

2 Cohort Profile: The Kilifi Vaccine Monitoring Study

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23 Word count

24

25 Text 3183

26 Abstract 235

27

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2 **Summary**

3 Through the initiative of Gavi, The Vaccine Alliance, new vaccines are being
4 introduced at an unprecedented rate in most of the developing world while
5 assessments of vaccine impact, effectiveness and safety under real life conditions are
6 only rarely undertaken, especially in sub-Saharan Africa.

7 The Kilifi Vaccine Monitoring Study (KiVMS) is a large continuous population based
8 cohort study in Kenya designed to enable assessments of vaccine safety, direct and
9 indirect protection, and population immunity via nested sero-prevalence surveys. In
10 addition, it provides data to support mathematical models of the benefits and cost
11 effectiveness analyses for vaccines. It is being used to validate methods for assessing
12 vaccine coverage, to identify sub populations with low immunisation coverage as
13 targets for interventions, and to assess the non-specific effects of vaccination.

14 These are all facilitated by the unique integration of a vaccine registry or
15 immunisation system, a morbidity surveillance system (at the Kilifi County Hospital)
16 and the Kilifi Health and Demographic Surveillance System (HDSS). Participants are
17 recruited at birth or in-migration into the study area- Kilifi, a rural Indian Ocean
18 coastal part of Kenya. Vaccination events are recorded in real-time in the study area,
19 adult and paediatric hospital admissions undergo detailed clinical and laboratory
20 evaluation(s), and re-enumeration of all births, deaths, and migration events occurs 3
21 times a year.

2 Requests for data and other enquiries can be submitted to the data governance
3 committee, KEMRI-Wellcome Trust Research Programme [dgc@kemri-
4 wellcome.org and MOdhiambo@kemri-wellcome.org]

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2 **Why was the cohort set up?**

3 Childhood vaccination programmes have significantly reduced childhood morbidity
4 and mortality. (1) Since 2000, there has been an unprecedented expansion of routine
5 childhood vaccination and increased access to new vaccines in developing countries.
6 (2, 3) Vaccines protect the individual recipient (direct protection) but they may also
7 protect the whole population (indirect protection) if they interrupt the chain of
8 transmission of the target disease. (4, 5) Good quality population and individual level
9 epidemiological data are needed to estimate direct and indirect effects and inform
10 vaccination policy at national level. To assure society that a vaccine programme is
11 safe, it is also necessary to monitor for adverse events following immunisation
12 (AEFI).

13 During the introduction and expansion of access to new vaccines in low and middle-
14 income countries (LMICs), relatively little investments are allocated to evaluate the
15 impact and cost effectiveness of vaccination programmes which are required to
16 achieve long-term sustainability of new vaccine programmes in LMICs. The capacity
17 for these kinds of impact assessments has lagged significantly behind the introduction
18 of new vaccines. As a result, only a very small number of low-income countries have
19 the platforms required to assess vaccine impact, effectiveness and safety. Some
20 countries have national or sub-national platforms for monitoring vaccine coverage e.g.
21 in Health and Demographic Surveillance Systems, periodic multi-indicator cluster
22 surveys, and Demographic and Health Surveys (DHS). Although these can be linked
23 to mortality surveillance in HDSS sites to determine the population effects of
24 vaccines, data quality and interpretation is limited.

2 The Kenya Medical Research Institute-Wellcome Trust Research Programme
3 (KWTRP) in Kilifi set up the *Haemophilus influenzae type b* (Hib) conjugate vaccine
4 effectiveness study in 2000. It was further expanded in 2008 with addition of the real
5 time vaccine-monitoring component, in anticipation of the introduction of
6 pneumococcal conjugate vaccine (PCV) in Kenya. The objective of the Kilifi Vaccine
7 Monitoring Study (KiVMS), a long-term continuous cohort study, is to investigate
8 effectiveness, impact, coverage, safety and indirect vaccine effects by recruiting birth
9 cohorts as well as cohorts of older children and adults where applicable, within a well-
10 characterised population and area. In addition, KiVMS is used to explore the
11 determinants of vaccine coverage and acceptability in the population. Built on the
12 platform of a Health and Demographic Surveillance System (HDSS), KiVMS
13 integrates morbidity surveillance systems at the County Department of Health
14 (CDOH), Kilifi and a population-based, computerized information system for
15 collecting vaccination data. Therefore it has the following essential attributes:
16 continuously updated demographic data from the population of interest (e.g. births,
17 deaths and migration); and complete and accurate vaccination records for the
18 catchment population. Vaccine information systems are rare in tropical Africa.

