SYSTEMATIC REVIEW

Serological Surveys for complementing assessments of vaccination coverage in sub-Saharan Africa: A systematic review [version 1; peer review: 3 approved with reservations]

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Abstract

Background: Serosurveys of biomarkers of infection/vaccination are widely used for evaluating vaccine-induced immunity and monitoring the effectiveness of immunisation programmes in developed countries. In sub-Saharan Africa (sSA) where vaccination coverage (VC) estimates are often incomplete, inaccurate and overestimate effective population immunity, the use of serosurveys is limited.
Methods: We conducted a review of the use of serosurveys to assess/complement assessments of VC in sSA by searching electronic databases (PubMed, Embase, Web of Science, Popline, Ovid and Africa Wide Information) for English language articles published from 1st January 1940 to 31st January 2017. We also searched the references of retrieved articles. SSA was defined as all of Africa excluding the countries in North Africa. We included only articles that measured VC and assessed the quality of these studies using the Newcastle-Ottawa Scale.
Results: We found 1056 unique records, reviewed 20 eligible studies of which just 12 met our inclusion criteria. These 12 studies were serosurveys of measles, tetanus, polio and yellow fever. Antibodies induced by natural infection confounded serological test results and there was significant discordance between vaccination history and the presence of antibodies in all except for tetanus vaccine. No study looked at Hepatitis B.
Conclusions: Serosurveys for tetanus or tetanus containing vaccines may be directly useful for ascertainment of vaccination exposure or reliably complement current survey methods that measure VC. Given the limited experience in using serosurveys for this purpose in sSA, well-designed serosurveys of tetanus and possibly hepatitis B are required to further validate/evaluate their performance.

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Keywords
Serosurveys, Serological surveys, crude vaccination coverage, effective vaccination coverage, sub-Saharan Africa

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Introduction

Serological surveys (serosurveys) provide invaluable insight into the natural history and epidemiology of infection and can be used to: assess the effectiveness of vaccine campaigns, determine proximity to theoretical thresholds for disease elimination, estimate the burden of disease for immunising and/or chronic infections, and identify gaps in population immunity to inform interventions such as supplementary immunisation activities[1–4]. As a tool in seroepidemiology, serosurveys have been a significant component of disease control and elimination strategies for acute viral vaccine preventable disease (VPDs) like measles, rubella, and polio in high-income countries. They have also been used to demonstrate the continued effectiveness of vaccination programmes[5], and to guide revisions/adjustments to vaccination strategies for pertussis, diphtheria and *Haemophillus influenza* B (Hib)[6–8].

Despite some of the well-known limitations of serological surveys, it is believed they can play a role in improving the accuracy of estimates of vaccination coverage (VC), or be used independently to assess VC particularly in developing countries[9]. Receipt of the third dose of the combined diphtheria, tetanus and pertussis vaccine (DPT3) assessed at 1 year of age is currently the most widely used proxy for childhood vaccination coverage worldwide[10]. VC is also an indicator of health care delivery, a performance metric for national immunisation programmes, and a global health target indicator. It is typically obtained from administrative records (health facility registers and vaccine doses consumed) or household surveys of retained immunisation cards and/or caregiver recall of childhood vaccination history. These methods have well known limitations that frequently result in over- or underestimates of VC[9]. Since receipt of a vaccine does not always induce protective immunity, these methods report a crude VC, and there is frequently a gap between crude (beyond those related to the intrinsic properties of the vaccine) and effective VC given the recurrent outbreaks of VPDs in settings reporting high crude VC[11,12].

Ideally, overall evaluations of national immunisation programmes in low and middle income countries (LMICs) and for effectiveness of specific vaccination programmes should include direct measurement of population immunity in serological surveys. Compared to high-income countries, there appears to be very limited experience with the use of serological surveys in sub-Saharan Africa (sSA) LMICs to complement measures of crude VC and determine effective VC or population immunity. Consequently, there is very little application of seroepidemiology in monitoring the effectiveness of vaccination programmes and for informing vaccine policy in sSA.

This overall aim of this study is to assess the extent to which serological surveys have been carried out in sSA to complement assessments crude VC. We carried out a systematic review of studies reporting on vaccinated populations who also had samples taken for serological tests with a view of comparing the test results to records of vaccination in sSA.

Methods

Literature search and selection criteria

This review was conducted in accordance with PRISMA guidelines (see checklist, Supplementary File 1)[13]. From 23rd February to March 2016, we searched the United States National Library of Medicine's PUBMED, Popline, Ovid, Africa Wide Information, EMBASE and the Web of Science™ (Thomas Reuters, PA, USA) databases for English-language publications reporting the use of serosurveys for classifying vaccination history or determining vaccine coverage. We repeated the search for the PUBMED database on 30th January 2017 to ensure studies published between March 2016 and January 2017 were not omitted.

