Vaccine xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Issues and considerations in the use of serologic biomarkers for classifying vaccination history in household surveys

Adam MacNeil*, Chung-won Lee, Vance Dietz

Strengthening Immunization Systems Branch, Global Immunization Division, Center for Global Health, The Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS A-04, Atlanta, GA 30333, USA

ARTICLE INFO

Article history:
Received 18 November 2013
Received in revised form 18 June 2014
Accepted 8 July 2014
Available online xxx

Keywords:
Immunization coverage
Vaccination history
Survey
Biomarker
Serology

ABSTRACT

Accurate estimates of vaccination coverage are crucial for assessing routine immunization program performance. Community based household surveys are frequently used to assess coverage within a country. In household surveys to assess routine immunization coverage, a child's vaccination history is classified on the basis of observation of the immunization card, parental recall of receipt of vaccination, or both; each of these methods has been shown to commonly be inaccurate. The use of serologic data as a biomarker of vaccination history is a potential additional approach to improve accuracy in classifying vaccination history. However, potential challenges, including the accuracy of serologic methods in classifying vaccination history, varying vaccine types and dosing schedules, and logistical and financial implications must be considered. We provide historic and scientific context for the potential use of serologic data to assess vaccination history and discuss in detail key areas of importance for consideration in the context of using serologic data for classifying vaccination history in household surveys. Further studies are needed to directly evaluate the performance of serologic data compared with use of immunization cards or parental recall for classification of vaccination history in household surveys, as well assess the impact of age at the time of sample collection on serologic titers, the predictive value of serology to identify a fully vaccinated child for multi-dose vaccines, and the cost impact and logistical issues on outcomes associated with different types of biological samples for serologic testing.

Published by Elsevier Ltd.

1. Introduction

Estimation of vaccination coverage is a fundamental aspect of the Expanded Programme on Immunization (EPI) and is crucial to immunization program planning and monitoring [1,2]. Additionally, coverage is essential for evaluating implementation strategies, such as Reach Every District (RED) [3]. Administrative estimates of coverage are calculated as the number of children vaccinated (numerator) divided by the number of children in the target population (denominator). However, data quality issues are common in both the numerator (reasons include inaccurate and/or incomplete data recording and reporting, and data manipulation) and in the denominator (reasons include inaccurate estimates of the target population and persons accessing immunization services outside of their catchment area), and studies indicate that coverage estimates derived from administrative data are commonly inaccurate in comparison to surveys [4–6].

Community based household coverage surveys are frequently used as an independent approach to assessing population coverage for vaccinations. Examples of commonly used surveys include the Demographic and Health Survey (DHS) and the Multiple Indicator Cluster Survey (MICS) [7,8]. Both surveys employ multi-level sampling approaches and assess numerous variables (with immunization as a component of the overall survey). Assessment of vaccination history is based on either records (typically the child's immunization card) or recall (typically from the parent), or both.

Wide variations in coverage estimates at national and sub-national levels and poor agreement between administrative and survey-based estimates of coverage have been previously noted [4,9]. For instance, Lim et al. compared DTP3 coverage estimates from available surveys and administrative reports and observed wide variability and frequent higher country-level estimates of coverage from administrative reports than from survey data, with global-level coverage estimates of 90% from country best-estimate reports and 74% from surveys in 2006 [9]. Survey-based methods

* Corresponding author. Tel.: +1 404 639 8169.
E-mail address: aho3@cdc.gov (A. MacNeil).

http://dx.doi.org/10.1016/j.vaccine.2014.07.005
0264-410X/Published by Elsevier Ltd.

Table 1
Key issues and questions for consideration in the use of serology to assess vaccination history.

Key issue	Questions for consideration	Implication on use of serology to assess vaccination history
Serology and classification of vaccination history	What is the sensitivity and specificity of the serologic method compared with other methods (immunization card review or parental recall) for assessing vaccination history?	The use of immunization cards and parental recall for assessment of vaccination history can result in inaccurate classification. However, use of serologic data may also result in inaccurate classification of vaccination history, due to false positive or false negative results. Consideration should be given to the predictive value of serologic methods for classification of individual vaccination history and how this compares with other methods for classification of vaccination history
Impact of vaccine type, doses, and duration of vaccine-induced immune response, and natural infection on serologic data	Are there issues in the ability of the serologic method to differentiate between vaccination and exposure to natural disease?	Infection by most natural (not through vaccination) pathogens results in the induction of a positive serologic response. Consideration should be given to the ability of the serologic assay to differentiate between natural exposure and vaccination, the likelihood of survey participants having previous exposure to the pathogen, and the impact on the interpretation of survey results
	For evaluation of multiple dose vaccines, is the serologic method able to reliably differentiate among individuals based on number of doses received?	In multi-dose vaccination series, a serologic response to vaccine antigens may be elicited before receipt of the complete series. For assessing multi-dose vaccine coverage (for instance, DTP3), consideration should be given to the ability of the serologic method to differentiate among the number of doses administered, and the potential impact of misclassification of vaccination history on survey results
	What is the age of the target survey population, and will waning of vaccine-induced immunity impact interpretation of serologic data?	Serologic responses to non-replicative vaccines can wane during childhood. Consideration should be given to the age of the target survey population, and the potential for waning immune responses and serologic data to result in misclassification of vaccination status
Logistical feasibility, cost implications, and impact on survey implementation	Is the serologic method logistically feasible and cost appropriate for the survey implementer?	Inclusion of biological sample collection and testing in a household survey has the potential to substantially increase the complexity and requisite financial resources; it is therefore important to consider the available resources, the goals of the survey, and potential added benefit in the use of serologic methods to assess vaccination history
	Is collection of biologic samples acceptable to the study population and will such collection not result in sampling bias, compared with non-invasive methods to assess vaccination history?	Collection of biologic samples has potential to decrease the number of individuals who agree to participate in the survey; it is important to consider to the likelihood of refusal among the study population and how non-participation will impact overall quality of survey data

may not be impacted by the same limitations as administrative coverage estimates; however, potential issues do exist with their use for estimation of coverage due to both random and systematic error [10,11].