19 Here, we describe the study population, and provide an overview of the data sources
20 and data management processes

21 **Who is in the cohort?**

22 **Setting**

23 Kenya is divided administratively into 47 counties. (6, 7) Kilifi County, on the Indian
24 Ocean Coast, is one of the poorest (6) and is typical of a rural equatorial Africa

2 setting. KiVMS is based in Kilifi with the area covered by the Kilifi HDSS (KHDSS)
3 as shown in figure 1. The KHDSS has a population of 280,000 covering an area of
4 891 km². (8)

5 **Inclusion**

6 The primary target of this study is the population of children aged <5 years, resident
7 in the study area. The KHDSS has a birth cohort of ≈8000 per annum. In addition, all
8 childhood in-migrants are recruited, along with their families, into the KiVMS during
9 re-enumeration rounds. From January 2011 to December 31, 2014, there were 33,962
10 children in the birth cohort database.

11 **Community engagement and governance**

12 KiVMS was conceived at the outset as collaboration between the Ministry of Health
13 and the KWTRP. A Memorandum of Understanding between both parties guides this
14 collaboration. Its purpose is to support national and regional policy making by
15 providing informative local data. In addition, this resource provides evidence to
16 support the functions of the newly established Kenya National Immunisation
17 Technical Advisory Group (KENITAG).

18 **Ethical approval**

19 The KEMRI Scientific and Ethics Review Unit approved this study and the activities
20 carried out on the KHDSS platform.

2 **What has been measured?**

3 *Basic demographic data*

4 Basic demographic data is obtained from the KHDSS platform. In brief, these include
5 GIS mapping of homestead location, household name and head, individuals, residency
6 status, births, deaths and migration. The KHDSS is a longitudinal surveillance of the
7 population living in a well-defined geographic area around Kilifi County Hospital
8 (KCH), which has been updated through household visits, monitoring vital events and
9 migration since the year 2000.(8)

10 *Ascertainment of vaccination*

11 Using an electronic vaccine monitoring system established at all 34 health facilities
12 delivering vaccines and 53-affiliated outreach sites in the KHDSS (Figure 1); data
13 clerks record vaccine data (table 1). Vaccine clinics are either government (26) or
14 privately (8) owned and located within or just outside the KHDSS boundaries.
15 Children presenting to these are matched to their unique personal record in the
16 population register. If their details do not exist in the KHDSS database, they are
17 registered as new once matched to the mother's homestead and details. If they are not
18 matched to a household, they are registered with a temporary identification pending
19 resolution of the associated data query. Manual registers provide a source of back-up
20 data for verification like the vaccine cards retained by mothers/care givers, which are
21 labelled with a unique identity number. Linkage of clinic and central server data is
22 achieved weekly; data captured at the clinics during daily operations are uploaded to
23 laptops brought on site by data supervisors and the latest version of the population
24 register is downloaded to data clerk's laptops. The population register is also updated
25 with data of children newly registered at the vaccine clinics and previously unknown

2 to the KHDSS. All of the data are delivered to the central data server at the KWTRP.
3 The synchronisation lag time is usually 1-week. The linkages between the constituent
4 parts of the KiVMS are outlined in **Figure 2**.

5 *Morbidity Surveillance*

6 All paediatric and adult admissions undergo detailed clinical and laboratory
7 evaluation(s) for vaccine preventable diseases surveillance at the KCH - a 172-bed
8 (and 20-cot) facility at the centre of the KHDSS area that provides primary care and
9 serves as a first-level referral hospital. (8) It is equipped for basic haematological and
10 biochemical tests and advanced microbiological culture. It also offers basic radio-
11 diagnostic support. (12) Records of births and maternal deaths are also recorded from
12 the maternity section in real time. KiVMS is supported by a bespoke database and
13 platform that integrates electronic health records at KCH with vaccination records and
14 the KHDSS population register. Individuals at admission or delivery are matched with
15 the population register, creating a permanent link between the patients' residence
16 record and the hospital event. Individuals are matched on five criteria: name, sex, date
17 of birth, residence and homestead characteristics.

18 *Cross sectional surveys*

19 Surveys of intermediary markers of vaccine impact, such as nasopharyngeal carriage
20 of pneumococci or serological responses to vaccine preventable diseases, are assessed
21 through recurrent standardised surveys by age-stratified random sampling of the entire
22 population. These have been used to determine the interruption of transmission of
23 pneumococci (9) and the population immunity to Hib vaccine (10). In addition, we

2 propose to validate epidemiological measures of vaccine coverage using these
3 samples.