The search query used was (((((serologic tests) OR serologic surveys) AND immunization coverage) OR vaccination coverage) AND sub-Saharan Africa, which produced the following search details in PUBMED. ((((“serologic tests”[MeSH Terms] OR (“serologic”[All Fields] AND “tests”[All Fields]) OR “serologic tests”[All Fields]) OR (serologic[All Fields] AND (“surveys and questionnaires”[MeSH Terms] OR (“surveys”[All Fields] AND “questionnaires”[All Fields]) OR “surveys and questionnaires”[All Fields] OR “surveys”[All Fields]))) AND ((“immunisation”[All Fields] OR “vaccination”[MeSH Terms] OR “vaccination”[All Fields] OR “immunization”[All Fields] OR “immunization”[MeSH Terms]) AND (“AHIP Cover”[Journal] OR “coverage”[All Fields]))) OR ((“vaccination”[MeSH Terms] OR “vaccination”[All Fields]) AND (“AHIP Cover”[Journal] OR “coverage”[All Fields]))) AND (“Africa south of the Sahara”[MeSH Terms] OR (“Africa”[All Fields] AND “south”[All Fields] AND “Sahara”[All Fields]) OR “Africa south of the Sahara”[All Fields] OR (“sub”[All Fields] AND “Saharan”[All Fields] AND “Africa”[All Fields]) OR “sub Saharan Africa”[All Fields]). The same query was used to search the EMBASE database.

We included English language articles reporting primary data from a serological survey that included assessments of VC from research conducted in sSA. We defined sSA as the whole of Africa except Northern Africa. Reviews, reports of serosurveys or vaccination coverage alone were not included. Full text copies of the relevant articles meeting our inclusion criteria were obtained. In addition, their references were individually checked to identify other related papers meeting the study inclusion criteria (see Figure 1). Retrieved citations were extracted to Endnote™ X7 (Thomas Reuters, PA, USA). The following variables were extracted from each included article- country/setting of study, year of study, sample size, age of participants, vaccine administered, biological specimen used for serology, type of serological test done, numbers who received vaccines from vaccine records and numbers of positive serology results. The key outcome of interest was vaccination coverage assessed by receipt of vaccines compared to results of serological tests.

Quality assessment

As recommended by the Cochrane Public Health Review Group[14] and used in other reviews[15], the Newcastle Ottawa Scale (NOS) was used to assess the quality of each eligible study, to ascertain the risk of bias; and internal and external validity[16]. Studies were assessed in three domains: selection of the study groups, comparability of the study groups, and the ascertainment of the outcome of interest and a point system is awarded for each item evaluated[16]. With a total of 10 points, studies with ≥8, 6–7, 4–5, and ≤3 points respectively were evaluated as very good, good, satisfactory and unsatisfactory studies. (see Supplementary File 2).