Sources of systematic error in community based surveys include selection bias, information bias, data transcription and entry errors, and missing data [10]. Information bias can be a significant problem in classification of vaccination history, both by child immunization card observation and parental recall methods [10]. Observation relies on the availability of the immunization card at the time of the survey visit, whereas parental recall bias has potential for inaccurate classification of vaccination history. Miles et al. recently performed a review of the literature comparing the accuracy of immunization history based on immunization card, parental recall, or both sources with provider-based records. Using provider records as the gold standard, median coverage estimates among studies varied from 61% points under- to 1% point over-estimation using immunization cards; 58 percentage points under- to 45% points over-estimation using parental recall; and 40% points under- to 56% points over-estimation using a combination of the two. Of the available literature, five of these studies were conduct in low-middle income countries and indicated lower coverage estimates for use of recall, or card and recall, in comparison to provider records [12].

Recently there has been increasing interest in the potential use of biomarkers in community based household surveys [10,13]. As noted by Cutts et al. [10], there are potential limitations in the utility of biomarkers – notably, serology – to validate vaccination coverage in community based household surveys. Vaccines typically require multiple doses, have varying formats, and numerous methodologies exist for assessing immune response. While serologic data is commonly used to assess population immunity to a pathogen, little applied research has evaluated its use in the classification of vaccination history, as a measure of EPI performance.

Currently, limited publications are available to directly assess the use of serologic data in community based surveys to improve the accuracy of coverage estimates. The objective of this paper is to discuss issues for consideration in the use of biomarkers in coverage surveys, with a specific focus on serologic methods to assess vaccination history. We discuss three key areas which may impact the ability to effectively use serologic data in assessing vaccination coverage: (1) serology and classification of vaccination history; (2) impact of vaccine type, doses, and duration of vaccine-induced immune response on serologic data; and (3) logistic feasibility, cost

Please cite this article in press as: MacNeil A, et al. Issues and considerations in the use of serologic biomarkers for classifying vaccination history in household surveys. Vaccine (2014), http://dx.doi.org/10.1016/j.vaccine.2014.07.005

Table 2
Fundamental concepts in understanding the potential role of biomarkers to assess vaccination history.

The definition of a serologic biomarker of vaccination	The presence of an antibody titer to an antigenic component of a vaccine that is an indicator of history of vaccination with a specific number of doses of the vaccine
The difference between serosurveys and coverage surveys	The objective of a serosurvey is to assess population immunity. The objective of a coverage survey is to assess the proportion of a population that received a specific vaccine dose or doses
The difference between sensitivity and specificity of serologic assays versus predictive value positive (PVP) and predictive value negative (PVN), to assess vaccination history	Sensitivity and specificity are inherent characteristics of the laboratory assay and are not impacted by the immunization coverage in the study population. PVP and PVN are affected by the overall level of immunization coverage in the population
The difference between direct outputs (numeric readings) from serologic assays and final serologic classification	Direct outputs of serologic assays typically are constituted by a continuous range of values. Final interpretation involves a dichotomous classification of either positive or negative
The general difference between serologic responses generated to live (e.g. measles, rubella, yellow fever vaccines) and non-replicative vaccines (e.g. DTP, hepatitis B vaccines)	Live vaccines cause an infection in the immunized individual and result in circulating antibodies that typically persist for many years. Non-replicative vaccines have a shorter half-life and necessitate multiple doses of vaccine to induce protective levels of antibodies

implications, and impact of collection of biomarker data on survey implementation. For each area, we pose a series of questions which we believe are important for evaluating the usefulness and limitations of serologic data to assess individual vaccination history in household surveys (Table 1).

2. Biomarkers, serology, and assessment of vaccination history

2.1. Biomarkers as a measure of vaccination history

2.1.1. Definitions

The Merriam Webster dictionary defines a biomarker as "a distinctive biological or biologically derived indicator of a process, event, or condition". For assessment of vaccination history in a coverage survey, an ideal biomarker would be a biological indicator directly associated vaccination history that could be assessed objectively by the survey implementer. Examples of biomarkers of potential use in assessing vaccination history include visual biomarkers (such as vaccine-induced scarring) and serologic biomarkers (such as the presence of an antibody titer to an antigenic component of the vaccine). For this manuscript, we will define a serologic biomarker of vaccination as *the presence of an antibody titer to an antigenic component of a vaccine that is an indicator of history of vaccination with a specific number of doses of the vaccine* (Table 2).

2.1.2. Performance measures

Important performance measures to consider for potential biomarkers in immunization coverage surveys include the sensitivity, specificity, predictive value positive (PVP), and predictive value negative (PVN) of the biomarker in correctly classifying vaccination history. Among these measures, sensitivity and specificity are inherent characteristics of the assessment method (and thus not impacted by the immunization coverage in the study population), whereas PVP and PVN are affected by the overall level of immunization coverage in the population. In coverage surveys, sensitivity and specificity of biomarkers represent the proportion of vaccinated individuals who are classified as having received the vaccine based on the presence of the biomarker and the proportion of unvaccinated individuals who are classified as not having received the vaccine based on the absence of the biomarker, respectively.

The time of sample collection, relative the vaccination history, is anticipated to have an impact on the performance of biomarkers. As will be discussed in more detail, serologic responses to vaccines wane over time. Thus, the sensitivity of a serologic biomarker for a vaccine may also decrease over time relative to date of vaccination. Similarly, exposure to natural infection and induction of antibody response to vaccine-associated antigens would have the impact of decreasing the specificity of performance of the biomarker.