4 **How often have they been followed up?**

5 Vaccination data is recorded at every vaccine clinic visit. Re-enumeration of births,
6 deaths, and migration events in the KHDSS occurs 3 times a year. (8) Nasopharyngeal
7 carriage studies are carried out annually and the serological surveys bi-annually. (9) In
8 addition, births are recorded continuously as they occur or at first contact in the
9 community during re-enumeration or at clinics during vaccination visits. Morbidity
10 surveillance at the KCH is continuous.

11 **What has been found? Key findings and publications**

12 *Vaccine impact using before-after studies*

13 The introduction, in 2001, of Hib conjugate vaccine (as Pentavalent vaccine with
14 diphtheria, tetanus, whole-cell pertussis and hepatitis B antigens) was the precipitant
15 for the development of the KiVMS. Using population linked morbidity surveillance;
16 we showed an 88% effectiveness of the vaccination programme against invasive Hib
17 disease incidence among children aged less than 5 years within 3 years of introducing
18 the vaccine. (11) Fifteen years on, and without a booster dose, vaccine effectiveness is
19 93% and serosurveys confirm enduring population immunity. (10)

20 KiVMS currently supports the Pneumococcal Conjugate Vaccine Impact Study
21 (PCVIS), a before-after study of the impact of the 10-valent pneumococcal conjugate
22 vaccine (PCV-10) introduced in January 2011. Linkages between the vaccine registry
23 and morbidity surveillance databases permit an individual-based cohort analysis of the

2 entire population by connecting rates of IPD to vaccine status. Dividing the numbers
3 of IPD cases by the person-years of observation in different exposure strata
4 (unvaccinated, partially and fully vaccinated) provides estimates of the total and
5 indirect effects of PCV-10. The impact on the incidence of clinical and radiologically
6 confirmed pneumonia and invasive pneumococcal disease will be reported in 2016.

7 KiVMS was recently adapted to estimate the impact of the newly introduced rotavirus
8 vaccine. Between 2002-2004, incidence of hospitalisations with Group A rotavirus
9 gastroenteritis was 1,431 (95% Confidence Intervals [CI] 1,275–1,600) per 100,000
10 person years of observation (pyo) in infants. (12) On-going surveillance shows these
11 rates have declined appreciably over time pre vaccine introduction in July 2014. It is
12 important to adjust for secular trends like these in assessments of vaccine impact
13 especially if this change is thought to be due to changes in associated risk factors.
14 Rotavirus vaccination impact data will be available in 2017.

15 *Epidemiological studies of transmission and seroprevalence*

16 Following the introduction of PCV-10 with a catch-up campaign in all children aged
17 <5 years in the KHDSS, annual studies of nasopharyngeal carriage demonstrated a
18 reduction of 64% (95% CI 49-74%) in the prevalence of vaccine serotype
19 pneumococci among children aged <5 years. There was also a 66% (95% CI 38-82%)
20 reduction in carriage prevalence among unvaccinated older children and adults,
21 illustrating a profound and rapid indirect protection and predicting a decline in IPD
22 across the whole population. (9)

2 *Assessments of vaccine coverage, timeliness and equity*

3 KiVMS provides a platform to validate administrative and survey-based methods for
4 assessing vaccine coverage. Similar to others, (13) we found that compared to survey
5 data, administrative estimates exaggerate vaccine coverage.(14) Within KHDSS, we
6 have observed that seasonality and family size are strong factors that determine
7 coverage. (14, 15) KiVMS allows for review of patterns of coverage over time to
8 monitor programme performance by birth cohort and locations (Figures 3A-B); it
9 gives insights into equity of access by its sensitivity for identification of sub-
10 populations with low vaccination coverage (Figure 3C); and can also be used to
11 investigate vaccine failures and target interventions. Predictors of vaccine inequity
12 and hesitancy in at-risk groups such as recent migrants, young mothers and in
13 geographic pockets of poor coverage can also be investigated.

14 *Complex before and after studies*

15 Before-after studies are susceptible to similar biases as case-control studies. In routine
16 practice, the population of children who are not immunised may differ from the
17 majority with respect to background incidence or extent to which their disease
18 outcome can be fully ascertained. An accurate estimate of effectiveness for individual
19 protection (direct effect) can only be obtained by adjusting for confounding by
20 ‘healthy’ vaccinees (16). It is important to identify these ascertainment biases and
21 control for them to the extent possible, for example by estimating the protection from
22 disease by receipt of an unrelated vaccine. The schematic shown in Figure 4
23 highlights the various cohort and incidence rate comparisons required to estimate the
24 overall vaccine impact as well as the direct and indirect protection of a vaccine.