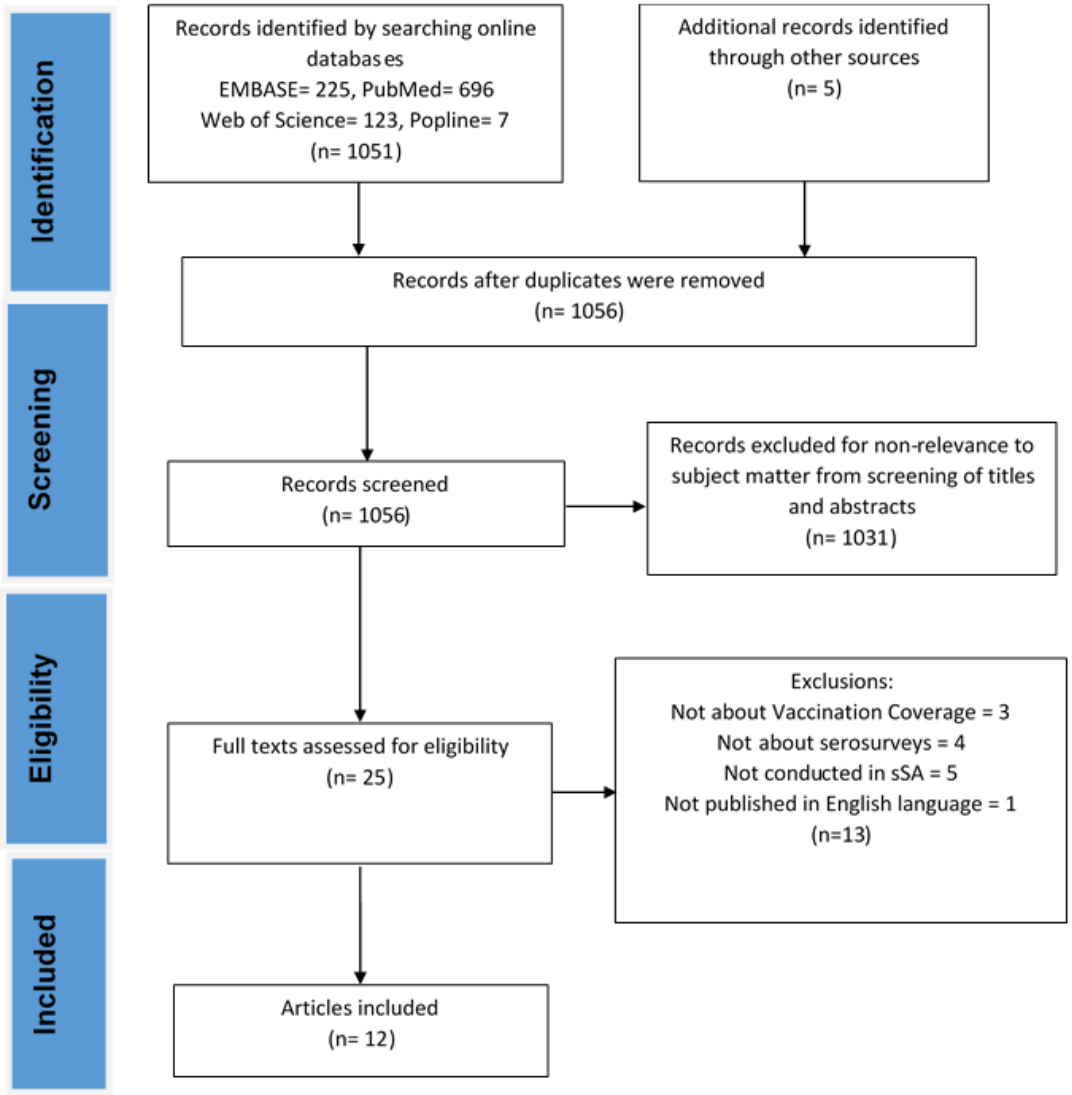

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the outcome of the literature search. (sSA – sub-Saharan Africa).

Data synthesis

Since the studies eligible for inclusion in this review were few, and showed significant heterogeneity in study design and ascertainment of outcomes, a meta-analysis for derivation of pooled estimate of effect was not possible. Instead, a narrative approach was used to describe findings from each study grouped by outcome measures.

Results

Search results

As shown in Figure 1, literature search yielded 1056 articles but only 12 of them were relevant to this review. These 12 were from Western (Nigeria[17,18], Gambia[19], Mali[20] and Ivory Coast[21]); Eastern (Ethiopia[22,23], Kenya[24], Tanzania[25], and Sudan[26]) and Southern (Malawi[27,28]) regions of Africa. There were no studies from the Central African region. Although there were publications from all but one region of sSA, only 9 of 39 countries were represented.

The reviewed articles reported serosurveys of 3 viral replicating vaccines – polio, measles, yellow fever and one toxoid – tetanus (see Table 1). There were a total of 10 studies on measles[17–19,21–25,28,29], 1 on polio[19], 1 on yellow fever[26] and 3 on tetanus[19,20,22]. In these surveys, results were compared to vaccination history ascertained by caregiver recall, presence of a known vaccination scar and/or vaccination record (card or clinic records).

Quality appraisal

Table 2 summarizes the overall and category-specific quality of the included studies, along with some limitations. A rating of very good was given to three studies[21,22,24], majority i.e. 8 studies[17,19,20,23,25–28] were assessed as good while one[18] was rated just satisfactory.

Measles vaccine

In the study by Breman *et al.*[21] in Cote d'Ivoire, pre-campaign vaccination history and crude coverage were determined by history of vaccination and/or the presence of a scar following smallpox vaccination. The pre-campaign crude VC was 53.6%, but serological surveys showed 98.3% (243/247) and 91.7% (297/324) of children 6–8 and 9–24 months old respectively lacked measles antibodies. About 2.5% of children who reported not having received any vaccination had evidence of a vaccination scar. Among the children whose families reported a history of measles or vaccination before the recent campaign, only 45.5% (27/62) had measles antibodies. For susceptible children vaccinated during the campaign, 84.3% (107/127) and 94.7% (161/170) of 6–8 month and 9–24-month-olds seroconverted respectively.

Three decades later, investigators in Malawi found the same discrepancy between vaccination history and serosurvey results[27]. This 2015 study found poor sensitivity and positive predictive value (PPV, 75.8% and 79.9% respectively) for vaccination and infection history as predictors of positive measles serological tests.

Specificity was 10.3% and the negative predictive value (NPV) was also poor at 8.3 %[27]. Although the population in this more recent study was older and aged ≥18 months (median age 37 years), a 2001 study in the same setting reported the same discordance between seropositivity and vaccination history in 246 children <5 years. Here, 17% (4/23) and 67% (54/81) of children aged 8–12 and 12–23 months old were positive for measles antibody but the history of measles vaccination was 26% and 80% respectively[28].

In a Gambian study, antibody test results following routine vaccination were compared against the vaccination records of 689 children aged 3 to 4 years. Vaccination records were retrieved from the Gambia Hepatitis Intervention Study (GHIS) main database and missing data obtained from vaccine card records during follow-up home visits. They found seroconversion in 91% (608/665) of the children with history of receiving the measles vaccine, 25% (14/57) of children without antibodies had been vaccinated before the age of 9 months and 7 of 24 children who did not receive the vaccine acquired measles antibodies possibly through natural infection[19]. The authors excluded children with incomplete vaccination histories either because they could not be traced for follow-up home visits or their immunization card were lost.

Ogunmekan *et al.*[17] measured measles antibody titres in 204 Nigerian children aged 6 to 12 months pre- and post-vaccination. On follow-up testing 6–8 weeks later, only 53.2% (91/171) of children without pre-vaccination antibodies seroconverted. The low seroconversion rates were attributed to low potency vaccines. No history of measles was given for the 33 children who were sero-positive before vaccination. However, in a more recent Nigerian report, Fowotade *et al.*[18] reported a significantly higher post vaccination seroconversion of 68.8% (196/286) in children 9–12 months old.

Contrary to the results from Nigeria, a better concordance was observed between crude and effective coverage (98.8% (878/889) and 94% (836/889) respectively) in Tanzanian children aged 18 months to 5 years[25].