2.2. Historic use of biomarkers to assess vaccination history

Widespread vaccination campaigns played an important role in eradication of smallpox. The smallpox vaccine (live vaccinia virus) is administered percutaneously. Successful vaccination results in a localized infection at the vaccination site, resulting in a scar [14]. The presence of this scar is a biologic indicator of smallpox vaccination that can be used to assess vaccination history. Henderson et al. conducted an extensive survey in West Africa in 1968–1969 as part of an evaluation of the mass vaccination campaigns implemented during smallpox eradication efforts, and using the presence of a scar as an indicator of vaccination, reported vaccination coverage of greater than 82% [15]. In an assessment of a measles-smallpox vaccination campaign in Côte d'Ivoire in 1975, Breman et al. found the presence of a smallpox vaccination scar to be a strong predictor of measles seroconversion among previously susceptible children [16].

Bacillus Calmette–Guérin (BCG) vaccination is administered immediately after birth as part of the routine immunization schedule in many countries, to prevent tuberculous meningitis and disseminated tuberculosis in children [17]. As with the smallpox vaccine, BCG administration generally results in scar formation. While some data suggest BCG scarring may be an effective predictor of BCG vaccination [18], it also has potential limitations. Floyd et al. found high sensitivity and repeatability in readings of BCG scarring when the vaccination had been administered to children at least 3 months of age; however, sensitivity was poor among children who had been vaccinated within one month of birth [19]. Other studies have similarly reported absence of scars in approximately 5–20% of children when BCG vaccine is administered early in life [20–22].

2.3. Use of serology as a biomarker of vaccination history

2.3.1. Immune responses to vaccination

A protective immune response is the expected outcome of an effective vaccination (or vaccination series), and thus immunologic responses also have the potential to serve as biomarkers of vaccination history. The development of the adaptive immune response to a foreign antigen (from a vaccine or an actual pathogen) is a complex process and can include both antigen-specific antibody and cell-mediated immune responses. With respect to antibody responses, the primary mediator is the antigen-specific B-cell, which secretes antibodies which function through multiple potential mechanisms, including binding to functional sites on the pathogen, neutralizing replication, promoting phagocytosis, and activating complement cascade. Primary exposure to a foreign antigen results in primary production of low-affinity IgM antibodies and in longer-term transition through somatic hypermutation and affinity maturation to B-cells producing other classes of antibodies; notably IgG antibodies (predominant serum antibody)

Please cite this article in press as: MacNeil A, et al. Issues and considerations in the use of serologic biomarkers for classifying vaccination history in household surveys. Vaccine (2014), http://dx.doi.org/10.1016/j.vaccine.2014.07.005

and IgA antibodies (present in mucosal surfaces). Adaptive cell-mediated immune responses include responses mediated by CD8+ T cells, which can have a direct or indirect role in killing pathogens, or by CD4+ T cells, which support immune functions in clearing pathogens [23]. While some vaccines induce a cell-mediated response [24], most protect through the induction of antibodies [25], and most correlates of protection are based on measures of antibody level [25,26].

The strength of an antibody response to a specific antigen may vary widely among individuals. Reasons for variability include differences in the magnitude of antibody response to specific antigens, temporal dynamics of circulating antibodies and antigen-specific B-cell populations relative to exposure to the antigen, and inherent biologic variability in human populations. From an immunization response standpoint, vaccines can generally be differentiated between live and non-replicating vaccines. Live vaccines, including vaccinia, measles, mumps, and rubella, cause an infection in the immunized individual and result in circulating antibodies that typically persist for many years. In contrast, antibody levels generated in response to non-replicating vaccines, such as tetanus and diphtheria, have a substantially shorter half-life and necessitate multiple doses of vaccine in the primary series, as well as potential booster doses to maintain protective levels [23,27,28].

2.3.2. Vaccination and population immunity

The effectiveness of a vaccine at generating a detectable biologic response has an important impact on performance measures. For instance, if a vaccine fails to induce a biologically measurable response in a certain proportion of vaccinated individuals, the sensitivity of the biomarker to assess vaccination history will be less than 100%. Similarly, if a vaccine in a 3-dose series induces a biologically measurable response after 1 or 2 doses, the specificity of the biomarker for assessing 3-dose immunization history will be less than 100%.

It is also important to note the difference between the objective of a serosurvey, in which the goal is *to assess population immunity*, and the objective of a coverage survey, in which the goal is *to assess the proportion of a population that received a specific vaccine dose or doses*. For example, the first dose of measles-containing vaccine, when administered at 9 months of age, results in seroconversion in approximately 85–90% of infants [29]. If a serosurvey were to be performed in a population of 1 year-olds, all of whom were vaccinated at 9 months of age, it would be concluded that 10–15% of infants *were not immune* to the measles virus, an important conclusion for understanding the risk of measles virus transmission. However, if the same serologic method was used to assess vaccination history in the same population, it would lead to the inaccurate conclusion that 10–15% of children *were not vaccinated*.

3. Key issues in serology to assess vaccination coverage

3.1. Serology and classification of vaccination history

A variety of laboratory methods have been developed for assessing serologic response. These can generally be divided into assays which involve detection of biophysical antibody binding to a specific antigen (or antigens), such as enzyme-linked immunosorbent assays (ELISAs) and immunofluorescent assays (IFAs), and assays that measure direct biologic function of antibodies, such as neutralization assays (Table 3). Assays which involve detection of biophysical antibody binding can allow for differentiation of antibody type and binding to specific antigens, and measure antibody avidity, however, do not measure the actual biologic function of the antibodies. Neutralization assays quantify the ability of antibodies to perform neutralizing immune functions, as opposed to only quantifying the presence of antibody binding [30]. Regardless of the type of serologic assay, direct outputs of serologic assays typically are constituted by a continuous range of numeric values. Depending on the assay, the results may be presented visually, as numeric measurements of optical or fluorescent outputs, or as numeric measurements of biologic function. Final interpretation typically involves a dichotomous classification of either (sero-) positive or negative, with some formats having an intermediate classification of 'low positive', 'indeterminant', or 'equivocal'.