2 A further complexity arises from secular changes in disease risk factors. As vaccine
3 ‘exposure’ is always associated with time in a before-after study, any risk factor that
4 also varies with time may be a confounder. In tropical Africa, the risk factors for
5 vaccine preventable diseases are complex and may include malaria, malnutrition and
6 HIV infection. Analyses of incidence ratios attributable to vaccination in an
7 interrupted time series analyses for example (17), can adjust for secular trends in
8 major confounders but only if these data are available. By virtue of its setting within a
9 community and hospital-based research station of over 25 years duration, the KiVMS
10 has access to data on many of these variables. (18)

11 *Vaccine Safety Monitoring*

12 KiVMS follows a relatively small annual birth cohort compared to the national
13 immunisation programme but it has the capacity to accurately define temporal
14 associations between recent vaccination and deaths or serious life-threatening events
15 presenting to hospital. When the WHO considered the introduction of PCV10 as a
16 two-dose vial without a preservative, they were concerned about the theoretical risk of
17 bacterial contamination of an opened vial leading to AEFI after the second dose in the
18 vial. We studied the problem for the first two years of introduction. The absence of
19 any measurable safety signal in vaccination site abscesses, sepsis or death after
20 immunisation helped in the approval of PCV10 introduction into other countries using
21 the 2-dose vial. (19)

22 Because the mortality burden attributable to many vaccine preventable diseases is
23 high in sSA, the issue of vaccine safety has not been the primary focus of society.
24 However, experience from developed countries suggests that vaccines may be valued

2 less highly once the target disease has been brought under control and assurances of
3 safety are essential for the sustainability of the programme.

4 In 2014, Kenya scaled up its maternal tetanus vaccination programme because earlier
5 efforts and success had brought the country within range of the global maternal and
6 neonatal tetanus elimination threshold i.e. incidence < than 1 case per 1,000 live births
7 (20). Unfortunately, a group of religious leaders accused the government of planning
8 to sterilise women by giving Beta-Human Chorionic Gonadotropin (HCG)-containing
9 tetanus vaccines and campaigned against this initiative. (21) To support their position,
10 they argued the expanded programme was not justified because there were no more
11 cases of neonatal tetanus in the country. However, data from Kilifi clearly showed the
12 impact of the immunisation programme and the need to build on the progress
13 achieved already. (22)

14 **What are the main strengths and weaknesses?**

15 The evaluation of population impact and safety in the diverse epidemiological settings
16 where vaccines are introduced receives less attention compared to Phase III Trials to
17 demonstrate individual vaccine efficacy. Although KiVMS has evolved to meet a
18 specific need in Kenya, its principal strength is its unique integration of a vaccine
19 registry and a morbidity surveillance system on top of the largest HDSS in Africa. As
20 a cohort study and integrated surveillance platform, it facilitates population level
21 vaccine impact assessments. The benefits of such a set-up have recently been
22 recognised by the INDEPTH network in its recently proposed model: the
23 Comprehensive Health and Epidemiological Surveillance System (CHESS). (23) It is
24 a very efficient study template for gathering data on vaccine effectiveness and safety

2 that can be copied or deployed across heterogeneous locations in the developing
3 world. It has provided evidence of direct and indirect vaccine effectiveness (9, 11),
4 vaccine safety (19), provided insights into vaccination coverage (14, 15) and
5 facilitated cost effectiveness analyses using models for pneumococcal,(24) rotavirus
6 (25) and Hib vaccines (26), that have directly influenced national and regional policy.

7 Vaccine monitoring is conducted in clinics entirely by CDOH staff. The KWTRP
8 provides the design, training, data collation, cleaning and analysis. This integration
9 with the health ministry personnel is another strength of KIVMS that has shaped
10 significantly by more than a decade of collaboration. This has proven essential both
11 for the smooth running of the programme and for the effective use of results.

12 The KEMRI SERU approved the creation of KiVMS as part of the KWTRP.
13 Importantly, all community-based research at the KWTRP is part of an integrated
14 system of community engagement using a wide range of channels including
15 community representative groups and open public meetings to ensure that the research
16 conducted under KiVMS is locally relevant.