The utility of non-invasive biological specimens specifically oral-fluid (OF) for determining measles vaccine coverage was investigated by Nigatu W. *et al.*[23] among 1928 children aged 9 months to 5 years (pre-vaccination) and 745 individuals aged 9 months to 19 years (post-vaccination). There were differences in age-groups sampled pre- and post-vaccination because the post-vaccination survey carried out 6 months after the measles campaign was aimed at assessing population immunity and age susceptibility to measles. The study team documented receipt of measles vaccines delivered routinely and/or by supplementary immunisation activities. Pre-vaccination measles seroprevalence was 49% (1507/3075) in vaccinated and 21% (147/700) in unvaccinated children. The post-vaccination prevalence of measles antibodies was 80% in the 0–4 and 5–9 year olds, increasing to 96% in the 15–19 year olds as shown in Table 1. However, sensitivity of OF for antibody testing declined from 95% in individuals with measles IgG ≥1000 mIU/ml to 75% in individuals with measles IgG ≤1000 mIU/ml. In another study conducted in rural Kenya that evaluated the performance of OF as a measure of the effectiveness of a measles vaccination campaign, the pre-campaign and post-campaign measles seroprevalence was 60% (520/866) and 87% (753/866) respectively with a 70% reduction in the prevalence of the susceptible population at 85% crude coverage[24]. In addition, the proportion of weakly positive individuals by the assay used increased from 35% pre-campaign to 54% post-campaign.

Polio vaccine

In the single study of polio vaccine in West Africa, investigators assessed the effect of supplementary oral polio virus (OPV) vaccine doses in Gambian children aged 3 to 4 years[19]. Blood samples were tested for antibodies to polio virus types 1 and 3 using the standard polio neutralization assay. Seroprevalence for OPV 1 and OPV 3 was 81.5% (22/27) and 89% (24/27) respectively in children who had 3 recorded vaccine doses.

Yellow Fever vaccine

A household-based sero-epidemiologic survey of all age groups was conducted in Sudan after a mass vaccination campaign in response to yellow fever (YF) epidemic[26]. The serosurvey was designed to describe the epidemiology of the outbreak and to measure YF vaccine coverage. All the 84 (96.6%) and 3 (3.4%) individuals who reported having received and not having received the vaccines during the campaign respectively, had positive serological results for YF IgM antibodies. Of the 3 individuals who had positive serologic results despite no history of vaccination, 2 reported previous YF infection and 1 reported a Chikungunya virus-like illness.

Tetanus vaccine

Tapia *et al.*[20] collected serum and oral fluid (OF) from Malian infants, toddlers and adults males without a history of tetanus

Table 1. Summary of all studies included in the review.

Author [Ref.]	Study setting	Study year	Age group	Sample size	Vaccine	Specimen	Crude coverage (%)	Effective coverage (%)
Travassos *et al.*[22]	Ethiopia	2016	12–23 and 6–8 months	1200	Tetanus	Serum	12–23 months District 1: *87* District 2: *41* District 3: *35* 6–8 months District 1: *58* District 2: *29* District 3: *40*	12–23 months District 1: *93* District 2: *60* District 3: *53* 6–8 months District 1: *68* District 2: *41* District 3: *31*
Polonsky *et al.*[27]	Malawi	2015	8 months to 29 years	2106	Measles	Serum	*62*	< 15 years: *92* 15–29 years: *60*
Fowotade *et al.*[18]	Nigeria	2015	9–12 months	400	Measles	Serum	*100*	*68.8*
Farnon *et al.*[26]	Sudan	2010	Not Specified	84	Yellow fever	Serum	*96.6*	*100*
Ohuma *et al.*[24]	Kenya	2009	9 months to 14 years	Pre-campaign: 886 Post-campaign:598	Measles	Oral fluid	***85***	Pre-campaign: *60* Post-campaign: *87*
Nigatu *et al.*[23]	Ethiopia	2008	9 months to 19 years	1928	Measles	Serum	Pre-vaccination 9–65months: *79* 12–23 months: *84* Post-campaign 15–71 months: *88* 18–29 months: *87*	Pre-vaccination 9–11 months: *44* 5 years: ***60*** Post-campaign 0–4 years: *80* 5–9 years: *80* 15–19 years: *96*
Tapia *et al.* [20]	Mali	2006	2 to 23 months	188	Tetanus toxoid	Serum Oral fluid	Not Reported	Serum: *100* Oral Fluid: *79*
Takechi *et al.*[28]	Malawi	2001	0–5 years and 9 months to 15 years	246	Measles	Serum	District 1: *84* District 2: *79*	District 1: *80* District 2: *69*
Lyamuya *et al.*[25]	Tanzania	1999	18 months to 5 years	889	Measles	Serum	*98.8*	*94*
Fortuin *et al.*[19]	Gambia	1995	3–4 years	816	Measles Polio Tetanus	Serum	Measles: *97* Tetanus: *100* Polio: *100*	Measles: *91* Tetanus: *79* Polio: *89*
Ogunmekan *et al.*[17]	Nigeria	1981	6 months to 1 year	224	Measles	Serum	*100*	*53.2*
Breman *et al.*[21]	Ivory Coast	1975	0 to 72 months	1762	Measles	Serum	6–8 months: *54* 9–24 months: *52*	Pre-campaign 6–8 months: *1.6* 9–24 months: *8.3* Post-campaign 6–8 months: *84.3* 9–24 months: *94.7*

vaccination and measured specific tetanus antitoxin by enzyme-linked immunosorbent assay in serum (S-ELISA) and OF (OF-ELISA). The proportion of infants and adult males (negative controls) with antibody titres ≥ 0.15 IU/mL (protective level) was 100% (33/33) and 17% (6/35) in serum and 95.5% (32/33) and 11% (4/35) in OF respectively. All 33 toddlers who received all 3 doses DPT vaccine (DPT3) had serum titres ≥ 0.15 IU/mL (sensitivity= 100%, PPV= 94.3%) while 26 had OF titres ≥ 0.0015 IU/mL (sensitivity= 78.8%, PPV= 92.9%). However, titres of tetanus antitoxin in OF were a 100-fold lower compared to serum. Testing of serum performed better than OF with a sensitivity, PPV, specificity and NPV of 91.9%, 100%, 100%, and 73.6% respectively.

