over two consecutive influenza seasons in a randomized controlled trial. *Expert Rev Vaccines* 2016; **15:** 1055–62.

13 Nunes MC, Cutland CL, Jones S, et al. Duration of infant protection against influenza illness conferred by maternal immunization: secondary analysis of a randomized clinical trial. *JAMA Pediatr* 2016; **170:** 840–47.

14 Nunes MC, Cutland CL, Jones S, et al. Efficacy of maternal influenza vaccination against all-cause lower respiratory tract infection hospitalizations in young infants: results from a randomized controlled trial. *Clin Infect Dis* 2017; **65:** 1066–71.

15 Tapia MD, Sow SO, Tamboura B, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. *Lancet Infect Dis* 2016; **16:** 1026–35.

16 De Villiers PJ, Steele AD, Hiemstra LA, et al. Efficacy and safety of a live attenuated influenza vaccine in adults 60 years of age and older. *Vaccine* 2009; **28:** 228–34.

17 Forrest BD, Steele AD, Hiemstra L, Rappaport R, Ambrose CS, Gruber WC. A prospective, randomized, open-label trial comparing the safety and efficacy of trivalent live attenuated and inactivated influenza vaccines in adults 60 years of age and older. *Vaccine* 2011; **29:** 3633–39.

18 van Vuuren A, Rheeder P, Hak E. Effectiveness of influenza vaccination in the elderly in South Africa. *Epidemiol Infect* 2009; **137:** 994–1002.

19 Madhi SA, Dittmer S, Kuwanda L, et al. Efficacy and immunogenicity of influenza vaccine in HIV-infected children: a randomized, double-blind, placebo controlled trial. *AIDS* 2013; **27:** 369–79.

20 Katz MA, Lebo E, Emukule GO, et al. Uptake and effectiveness of a trivalent inactivated influenza vaccine in children in urban and rural Kenya, 2010 to 2012. *Pediatr Infect Dis J* 2016; **35:** 322–29.

21 van Riet E, Adegnika AA, Retra K, et al. Cellular and humoral responses to influenza in Gabonese children living in rural and semi-urban areas. *J Infect Dis* 2007; **196:** 1671–78.

22 Bruckner S, Agnandji ST, Berberich S, et al. Effect of antihelminthic treatment on vaccine immunogenicity to a seasonal influenza vaccine in primary school children in Gabon: a randomized placebo-controlled trial. *PLoS Negl Trop Dis* 2015; **9:** e0003768.

23 Bracco Neto H, Farhat CK, Tregnaghi MW, et al. Efficacy and safety of 1 and 2 doses of live attenuated influenza vaccine in vaccine-naive children. *Pediatr Infect Dis J* 2009; **28:** 365–71.

24 Victor JC, Lewis KD, Diallo A, et al. Efficacy of a Russian-backbone live attenuated influenza vaccine among children in Senegal: a randomised, double-blind, placebo-controlled trial. *Lancet Glob Health* 2016; **4:** e955–65.

25 Madhi SA, Maskew M, Koen A, et al. Trivalent inactivated influenza vaccine in African adults infected with human immunodeficient virus: double blind, randomized clinical trial of efficacy, immunogenicity, and safety. *Clin Infect Dis* 2011; **52:** 128–37.

26 Njuguna H, Ahmed J, Oria PA, et al. Uptake and effectiveness of monovalent influenza A (H1N1) pandemic 2009 vaccine among healthcare personnel in Kenya, 2010. *Vaccine* 2013; **31:** 4662–67.

27 Ntshoe GM, McAnerney JM, Tempia S, et al. Influenza epidemiology and vaccine effectiveness among patients with influenza-like illness, viral watch sentinel sites, South Africa, 2005–2009. *PLoS One* 2014; **9:** e94681.

28 McAnerney JM, Treurnicht F, Walaza S, et al. Evaluation of influenza vaccine effectiveness and description of circulating strains in outpatient settings in South Africa, 2014. *Influenza Other Respir Viruses* 2015; **9:** 209–15.

29 McAnerney JM, Walaza S, Cohen AL, et al. Effectiveness and knowledge, attitudes and practices of seasonal influenza vaccine in primary healthcare settings in South Africa, 2010–2013. *Influenza Other Respir Viruses* 2015; **9:** 143–50.

30 McAnerney JM, Walaza S, Tempia S, et al. Estimating vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings in South Africa, 2015. *Influenza Other Respir Viruses* 2017; **11:** 177–81.