An inherent problem arising from categorizing a continuous range of output values into a dichotomous classification is identifying a cut-off value or appropriate numeric range for assigning positive or negative classifications. Well-defined serologic correlates of protection (with a dichotomous cut-off value) have been identified for most vaccine preventable diseases [25,26] on the basis of biologic protection from infection or disease. However, serologic correlates of protection are only as predictive of vaccination history as the underlying effectiveness of the vaccine at generating a biologically protective immune response. Statistical methods for identifying cut-off values also have an important role in serologic assays [31–33]; however, these cannot fully account for misclassification error in classifying individual's serostatus when the distribution of output values for seronegative and seropositive populations overlap.

In an ideal serologic assay, a clear difference in numeric values between seronegative and seropositive individuals would determine a definitive cut-off value for classifying individuals as 'vaccinated' or 'not vaccinated'. For example, a study by Sharma et al. assessed rubella serostatus in 90 individuals pre-and post-vaccination and demonstrated seroconversion in all individuals, with no overlap in antibody titers between the entire set of pre- and post-vaccination sera [34].

In practice, however, standardization of cut-offs for classification of serologic positive versus negative is often not so clear-cut. Allwinn et al. compared the performance of 6 different assays for detection of anti-mumps antibodies in serum from 227 individuals and found that the proportion who were seropositive varied from 53% to 82%, depending on the assay used [35]. Because of recognized issues in the comparability of serology assays between countries the European Sero-Epidemiology Network has implemented standardization studies using serum panels across a number of countries [36]. Multiple studies have demonstrated variability between laboratories and resulted in standardization of cut-off values and agreement in seroclassification for vaccine preventable diseases including pertussis, diphtheria, measles, mumps, rubella, and hepatitis B [37–43].

3.2. Impact of vaccine type, doses, duration of vaccine-induced immune response, and natural infection on serologic data

Certain live vaccines (for instance measles, rubella, mumps, and yellow fever) elicit an immune response following a single dose of vaccine and are typically provided a single time for children 1 year of age or less. Since only a single dose of vaccine is necessary to stimulate an immune response, vaccination can be directly correlated with expected seropositive response. Because immune responses to live vaccines are typically long-lasting, serologic biomarkers have the potential to characterize vaccination history in older populations who were vaccinated years earlier [27,28]. However, live-attenuated vaccines typically have antigens which are close to those of wild-type pathogens. These limit a serologic assay's ability to differentiate between exposure to vaccination and natural disease, thereby diminishing the specificity of serology as a biomarker of vaccination. For instance, in a study examining serologic response to measles vaccination, Tapia et al. described the complete absence of measles-specific antibodies in a group of

Please cite this article in press as: MacNeil A, et al. Issues and considerations in the use of serologic biomarkers for classifying vaccination history in household surveys. Vaccine (2014), http://dx.doi.org/10.1016/j.vaccine.2014.07.005

Table 3
Laboratory approaches for measuring serologic (antibody) response. For a detailed discussion, see [30].

Type of antibody interaction	Examples of types of laboratory assays	Advantages	Disadvantages
Biophysical binding	Enzyme-linked immunosorbent assay (ELISA), Immunofluorescent assay (IFA)	Generally simpler and less time consuming than neutralization assays, can allow for differentiation of antibody type and binding to specific antigens, and measure antibody avidity	Binding may not measure actual neutralizing activity of antibodies
Biological function	Neutralization assay	Quantifies the ability of antibodies to perform neutralizing immune functions	Assays are time consuming and may not be suitable for high throughput procedures

(pre-vaccination) 6 month old children and 100% seroprevalence among 10–11 month old children post-vaccination, however, protective antibody titers were present among 50% of unvaccinated children 9–10 months of age in the same population, which the authors hypothesized may have been due to measles virus infection [44]. Even without evidence of disease, there is additionally the potential for pathogen carriage or asymptomatic shedding, which may impact serologic outcomes.

Many vaccines are non-replicative, and use inactivated pathogens or specific sub-unit, conjugated, or toxoid-specific antigens (such as the components of diphtheria-tetanus-pertussis [DTP] vaccines, hepatitis B, *Haemophilus influenzae* type b, and pneumococcal vaccines) to stimulate an immune response. In the instance of tetanus and hepatitis B vaccines, the absence of natural immunity (tetanus) and ability to differentiate natural infection from vaccination by serologic testing for multiple antigens (hepatitis B) [45] may allow a clear differentiation between positive responses due to vaccination and nature infection.

In contrast to live vaccines, non-replicative vaccines typically require a multi-dose primary series, with or without additional booster dose(s), in order to ensure that a protective immune response is generated and maintained. This raises significant challenges to using serology as a biomarker of vaccine history. For example, DTP-containing vaccines are recommended as a 3 dose series to be administered within the first year of life; coverage with all three doses (DTP3) is a commonly used indicator of a country's EPI performance [46,47]. Specific serologic measures that are strongly predictive of 3 dose coverage are, however, limited. Stewart et al. examined antibody responses to diphtheria, tetanus, and pertussis antigenic components of DTP vaccine in groups of children receiving 0, 2, and 3 doses [48]. While geometric mean antibody titers against diphtheria toxin and tetanus toxin were higher among children who had received 3 doses of vaccine than among those who had received 2 doses, all 2-dose recipients of vaccine had antibody responses above protective value, based on known correlates of protective antibody levels.

Immune responses to non-replicative vaccines often wane rapidly, limiting the capacity to assess vaccine coverage in older populations [27,28]. In a large population-based study in the United States, Gergen et al. found that only 82% of children 6–16 years of age were seropositive for anti-tetanus antibodies despite a reported rate of 96–97% completion of a 3-dose vaccination series in these children [49]. Similarly, recent epidemiologic data provide supporting evidence of waning immunity among recipients of acellular pertussis-containing vaccines [50,51]. In the instance of monitoring recently vaccinated children (for instance, assessing coverage in 12–23 month old children), the impact of waning immune responses may have less of an impact than on older populations.