Table 2. Results of quality assessment for included studies using the Newcastle-Ottawa Scale.

Study	Selection (max 5 points)				Comparability (2 points)	Outcome (3 points)		Total (10)	Limitations
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of exposure	Based on design & analysis	Assessment of outcome	Statistical test		
Travassos MA *et al.* (2016)[22]	*	*	*	*	**	* *	*	9	No baseline data for comparison, recall bias, misclassification
Fowotade A, *et al.* (2015)[18]	-	-	*	**	-	**	-	5	No sample size justification, selection bias, analysis not appropriate, poor vaccine potency
Polonsky JA, *et al.* (2015)[27]	*	-	-	*	**	*	*	6	Recall bias, misclassification, external validity
Farnon EC, *et al.* (2010)[26]	*	-	-	**	*	**	*	7	Sample size not justified, residual selection bias, recall bias, external validity
Ohuma EO, *et al.* (2008)[24]	*	*	-	*	**	**	*	8	Recall bias in ascertainment of exposure, information bias.
Nigatu W, *et al.* (2008)[23]	*	*	-	*	*	**	*	7	Selection bias, Recall bias, reliability issues-non-validated oral assay
Tapia MD, *et al.* (2006)[20]	*	-	-	**	-	**	*	6	Sample size not justified, selection bias, enrolment procedures unclear
Takechi M, *et al.* (2001)[28]	*	-	-	*	*	**	*	6	Recall bias, selection bias, misclassification,
Lyamuya EF, *et al.* (1999)[25]	*	-	-	*	**	*	*	6	No sample size justification, selection bias, Ascertainment bias
Fortuin M, *et al.* (1995)[19]	*	*	-	**	*	*	*	7	Selection bias, test kit sensitivity threshold
Ogunmekan DA, *et al.* (1981)[17]	-	-	-	**	*	**	*	6	Convenience sample, selection bias, no sample size justification, no significance testing
Breman JG, *et al.* (1975)[21]	*	*	-	*	**	**	*	8	Recall bias, misclassification

One star (*) is awarded to self-reported or less objectively measured outcomes and two (**) are awarded when outcomes are assessed by independent blind observers or with record linkage (see Supplementary File, SF1).

Discussion

This review confirms the limited use of serosurveys in assessments of or to complement estimates of VC in sSA. We find evidence for the utility of serological data for determinations of effective vaccination coverage, despite their inability to distinguish population immunity induced by vaccines from those resulting from natural infection.

This review also highlights significant gaps between crude and effective VC for many vaccines currently in use as reported elsewhere[23,27,29,30]. Clearly, crude VC does not correctly identify all the non- or partially immunised disease susceptible population. For example, an effective coverage of >95% is required to induce sufficiently high herd immunity to interrupt transmission of measles and this is inferred from the crude VC typically derived from administrative records and/or parental recall[29,31]. There are several reasons why there are persistent outbreaks of VPDs such as measles in sSA. There is poor coverage resulting from poor access to and/or utilization of immunization services. In addition, there are evidence of cold chain failures leading to the delivery of non-viable/less potent vaccines to those with vaccination records[31,32]. Without significant improvements to the cold chain and crude coverage, many countries in the sub-continent will not achieve global and regional vaccination targets required to interrupt transmission of many VPDs.

The lower seroconversion rates for measles vaccine in children <9 months old may be attributable to interference by maternal antibodies[22]. Lower seroconversion reduces protection post-vaccination. Since maternal antibodies wane over a period of 6–12 month[33,34], a 2-dose schedule that delivers and achieves VC ≥95% for a measles-containing vaccine later in childhood (from the 2nd year of life) is now deemed essential to on-going control efforts[35]. Because most cases of measles are subclinical, it was not surprising to find that a history of prior contact with or measles illness was poorly predictive of serological test results[36].

Just like for measles vaccine, reported vaccination and previous infection were poor predictors of protective immunity for oral polio. The trivalent oral poliovirus vaccine (tOPV), a combination of all 3 types of polioviruses, is the most commonly used polio vaccine in routine childhood immunization[37]. Typically, tOPV is administered at 6 weeks or 1st month of life at 4 week-intervals along with the DPT vaccine. Some countries administer an additional dose of tOPV at birth. TOPV and other preparations (monovalent or bivalent formulations containing types 1 and/or 3) are now used in campaigns to supplement routine childhood immunization[11]. The recent introduction of a single dose of injectable polio vaccine as part of the transition to replacing tOPV with bivalent OPV (bOPV, types 1 and 3) may lead to changing serological picture for polio in Africa. Therefore, serosurveys for polio may have value in countries in the pre-elimination phase of the disease[2].