31 Omer SB, Clark DR, Aqil AR, et al. Maternal influenza immunization and prevention of severe clinical pneumonia in young infants: analysis of randomized controlled trials conducted in Nepal, Mali and South Africa. *Pediatr Infect Dis J* 2018; **37:** 436–40.

32 Delem A, Van Rensburg W, Flaskett I. Comparison of the protective efficacies of the live vaccine RIT 4025 and an inactivated vaccine against a natural heterologous A/Victoria/3/75 infection. *J Hyg (Lond)* 1979; **83:** 221–29.

33 Darboe A, Danso E, Clarke E, et al. Enhancement of cytokine-driven NK cell IFN-gamma production after vaccination of HCMV infected Africans. *Eur J Immunol* 2017; **47:** 1040–50.

34 Ambrose CS, Wu X, Knuf M, Wutzler P. The efficacy of intranasal live attenuated influenza vaccine in children 2 through 17 years of age: a meta-analysis of 8 randomized controlled studies. *Vaccine* 2012; **30:** 886–92.

35 Trombetta CM, Montomoli E. Influenza immunology evaluation and correlates of protection: a focus on vaccines. *Expert Rev Vaccines* 2016; **15:** 967–76.

36 Tamerius JD, Shaman J, Alonso WJ, et al. Environmental predictors of seasonal influenza epidemics across temperate and tropical climates. *PLoS Pathog* 2013; **9:** e1003194.

37 Gessner BD, Shindo N, Briand S. Seasonal influenza epidemiology in sub-Saharan Africa: a systematic review. *Lancet Infect Dis* 2011; **11:** 223–35.

38 Xu C, Thompson MG, Cowling BJ. Influenza vaccination in tropical and subtropical areas. *Lancet Respir Med* 2017; **5:** 920–22.

39 Centers for Disease Control and Prevention. Seasonal Influenza Vaccine Effectiveness, 2005–2018. 2018. https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm (accessed Jun 10, 2018).

40 Neuzil KM, Bresee JS, de la Hoz F, et al. Data and product needs for influenza immunization programs in low- and middle-income countries: rationale and main conclusions of the WHO preferred product characteristics for next-generation influenza vaccines. *Vaccine* 2017; **35:** 5734–37.

41 Gavi, the vaccine alliance. Vaccine investment strategy 2017. https://www.gavi.org/about/strategy/vaccine-investment-strategy/ (accessed May 21, 2018).

42 Caspard H, Gaglani M, Clipper L, et al. Effectiveness of live attenuated influenza vaccine and inactivated influenza vaccine in children 2–17 years of age in 2013–2014 in the United States. *Vaccine* 2016; **34:** 77–82.

43 Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med* 2007; **356:** 685–96.

44 Rhorer J, Ambrose CS, Dickinson S, et al. Efficacy of live attenuated influenza vaccine in children: a meta-analysis of nine randomized clinical trials. *Vaccine* 2009; **27:** 1101–10.

45 Pebody RG, Green HK, Andrews N, et al. Uptake and impact of a new live attenuated influenza vaccine programme in England: early results of a pilot in primary school-age children, 2013/14 influenza season. *Euro Surveill* 2014; **19:** 20823.

46 Rumke HC, Richardus JH, Rombo L, et al. Selection of an adjuvant for seasonal influenza vaccine in elderly people: modelling immunogenicity from a randomized trial. *BMC Infect Dis* 2013; **13:** 348.

47 Domnich A, Arata L, Amicizia D, Puig-Barbera J, Gasparini R, Panatto D. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: a systematic review and meta-analysis. *Vaccine* 2017; **35:** 513–20.

48 Wilkinson K, Wei Y, Szwajcer A, et al. Efficacy and safety of high-dose influenza vaccine in elderly adults: a systematic review and meta-analysis. *Vaccine* 2017; **35:** 2775–80.

49 Madhi SA, Klugman KP. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. *Nat Med* 2004; **10:** 811–13.

50 Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000; **342:** 225–31.

51 Orenstein EW, Orenstein LA, Diarra K, et al. Cost-effectiveness of maternal influenza immunization in Bamako, Mali: a decision analysis. *PLoS One* 2017; **12:** e0171499.

52 Knight GM, Clarkson M, de Silva TI. Potential impact of influenza vaccine roll-out on antibiotic use in Africa. *J Antimicrob Chemother* 2018; **73:** 2197–200.