Finally, the impact of administration of vaccines outside of the routine immunization schedule, the timing vaccine administration, and the impact of booster doses may also affect interpretation of serologic results. National or sub-national campaigns are commonly conducted in many countries, both to provide an opportunity to catch-up children who missed opportunities to receive vaccination through the routine immunization schedule, as well as to provide booster immunity to children who have received their full vaccination series. The impact of immunization campaigns on the overall population-level antibody titers to a specific antigen has potential to further challenge the interpretation of serologic data. Additionally, the timing of vaccine administration relative to age may impact the likelihood of developing a serologic response, as has been shown with measles vaccine [29].

3.3. Logistical feasibility, cost implications, and impact on survey implementation

Multiple biologic sample types can be used to assess serologic response to an antigen, including venous blood samples (such as serum or plasma), dried blood spots, and oral fluid swabs. Venous blood samples are frequently used in the development or characterization of serologic assays. However, there are important logistical limitations to the collection and use of venous blood. First, it is an invasive method that requires skilled personnel with training in phlebotomy. In addition, compared with dried blood spots and oral fluid swabs, more equipment is needed for collection, and the volume of biological waste is greater. Finally, venous blood may require more careful handling in the field and requires timely processing or delivery to temperature-controlled settings.

Dried blood spots and oral swabs have potential to overcome the limitations of collection methodology, equipment, sample stability, and need for the cold chain, associated with venous blood collection. Numerous studies have used dried blood spots and oral fluid swabs for assessing serologic status with respect to measles, rubella, hepatitis B, and tetanus, and many of these assays generate results comparable to samples collected through venous blood [44,52–59]. Two recent manuscripts which included serology from oral fluid swabs as a measure of seroprotection, in comparison to other data sources (serology from venous serum, recall, vaccination cards, and clinic records) report poor sensitivity of oral fluid swabs and described the potential impact of variable sample collection techniques and ambient temperature on serologic results from oral fluid samples [60,61].

Regardless of the test type, the implementation of standardized practices in the field remains crucial to consistent implementation serologic testing in immunization coverage surveys. Consideration must be given to the costs and supervisory capacity, involving biological specimens to ensure safe collection and proper handling, processing, and testing of biological specimens.

Additional consideration should be given to the logistical and cost implications of incorporating serology into immunization coverage surveys. From a logistical standpoint, the use of a central laboratory for serology adds additional requirements for reverse cold chain (for venous blood), specimen storage and shipping, and personnel to perform testing, as well as potential data challenges in recording and linking biologic specimens with individual-level data collected in the field. The use of point-of-care tests, which allow the surveyer to rapidly obtain test results in the field, may present a potential approach to streamline some of these logistical challenges. While the number of commercially available tests for assessing antibody responses to vaccine-associated antigens may

Please cite this article in press as: MacNeil A, et al. Issues and considerations in the use of serologic biomarkers for classifying vaccination history in household surveys. Vaccine (2014), http://dx.doi.org/10.1016/j.vaccine.2014.07.005

currently be limited [62], point-of-care tests have been effectively used in population-based hepatitis B surface antigen seroprevalence studies, to assess the impact of the hepatitis B vaccination program on chronic virus infection in the population [63].

The cost impact of serologic testing must also be considered. For a point-of-care test, this impact may be largely limited to the cost of the actual test and human resource time of performing tests in the field. Testing at a central laboratory will increase costs associated with specimen shipping, human resources for additional laboratory staff to process and test specimens, as well has the cost of laboratory space, reagents, and equipment.

Finally, the potential impact of acceptability of biological sample collection on response rates and outcomes in immunization coverage surveys should be noted. For instance, venous blood collection may be viewed as painful or dangerous and might inhibit participation in some populations. This could result in lower response rates and potentially biased immunization coverage estimates. Collection of dried blood spots involves a skin prick to induce bleeding and may also be viewed as too painful or invasive. Oral swabs may be associated with other health interventions (for instance, testing for HIV infection) and might be viewed negatively in some populations.

4. Conclusions

Accurate estimation of immunization coverage is crucial for proper monitoring of EPI. Problems with administrative coverage-based estimates are well recognized. While immunization coverage surveys are commonly used as an alternative approach for estimating vaccination coverage, there are challenges in the classification of vaccination history, related both to parental recall and immunization card review. The use of serology to assess vaccination history represents a possible additional approach. However, potential limitations of this approach must also be considered, including those inherent to the nature of serologic assays, the serologic profile generated by specific vaccines, and the logistic implications of incorporating biologic assays into immunization coverage surveys. Additionally, for any consideration of widespread use of biomarkers in immunization coverage surveys, further efforts to standardize assays and interpretations among partners and across implementing laboratories should be addressed.

Reports of serosurveys conducted to assess population immunity to infectious agents are common in the public health literature. In contrast, limited data are available to directly assess the performance of serologic assays to characterize vaccination history compared with history derived from recall or immunization card review. Studies in Burundi and the Central Africa Republic have compared seroprevalence of tetanus toxoid immunity with self-reported vaccination history in adult women, collected during population-based surveys, and found relatively close agreement [64,65] and recent research out of Bangladesh indicated poor sensitivity of anti-measles immunity measured by serology from oral fluid samples in comparison to vaccination history documented by recall, child immunization card, or health facility records [61]. Further studies comparing performance of serologic testing with immunization cards or recall are warranted, particularly for younger populations.

While the use of serologic data has potential to improve characterization of vaccination history, many challenges to incorporating these data into coverage surveys exist. We believe that biomarkers have potential as a useful source of complementary data in coverage surveys for assessing routine vaccination coverage; however, they may not be a sufficient standalone alternative to other methods for assessing vaccination history. Of particular importance is the use of DTP3 coverage as an indicator for EPI monitoring [46,47]. As a non-replicative vaccine with rapidly waning immunity and a multi-dose format, the standalone predictive value of serologic data to classify DTP3 coverage in a population is likely limited.