Unlike for measles, polio and yellow fever where the immune response induced by the vaccine is indistinguishable from that due to natural infection,[9] the presence of the antibody to tetanus toxin is usually, with rare exceptions, the result of immunization and not natural infection or subclinical exposure[38]. Therefore, serological tests for tetanus antitoxin could prove very helpful in ascertaining effective vaccination coverage for tetanus vaccine and as a surrogate for other co-administered vaccines. Although Tapia *et al*, showed a significant difference between tetanus antitoxin titres and receipt of the vaccine, these serological tests have not yet been sufficiently investigated to demonstrate the desired dose-response relationship between target markers and number of vaccine doses received[39]. Hepatitis B is thought to offer the same advantage as the testing of multiple antigens may help distinguish between a positive result due to natural infection and one following vaccination[40]. Despite the use of Hepatitis B seroprevalence data for determining the burden of disease and making recommendations for vaccination for several decades now[41], none of the studies in this review investigated Hepatitis B.

Serological surveys may underestimate effective vaccination coverage due to waning immunity following vaccination as antibodies decay over time to concentrations that may be below the threshold for detection of currently available tests[9]. The risk for this is higher in older children and adults. However, most studies included in this review were conducted in the context of pre- and post-vaccination campaign evaluations so they involved mostly younger age groups (6–72 months) and occurred shortly after vaccination.

One important limitation of serological surveys is the risk of or low participation because of the requirement of invasive samples e.g. venous and capillary blood for testing. Unsurprisingly, this has stimulated an interest in the use of less invasive samples such as OF[42–44] and dried blood spots[45,46]. The use of oral fluid has been proposed as an alternative to overcome the risk of low participation due to venepuncture[9]. However, it appears the sensitivity of OF for measles antibody testing may vary according to serum measles IgG concentration[23]. In addition, serological assays of OF may be less sensitive in individuals with vaccine-induced immunity[23,47]. This is probably related to the serum antibody concentrations which are typically higher when induced by natural infection. The observed lower NPV for this specimen also suggests that the effectiveness of the vaccination programmes may be under-estimated by use of oral fluid assays[20]. Other evaluations of OF assays in Ethiopia and Kenya have yielded good results. However, the study in Kenya had no results from serum samples for comparison unlike the Ethiopian study that found a tight correlation between antibody prevalence in oral fluid and seroprevalence for measles for all age groups studied and for rubella in age groups <20 years[24,48]. Although these two studies highlight the potential for use of oral fluid as a replacement for serum in antibody prevalence surveys, this is an area that requires further investigation. This is important in the light of other studies outside the region that report poor sensitivity of OF and the deleterious impact of environmental conditions such as temperature and sample collection techniques on results from OF samples[29,42]. Although there is a longer history of using dried blood spots (DBS) as an alternative to venepuncture for serodiagnosis of many infectious diseases[49], technical difficulties-eluting serum from DBS, the presence of haemoglobin and other debris that increase background reads in ELISA assays and

cause lower sensitivity- have made them unpopular for vaccine serology[1].

Our review had a few limitations. Many of the included studies did not justify their sample size, had a risk of residual selection bias in common (mainly because participants were not always randomly selected or the selection process was not well described) and ascertainment of vaccination was not always record-based (risk of ascertainment and recall bias). Finally, we may have missed important articles published in French and/or Portuguese which are also relevant to sSA.

Conclusion

The use of serological data has the potential to improve ascertainment of vaccination history in sSA. Serological tests of anti-tetanus antibodies may prove to be a reliable surrogate marker of vaccination because they are not confounded by naturally induced antibodies. There are knowledge gaps in the use of serological surveys for tetanus and hepatitis B and whether they are likely to show a dose-response relationship to the number of vaccine doses received. This is an important area of future research. Finally, more investigations to assess and optimize the performance of non-invasive samples such as OF and DBS for vaccine serosurveys are also required.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Competing interests

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Supplementary material

Supplementary File 1. PRISMA 2009 Checklist.

Click here to access the data.

Supplementary File 2. Newcastle-Ottawa Scale adapted for cross-sectional studies.

Click here to access the data.

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Version 1

Reviewer Report 04 May 2018

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?

William J. Moss
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The authors conducted a systematic review of English language published papers comparing vaccine coverage estimates and seroprevalence in sub-Saharan Africa. Only 12 papers met the inclusion criteria, ten of which were on measles.

1. It is mistaken to view serosurveys for vaccine-preventable diseases as a measure of vaccine coverage, although this appears to be the motivation for this systematic review as the “key outcome of interest was vaccination coverage assessed by receipt of vaccines compared to results of serological tests”. For reasons stated by the authors, vaccine coverage estimates and serological surveys, although correlated, measure two different outcomes and one would not expect these measures to be identical, even if the measure of vaccine coverage was accurate. Vaccine coverage estimates the number and timeliness of vaccine doses received whereas serology estimates the proportion of individuals with measurable antibody levels, induced by immunization or exposure to the pathogen. Serological surveys are the tool to estimate population immunity, not vaccination coverage. Using serology to adjust estimates of vaccination coverage requires sophisticated statistical methods such as latent class models.

2. Serosurveys without concurrent estimates of vaccination coverage can be valuable to immunization programs but would not have been included in this systematic review. Such serosurveys can leverage biorepositories or samples collected from representative surveys for other purposes, and can provide information on low levels of population immunity in specific geographical areas or age groups.