17 As expected of a resource poor setting, there are challenges of logistics and
18 infrastructure. The limited coverage and instability of power supplies, along with
19 inadequate roads and mobile phone networks present tremendous challenges. As the
20 project did not have capacity for electronic data capture during outreach services
21 (where health care workers travel intermittently to numerous alternative delivery
22 points e.g. schools), back-up paper systems were deployed. Supplementary
23 immunisation activities (e.g. for measles and polio) are also conducted in KHDSS

2 communities from time-to-time. However, the present infrastructure of KiVMS only
3 allows for the recording of routinely delivered vaccinations.

4 In KiVMS, it is critical to identify individuals accurately from the population register
5 and link them to events such as vaccination or hospital admission. Identification is
6 generally easier at vaccine clinics than hospitals because mothers and data clerks
7 know the local area in detail and geographical residence is a key identity criterion.
8 However vaccine clinics are very busy environments and personal ID matching is still
9 slow, and occasionally inaccurate. An incident record is opened when ID mismatches
10 occurs which is resolved by data supervisors and managers of the vaccine registry and
11 KHDSS at the KWTRP. Fingerprinting technology solutions were considered but
12 would not work for our primary target population-young infants- as their fingerprint
13 patterns are not reliably distinguished at this age.

14 Although KHDSS detects in and out migrations in its study area, the data capture in
15 local clinics cannot record vaccinations received by migrants if they had received all
16 of their vaccines prior to moving into the area and do not visit the vaccine clinics, or
17 experience hospitalisation at KCH. In addition, migration itself may be a risk factor
18 for poor uptake. (27, 28) Consequently, data for migrants is less complete and there is
19 a risk of misclassification. To capture these data as far as it is practically possible, we
20 instituted vaccine-card surveillance for KHDSS in-migrants aged <5 years, which are
21 effectively a small population sample, during re-enumeration rounds. This will
22 improve completeness of data for this small but often at risk group. In table 2, we
23 show the merits of an electronic vaccine registry compared to use of HDSS
24 enumeration rounds for routine collection of all vaccine data.

2 KHDSS, the largest surveillance of its kind in tropical Africa, is suitable for the study
3 of vaccine impacts against common diseases (e.g. invasive Hib and pneumococcal
4 disease) but cannot provide the richness of detail e.g. strain-specific or age-specific
5 vaccine efficacy afforded by national surveillance systems. This limitation is most
6 apparent in the study of vaccine safety as the levels of severe AEFI for licensed
7 vaccines are infrequent in epidemiological terms and cannot easily be associated with
8 vaccine in a population of this size. One solution to this is to link several HDSS
9 platforms together, within country, as we have done in Kenya to examine PCV10
10 safety. (19)

11 **Can I get hold of the data? Where can I find out more?**

12 Investigators with interest in datasets or collaborations can contact Millicent
13 Odhiambo (modhiambo@kemri-wellcome.org) and the KWTRP data governance
14 committee (dgc@kemri-wellcome.org) with a statement of request and formal
15 application for data transfer. In addition, they can contact the principal investigator,
16 Professor Anthony Scott (ascott@kemri-wellcome.org) and/or co-investigator, Dr.
17 Ifedayo Adetifa (IAdetifa@kemri-wellcome.org). There is more information on the
18 KWTRP website, www.kemri-wellcome.org.

Key Messages

- The Kilifi Vaccine Monitoring Study (KiVMS) is a long-term continuous cohort study set up to investigate the effectiveness, impact, coverage, safety and indirect vaccine effects by recruiting birth cohorts and where applicable, cohorts of older and adults.
- It is based in the area covered by the Kilifi Health and Demographic Surveillance System, Kilifi, Kenya and currently has records of 33, 962 children in the birth cohort database.
- A major strength of KiVMS is its unique integration of a vaccine registry, a morbidity surveillance system and the largest health and demographic surveillance system (HDSS) in Africa.
- Requests for data and/or collaboration should be sent to dgc@kemri-wellcome.org and MOdhiambo@kemri-wellcome.org

2 *Funding*

3 KiVMS is funded by a number of sources notably Gavi, The Vaccine Alliance, and
4 the Wellcome Trust. JAGS, TNW and JN are funded through fellowships from the
5 Wellcome Trust (098532, 091758 and 090853 respectively)

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2 **Acknowledgements**

3 We thank the people of Kilifi County and the staff at the offices of the County
4 Commissioner, the County Medical Officer of Health and the Medical Superintendent
5 at Kilifi County Hospital. We acknowledge the tremendous work of the Kilifi sub-
6 County Public Health Department team, all field staff, data clerks and analysts
7 responsible for collection and processing of vaccination, morbidity and mortality data.

8 Thanks to Christopher Nyundo for producing the maps.

9 This article is published with the permission of the Director of the Kenya Medical
10 Research Institute.

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