Table 4
Priority areas of research needed to better assess the utility of serologic biomarkers in coverage surveys.

Evaluation of performance of serologic assays in relation to other measures of vaccination history
Characterization of the impact of age at the time of sample collection on serologic titers
Assessment of the predictive value of serology to identify a fully vaccinated child for multi-dose vaccines
Evaluation of the cost impact and logistical issues with different types of biological samples for serologic testing on survey outcomes
Assessment of the potential usage of serologic testing in only a sub-set of individuals, to validate vaccine history, for survey methodologies

The outcome of an effective EPI should be high population immunity to a pathogen, as a consequence of vaccination. While high population immunity is an expected outcome of high vaccination coverage, factors such as imperfect vaccine efficacy (<100%) and waning of vaccine-induced immunity can result in lower population immunity than overall vaccination coverage would suggest; whereas natural transmission of the pathogen will result in the higher population immunity than indicated by vaccination history. Serosurveys are a direct measure of population immunity, and thus have an important value for assessing the overall potential for spread of a pathogen within a population. In contrast, the assessment of vaccination coverage is important from a programmatic perspective, for understanding the performance of the EPI in meeting its performance targets.

As biomarkers, including serologic data, are not commonly used to assess immunization coverage, there is limited precedence for drawing firm conclusions about their potential role in coverage surveys. We believe that areas for future research should include further evaluation of performance of serologic assays in relation to other measures of vaccination history, the impact of age at the time of sample collection on serologic titers, the predictive value of serology to identify a fully vaccinated child for multi-dose vaccines, the cost impact and logistical issues associated with different types of biological samples for serologic testing on survey outcomes, and the potential usage of serologic testing in only a sub-set of individuals, to validate vaccine history, for survey methodologies (Table 4).

The long-term potential for implementation of biomarkers in immunization coverage surveys will likely depend on the added value of the additional information provided in terms of EPI performance improvement. The issues we have discussed, and associated questions, represent a potential framework for consideration of challenges in incorporation of biomarkers for drawing conclusions about performance of the immunization system. Through further research and discussion among countries, partner agencies, and survey implementers, the potential impact of incorporation of biomarkers in coverage surveys will be better understood.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Acknowledgements

We thank Peter Bloland and Jacqueline Gindler for helpful comments.

Please cite this article in press as: MacNeil A, et al. Issues and considerations in the use of serologic biomarkers for classifying vaccination history in household surveys. Vaccine (2014), http://dx.doi.org/10.1016/j.vaccine.2014.07.005