3. Although the authors conclude that serological surveys can be used to estimate vaccine exposure or coverage for tetanus toxoid, the key metric is the number of doses received. The issue is whether serology can be used to estimate receipt of DTP3.

4. The “narrative” descriptions of the studies, particularly measles, can be confusing. When the

authors report sensitivity, specificity and positive and negative predictive values, they need to make clear what is the gold standard and what is being compared. Several studies appear to be vaccine immunogenicity studies (e.g. the measles study from The Gambia for which they report seroconversion, and the study from Nigeria). Vaccine immunogenicity studies are different than studies assessing population immunity through serological surveys.

5. The authors included serosurveys that used oral fluid rather than blood samples, but this review does not provide a sufficient evidence to assess the advantages and limitations of oral fluid samples.

6. Dried blood spots are a method of storing blood samples not a method of collecting blood samples. One could perform venepuncture and spot the whole blood as dried blood spots. It is mistaken to refer to dried blood spots as a less invasive means of collecting blood or as an alternative to venepuncture, although frequently finger prick blood collection is used. I disagree that dried blood spots are “unpopular” for serological studies.

7. The review does not address the assays used to measure seroprevalence nor the challenges and cost of conducting serological surveys in sub-Saharan Africa.

Minor comments

1. The statement that most cases of measles are subclinical is not correct.

2. The word “hepatitis” in “hepatitis B” should not be capitalized.

3. The authors need to make clear why they used smallpox scar as a surrogate marker of measles vaccination in the study by Breman. For this study, I suggest reporting the proportions seropositive rather than seronegative to be consistent with the rest of the text.

4. For the measles study in Tanzania, I do not think it appropriate to refer to the seroprevalence results as “effective vaccine coverage” in a setting with potential wild-type measles virus transmission.

5. For the yellow fever serosurvey in Sudan, the authors should more clearly describe how the serosurvey was used to both describe the epidemiology of the outbreak and measure yellow fever vaccine coverage at the same time.

6. I would be cautious in using the term “effective coverage” in Table 1 for diseases other than tetanus unless it was certain wild-type virus was eliminated. “Seroprevalence” would be more accurate.

7. The authors should be more specific when they state with regard to hepatitis B: “as the testing of multiple antigens may help distinguish between a positive result due to natural infection and one following vaccination”. What antigens and what antibodies?

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Partly

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 17 April 2018

https://doi.org/10.21956/wellcomeopenres.15089.r32279

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Mary E. Ramsay
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This systematic review is a clearly written manuscript with targeted and fairly limited scope to look at the use of seroprevalence studies for determining vaccine coverage in Africa. The methods and results are clearly documented and the conclusions supported by their findings.

As the stated aim was to identify papers where both aspects (serological status and coverage) were measured, the authors identified a relatively small number of studies for inclusion in their review. This may explain why the previous reviewer was able to identify multiple “missing” papers that have studied seroprevalence, but many of these may not have simultaneously evaluated coverage. I did check one or two of the papers suggested by Reviewer 1 and I think this may be the case – I would assume these studies were rejected at the initial screening of the abstract. If so, then, although the review may have achieved the stated aim, the usefulness of the study for those working in the field is more limited. As vaccine coverage data is routinely collected from most countries in the Region, a broader review of seroprevalence, when combined with routine coverage data, could have potentially provided more insight into the value of such studies.

Based on the above conclusion, the authors should make the scope of the review clearer and perhaps add a comment to explain why many studies (such as those suggested by Reviewer 1) were excluded.

For the studies included in the review, the authors are able to make a small number of conclusions as to why seroprevalence studies may correlate poorly with vaccine coverage. Many of these aspects are not unique to Africa and I wonder if the authors could comment more about which aspects may be generalizable to different settings and regions.

One minor comment is that haemophilus influenzae is spelt without the “e”.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Partly

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Vaccine preventable disease surveillance

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 06 March 2018

https://doi.org/10.21956/wellcomeopenres.15089.r31160

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Heather Scobie
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This systematic review by Wanjiku and Adetifa has the potential to provide timely and specific information on serosurvey use for vaccine preventable diseases (VPDs) in Africa. In 2016, Cutts and Hanson made the point in their published review that sero-epidemiology an important but underutilized tool for designing and monitoring vaccination programs in lower and middle-income countries. The systematic review by Wanjiku and Adetifa complements this publication by providing a specific landscape analysis of the African region. While VPD serosurvey publications from the African Region are limited, I am concerned that the search may have missed existing

publications that should have been included given the defined objectives of the authors.

Major comments:

1. At the time the paper was published online without review (23Feb2018), the search was already 13 months out of date (last search 30Jan2017). Is there any reason why it was not feasible to update the search again closer to the publication date? Given the rapidly evolving topic area, I suggest including 2017 and 2018 articles up to publication time, if possible.

2. Given your topic area, it seems important to include a database that captures African journals not indexed by Pubmed. I would suggest African Journals Online (AJO) https://www.ajol.info/ I see in the first Methods paragraph, reference to searching Africa Wide Information is mentioned, which includes AJO. But in the next paragraph, searching only PUBMED and EMBASE are mentioned. Please clarify what databases were used and whether Africa Wide Information was included.

3. Confirm that you used the MESH term “Africa South of the Sahara” that would have captured individual country names. Otherwise, it’s not clear that papers with individual country names would be captured by searching “Africa” or “Sub-Saharan Africa.”