References

[1] Organization WH. http://www.who.int/immunization/givs/en/. 2013 [cited; Available from:.
[2] Organization WH. www.who.int/immunization/global_vaccine_action_plan/en/. 2013.
[3] Vandelaer J, Bilous J, Nshimirimana D. Reaching every district (RED) approach: a way to improve immunization performance. Bull World Health Organ 2008;86(3):A–B.
[4] Murray CJ, Shengelia B, Gupta N, Moussavi S, Tandon A, Thieren M. Validity of reported vaccination coverage in 45 countries. Lancet 2003;362(9389):1022–7.
[5] Ronveaux O, Rickert D, Hadler S, Groom H, Lloyd J, Bchir A, et al. The immunization data quality audit: verifying the quality and consistency of immunization monitoring systems. Bull World Health Organ 2005;83(7):503–10.
[6] Bosch-Capblanch X, Ronveaux O, Doyle V, Remedios V, Bchir A. Accuracy and quality of immunization information systems in forty-one low income countries. Trop Med Int Health: TM & IH 2009;14(1):2–10.
[7] DHS M. www.measuredhs.com. 2013.
[8] UNICEF. www.unicef.org/statistics/index_24302.html. 2013.
[9] Lim SS, Stein DB, Charrow A, Murray CJ. Tracking progress towards universal childhood immunisation and the impact of global initiatives: a systematic analysis of three-dose diphtheria, tetanus, and pertussis immunisation coverage. Lancet 2008;372(9655):2031–46.
[10] Cutts FT, Izurieta HS, Rhoda DA. Measuring coverage in MNCH: design, implementation, and interpretation challenges associated with tracking vaccination coverage using household surveys. PLoS Med 2013;10(5):e1001404.
[11] Eisele TP, Rhoda DA, Cutts FT, Keating J, Ren R, Barros AJ, et al. Measuring coverage in MNCH: total survey error and the interpretation of intervention coverage estimates from household surveys. PLoS Med 2013;10(5):e1001386.
[12] Miles M, Ryman TK, Dietz V, Zell E, Luman ET. Validity of vaccination cards and parental recall to estimate vaccination coverage: a systematic review of the literature. Vaccine 2013;31(12):1560–8.
[13] USAID. MEASURE Phase III demographic and health surveys contract. Section C—statement of work 2013 [cited 2013; Available from: http://pmi.gov/countries/contracts/measure_phase3.pdf.].
[14] Cono J, Casey CG, Bell DM. Smallpox vaccination and adverse reactions. Guidance for clinicians. MMWR Recomm Rep 2003;52(RR-4):1–28 (morbidity and mortality weekly report recommendations and reports/Centers for Disease Control).
[15] Henderson RH, Davis H, Eddins DL, Foege WH. Assessment of vaccination coverage, vaccination scar rates, and smallpox scarring in five areas of West Africa. Bull World Health Organ 1973;48(2):183–94.
[16] Breman JG, Coffi E, Bomba-Ire R, Foster SO, Herrmann KL. Evaluation of a measles–smallpox vaccination campaign by a sero-epidemiologic method. Am J Epidemiol 1975;102(6):564–71.
[17] World Health Organisation. BCG vaccine. WHO position paper. Wkly Epidemiol Rec 2004;79(4):27–38 (Health Section of the Secretariat of the League of Nations[[nl]]Section d'hygiene du Secretariat de la Societe des Nations).
[18] Pereira SM, Dourado I, Barreto ML, Cunha SS, Ichiara MY, Hijjar MA, et al. Sensitivity and specificity of BCG scar reading in Brazil. Int J Tuberc Lung Dis 2001;5(11):1067–70 (the official journal of the International Union against Tuberculosis and Lung Disease).
[19] Floyd S, Ponnighaus JM, Bliss L, Warndorff DK, Kasunga A, Mogha P, et al. BCG scars in northern Malawi: sensitivity and repeatability of scar reading, and factors affecting scar size. Int J Tuberc Lung Dis 2000;4(12):1133–42 (the official journal of the International Union against Tuberculosis and Lung Disease).
[20] Kheir AE, Alhaj AA, Ibrahim SA. The sensitivity of BCG scar as an indicator of previous vaccination among Sudanese infants. Vaccine 2011;29(46):8189–91.
[21] Roth A, Sodemann M, Jensen H, Poulsen A, Gustafson P, Gomes J, et al. Vaccination technique, PPD reaction and BCG scarring in a cohort of children born in Guinea-Bissau 2000–2002. Vaccine 2005;23(30):3991–8.
[22] Fine PE, Ponnighaus JM, Maine N. The distribution and implications of BCG scars in northern Malawi. Bull World Health Organ 1989;67(1):35–42.
[23] Siegrist C. Vaccine immunology. In: Plotkin SA, Orenstein W, Offit PA, editors. Vaccines. Saunders: Elsevier; 2013. p. 14–32.
[24] Plotkin SA. Immunologic correlates of protection induced by vaccination. Pediatr Infect Dis J 2001;20(1):63–75.
[25] Plotkin SA. Correlates of protection induced by vaccination. Clin Vaccine Immunol: CVI 2010;17(7):1055–65.
[26] Plotkin SA. Vaccines: correlates of vaccine-induced immunity. Clin Infect Dis 2008;47(3):401–9 (an official publication of the Infectious Diseases Society of America).
[27] Amanna IJ, Carlson NE, Slifka MK. Duration of humoral immunity to common viral and vaccine antigens. N Engl J Med 2007;357(19):1903–15.
[28] Pulendran B, Ahmed R. Immunological mechanisms of vaccination. Nat Immunol 2011;12(6):509–17.
[29] WHO. Measles vaccines: WHO position paper. Wkly Epidemiol Rec 2009;84(35):349–60 (Health Section of the Secretariat of the League of Nations[[nl]]Section d'hygiene du Secretariat de la Societe des Nations).
[30] Hangartner L, Zinkernagel RM, Hengartner H. Antiviral antibody responses: the two extremes of a wide spectrum. Nat Rev Immunol 2006;6(3):231–43.
[31] Swets JA. Measuring the accuracy of diagnostic systems. Science 1988;240(4857):1285–93.
[32] Gay NJ, Vyse AJ, Enquselassie F, Nigatu W, Nokes DJ. Improving sensitivity of oral fluid testing in IgG prevalence studies: application of mixture models to a rubella antibody survey. Epidemiol Infect 2003;130(2):285–91.
[33] Choi YK, Johnson WO, Thurmond MC. Diagnosis using predictive probabilities without cut-offs. Stat Med 2006;25(4):699–717.
[34] Sharma H, Chowdhari S, Raina TR, Bhardwaj S, Namjoshi G, Parekh S. Sero-surveillance to assess immunity to Rubella and assessment of immunogenicity and safety of a single dose of Rubella vaccine in school girls. Indian J Community Med 2010;35(1):134–7 (official publication of Indian Association of Preventive & Social Medicine).
[35] Allwinn R, Zeidler B, Steinhagen K, Rohwader E, Wicker S, Rabenau HF, et al. Assessment of mumps virus-specific antibodies by different serological assays: which test correlates best with mumps immunity? Eur J Clin Microbiol Infect Dis 2011;30(10):1223–8 (official publication of the European Society of Clinical Microbiology).
[36] Kafatos G, Andrews N, Nardone A, ESEN2 Project. Model selection methodology for inter-laboratory standardisation of antibody titres. Vaccine 2005;23(42):5022–7.
[37] Giammanco A, Nardone A, Pebody R, Kafatos G, Andrews N, Chiarini A, et al. European Sero-Epidemiology Network 2: standardisation of immunoassay results for pertussis requires homogeneity in the antigenic preparations. Vaccine 2008;26(35):4486–93.
[38] Tischer A, Andrews N, Kafatos G, Nardone A, Berbers G, Davidkin I, et al. Standardization of measles, mumps and rubella assays to enable comparisons of seroprevalence data across 21 European countries and Australia. Epidemiol Infect 2007;135(5):787–97.
[39] Andrews N, Pebody RG, Berbers G, Blondeau C, Crovari P, Davidkin I, et al. The European Sero-Epidemiology Network: standardizing the enzyme immunoassay results for measles, mumps and rubella. Epidemiol Infect 2000;125(1):127–41.
[40] Kafatos G, Anastassopoulou C, Nardone A, Andrews N, Barbara C, Boot HJ, et al. The European Sero-Epidemiology Network 2: standardization of assay results for hepatitis B virus. J Viral Hepat 2007;14(4):260–8.
[41] Nardone A, Miller E, Group E. Serological surveillance of rubella in Europe: European Sero-Epidemiology Network (ESEN2). Euro Surveill 2004;9(4):5–7 (bulletin Europeen sur les maladies transmissibles[[nl]]European communicable disease bulletin).
[42] Nardone A, Pebody RG, van den Hof S, Levy-Bruhl D, Plesner AM, Rota MC, et al. Sero-epidemiology of mumps in western Europe. Epidemiol Infect 2003;131(1):691–701.
[43] von Hunolstein C, Aggerbeck H, Andrews N, Berbers G, Fievet-Groyne F, Maple PA, et al. European sero-epidemiology network: standardisation of the results of diphtheria antitoxin assays. Vaccine 2000;18(28):3287–96.
[44] Tapia MD, Sow SO, Medina-Moreno S, Lim Y, Pasetti MF, Kotloff K, et al. A serosurvey to identify the window of vulnerability to wild-type measles among infants in rural Mali. Am J Trop Med Hyg 2005;73(1):26–31.
[45] Hepatitis B. Vaccines. Wkly Epidemiol Rec 2009;84(40):405–19 (Health Section of the Secretariat of the League of Nations[[nl]]Section d'hygiene du Secretariat de la Societe des Nations).
[46] Burton A, Monasch R, Lautenbach B, Gacic-Dobo M, Neill M, Karimov R, et al. WHO and UNICEF estimates of national infant immunization coverage: methods and processes. Bull World Health Organ 2009;87(7):535–41.
[47] Brown DW, Burton A, Gacic-Dobo M, Karimov RI, Vandelaer J, Okwo-Bele JM. A mid-term assessment of progress towards the immunization coverage goal of the Global Immunization Vision and Strategy (GIVS). BMC Public Health 2011;11:806.
[48] Stewart TA, Nolan TM, Hogg G, McEwen J. Antibodies to diphtheria, tetanus and pertussis in infants before and after immunization with DTP (Triple Antigen) vaccine. J Paediatr Child Health 1996;32(5):378–81.
[49] Gergen PJ, McQuillan GM, Kiely M, Ezzati-Rice TM, Sutter RW, Virella G. A population-based serologic survey of immunity to tetanus in the United States. N Engl J Med 1995;332(12):761–6.
[50] Cherry JD. Epidemic pertussis in 2012—the resurgence of a vaccine-preventable disease. N Engl J Med 2012;367(9):785–7.
[51] Cherry JD. Why do pertussis vaccines fail? Pediatrics 2012;129(5):968–70.
[52] Nokes DJ, Enquselassie F, Nigatu W, Vyse AJ, Cohen BJ, Brown DW, et al. Has oral fluid the potential to replace serum for the evaluation of population immunity levels? A study of measles, rubella and hepatitis B in rural Ethiopia. Bull World Health Organ 2001;79(7):588–95.
[53] Nigatu W, Samuel D, Cohen B, Cumberland P, Lemma E, Brown DW, et al. Evaluation of a measles vaccine campaign in Ethiopia using oral-fluid antibody surveys. Vaccine 2008;26(37):4769–74.
[54] Manikkavasagan G, Bukasa A, Brown KE, Cohen BJ, Ramsay ME. Oral fluid testing during 10 years of rubella elimination, England and Wales. Emerg Infect Dis 2010;16(10):1532–8.
[55] Ohuma EO, Okiro EA, Bett A, Abwao J, Were S, Samuel D, et al. Evaluation of a measles vaccine campaign by oral-fluid surveys in a rural Kenyan district: interpretation of antibody prevalence data using mixture models. Epidemiol Infect 2009;137(2):227–33.
[56] Hardelid P, Williams D, Dezateux C, Cubitt WD, Peckham CS, Tookey PA, et al. Agreement of rubella IgG antibody measured in serum and dried blood spots using two commercial enzyme-linked immunosorbent assays. J Med Virol 2008;80(2):360–4.
[57] Chakravarti A, Rawat D, Yadav S. Whole blood samples as an alternative to serum for detection of immunity to measles virus by ELISA. Diagn Microbiol Infect Dis 2003;47(4):563–7.
[58] Helfand RF, Keyserling HL, Williams I, Murray A, Mei J, Moscatiello C, et al. Comparative detection of measles and rubella IgM and IgG derived from filter paper blood and serum samples. J Med Virol 2001;65(4):751–7.

Please cite this article in press as: MacNeil A, et al. Issues and considerations in the use of serologic biomarkers for classifying vaccination history in household surveys. Vaccine (2014), http://dx.doi.org/10.1016/j.vaccine.2014.07.005

[59] Riddell MA, Byrnes GB, Leydon JA, Kelly HA. Dried venous blood samples for the detection and quantification of measles IgG using a commercial enzyme immunoassay. Bull World Health Organ 2003;81(10):701–7.
[60] Hayford KT, Al-Emran HM, Moss WJ, Shomik MS, Bishai D, Levine OS. Validation of an anti-measles virus-specific IgG assay with oral fluid samples for immunization surveillance in Bangladesh. J Virol Methods 2013;193(2):512–8.
[61] Hayford KT, Shomik MS, Al-Emran HM, Moss WJ, Bishai D, Levine OS. Measles vaccination coverage estimates from surveys, clinic records, and immune markers in oral fluid and blood: a population-based cross-sectional study. BMC Public Health 2013;13:1211.
[62] Posthuma-Trumpie GA, Korf J, van Amerongen A. Lateral flow (immuno)assay: its strengths, weaknesses, opportunities and threats. A literature survey. Anal Bioanal Chem 2009;393(2):569–82.
[63] Soeung SC, Rani M, Huong V, Sarath S, Kimly C, Kohei T. Results from nationwide hepatitis B serosurvey in Cambodia using simple and rapid laboratory test: implications for National Immunization Program. Am J Trop Med Hyg 2009;81(2):252–7.
[64] [No authors listed]. Expanded programme on immunization—estimating tetanus protection of women by serosurvey. Wkly Epidemiol Rec 1996;71(16):117–24 (Health Section of the Secretariat of the League of Nations[[nl]]Section d'hygiene du Secretariat de la Societe des Nations).
[65] 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. Bull World Health Organ 2002;80(9):696–703.

Please cite this article in press as: MacNeil A, et al. Issues and considerations in the use of serologic biomarkers for classifying vaccination history in household surveys. Vaccine (2014), http://dx.doi.org/10.1016/j.vaccine.2014.07.005