4. I’m not certain that your serosurvey terms would capture all of the published literature (see examples in #5-8 below). Did you try including “seroprevalence”, “sero-prevalence”, “seroepidemiology”, “sero-epidemiology”, “population immunity”, “immunity,” “prevalence AND antibodies”? “Serologic*” so as to include “serological,” or better yet “sero*” so as to include the permutations mentioned above? For example, if I search “Nigeria polio serosurvey,” I get zero hits, but if I search “Nigeria polio seroprevalence,” I get 13 hits.

5. I find many polio serosurveys from Nigeria not referenced in the paper (see below, which isn't a complete list) and also one from West Africa from Feb 2018 (https://www.ncbi.nlm.nih.gov/pubmed/29358054)[1]:

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4818560/[2]
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5036508/ [3]
- https://linkinghub.elsevier.com/retrieve/pii/S0264-410X(12)01334-5 [4]
- https://www.ncbi.nlm.nih.gov/pubmed/9598456 [5]
- https://www.ncbi.nlm.nih.gov/pubmed/2174579 [6]

6. A review of measles and rubella serosurveys was published recently: Dimech and Mulders, 2016 [7]. It looks like at least one articles captured in that review may have been missed here:

- Enquselassie *et al.* Seroepidemiology of measles in Addis Ababa, Ethiopia: Implications for control through vaccination. Epidemiology and Infection Volume 130, Issue 3, June 2003, Pages 507-519 [8]

7. This published review by Breakwell *et al.* appears to summarize HepB serosurveys including vaccination status in the Region: http://www.panafrican-med-journal.com/content/series/27/3/17/full/ [9]. The authors of the paper under review state “No study looked at Hepatitis B.” Can you please comment on why the HepB papers in Table 3 by Breakwell *et al.* were not captured for inclusion? It's unclear if HepB Surface Antigen testing was systematically missed because it is not an antibody test. These studies are more typically titled “prevalence of HepB surface antigen”. This is an additional Hep B reference that looks like it should

be included: Olayinka *et al.* "Seroprevalence of Hepatitis B Infection in Nigeria: A National Survey." Am. J. Trop. Med. Hyg., 95(4), 2016, pp. 902–907 [10].

8. For tetanus, I'm aware of serosurveys of adult women that included vaccination coverage in Central African Republic and Burundi which likely should have been included:
- Deming MS, Roungou JB, Kristiansen M, Heron I, Yango A, Guenengafo A, et al. Tetanus toxoid coverage as an indicator of serological protection against neonatal tetanus. Bulletin of the World Health Organization. 2002;80(9):696-703. [11]
- World Health Organization. Expanded programme on immunization--estimating tetanus protection of women by serosurvey. Wkly Epidemiol Rec. 1996;71(16):117-24. [12]

9. I'm surprised that in Figure 1 only three articles were excluded for being serosurveys not including vaccination coverage. I would guess that the majority of published serosurveys in Africa did not collect vaccination coverage (e.g., rubella serosurveys of adult women). Other articles may not report coverage in the abstract but do report it in the full text. An example would be Aboud *et al*., 2000 [13]. Inability to capture these articles should be a stated limitation of your review. If you re-categorized the 1031 articles that were "non-relevant" into smaller groups, and the number excluded because of not including vaccination coverage was high, you may be able to recommend inclusion of vaccination status in serosurveys where possible to inform interpretation of results and provide better information for the program.

Minor comments:

1. MacNeil *et al* 2014[14] summarizes the limitations of using serosurveys to assess vaccination coverage. In my experience, the limitations are not "well known" as the authors state in the introduction. A major result described in the abstract is discordance of coverage and serosurvey results for diseases where natural infection causes immunity. This limitation of serosurveys (inability to discriminate immunity from natural infection and vaccination, except for tetanus) seems worth describing in the introduction.

2. Another limitation of serosurveys that is not mentioned is misclassification bias related to use of non-gold standard tests, e.g., ELISAs with poor sensitivity and poor specificity. This issue is also discussed in MacNeil *et al* 2014[14] and deserves mention. It is especially problematic for tetanus where indirect ELISAs have challenges to discriminate at lower antibody titers around the threshold for seroprotection, discussed in Scobie 2016[15], the WHO Immunological Basis of Immunization Tetanus Module, and early literature:
- Hendriksen CF, vd Gun JW, Nagel J, Kreeftenberg JG. 1988. The toxin binding inhibition test as a reliable in vitro alternative to the toxin neutralization test in mice for the estimation of tetanus antitoxin in human sera. J Biol Stand 16:287–297. [16]
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- Dokmetjian J, Della Valle C, Lavigne V, de Lujan CM, Manghi MA. 2000. A possible explanation for the discrepancy between ELISA and neutralizing antibodies to tetanus toxin. Vaccine 18:2698–2703. [18]
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Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Partly

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immunization, VPD surveillance, serosurveillance

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Comments on this article

Version 1

Reader Comment 27 Feb 2019

Anna Bershteyn, Institute for Disease Modeling, USA

The article states that no serosurveys were found from central Africa. Please considering adding the 2013-2014 Demographic and Health Survey from the Democratic Republic of Congo.
C.f. https://dhsprogram.com/pubs/pdf/FR300/FR300.vpd.pdf
and https://www.sciencedirect.com/science/article/pii/S0264410X17311611

Competing Interests: I have no competing interests.