2019

PROTOCOL FOR SELECTION OF SENTINEL SITES FOR SCHISTOSOMIASIS & SOIL-TRANSMITTED HELMINTHS AND ANNUAL SENTINEL SITE SURVEILLANCE FOR ESWATINI

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ACRONYNMS

ALB Albendazole

ESPEN Expanded Special Project for Elimination of Negleted Tropical Diseases

IU Implementation unit

MDA Mass Drug Administration

MoH Ministry of Health

NTD Neglected Tropical Diseases

POC CCA Point-of-care Circulating cathodic antigen

PZQ Praziquantel

SAC School-age Children

STAG Strategic and Technical Advisory Group

STH Soil-Transmitted Helminths

WHO World Health Organisation

WHO-AFRO World Health Organisation Regional Office for Africa

SUMMARY

The Kingdom of Eswatini is endemic for schistosomiasis (SCH) and soil-transmitted helminth (STH) infections, two of the most prevalent Neglected Tropical Diseases (NTDs) in sub-Saharan Africa. Up to 275 schools were purposefully selected for mapping and 13,750 school children comprising of 25 girls and 25 boys aged 10-14 years from each school were screened during the baseline mapping in 2015. Following completion of the mapping exercise, Eswatini started mass drug administration (MDA) for SCH and STH in 2016, and have conducted 3 rounds of MDA so far. As is the case with majority of countries in the region, Eswatini has not implemented sentinel site surveillance for schistosomiasis due to paucity of resources and unclear guidance. Sentinels sites for schistosomiasis are critical for monitoring the programme in order to detect any problem such as low impact of the treatment, high reinfection, resurgence etc., and to correct these issues immediately. The current protocol informs the selection of sentinel sites for SCH in Eswatini, which is a small country with small population size. Briefly, sentinel sites were purposively selected based on the recommended proportionality to target population (school-age children), but additional locations were included to ensure better representation across the control landscape.

A representative sample of 22 sentinel sites (schools) were purposively selected from sampling frames [(i) population in an ecological/geographical zone; (ii) endemicity risk categories for schistosomiasis i.e. high (Prev. ≥50%), moderate (Prev. ≥ 1%0 and <50%) and low (Prev. >0% and <10%), (iii) treatment coverage threshold (desired target ≥75%; and less than desired target <75%) and (iv) species representation]. The protocol was developed by the WHO consultants with participation of Eswatini NTD program managers. It is expected that Eswatini will now implement sentinel site monitoring activities for SCH.

This protocol is developed in the context of two outstanding challenges for the schistosomiasis Global community which are currently being addressed by a WHO constituted Strategic and Technical Advisory Group (STAG) for schistosomiasis:

1. Need to redefine the implementation unit (IU) which is by default set at a District-level (there is an ambiguity in the size of Districts and in IUs which leads to implicit complications in later drug allocation as the focal nature of schistosomiasis is ignored)
2. Need to resolve the ambiguity/lack of clarity over definition of an 'ecological zone'.

BACKGROUND

A review by a schistosomiasis consultancy commissioned by ESPEN in November 2017 revealed that majority of countries in the region are not implementing sentinel site surveillance for schistosomiasis due to paucity of resources and/or unclear guidance. Where sentinel sites have been established, the processes used have not reflected the epidemiology of schistosomiasis and the focal disease status consideration in the strategy of setting sentinels sites. This is largely due to lack of detailed clear guidance for Programme Managers, in the current guidelines:

1. WHO, 2002: *Helminth control in school-age children. A guide for managers of control programmes: First Edition*

The guidance in this manual only provided an example from Cambodia on very limited information on Morbidity monitoring by the Cambodia control programme (Page 49), but does not provide any information on how to select sentinel sites.

2. WHO, 2006: *Preventive Chemotherapy in Human Helminthiasis - Coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers*. Page 33

   "Simple and measurable indicators applicable to each of the four helminthic diseases included in this manual are shown in Table 3. Detailed recommendations as to monitoring of impact will also be included in the separate manual on monitoring and evaluation of preventive chemotherapy interventions. Until this is available, preventive chemotherapy programmes should apply disease-specific procedures currently in use."

The guidance in this manual was scanty and yet to be developed, only providing the indicators to be monitored.

3. WHO, 2011: Helminth control in school-age children. A guide for managers of control programmes: Second Edition. Page 36-55.

   "To ensure that the control programme is adequately monitored, sentinel sites should be located in each homogeneous ecological zone (see section 2.1). Each such zone normally covers several districts in a country (see Example 9) and can also be composed of non-contiguous districts". Section 5.1.1 Location of sentinel sites: Page 48.
   "One sentinel site for every 200,000-300,000 targeted children is suggested; the proportion can be increased in the case of small-scale interventions....cluster sampling..." Section 5.1.2 Number of sentinel sites: Page 48.

The stratified sampling method described in this guidance does not take into consideration the focal nature of schistosomiasis, and the various peculiarities of representaiton of various intervention areas that need to be monitored.

The WHO, 2011 guideline also provides that sentinel site survey use a cross-sectional methodology, including baseline data collection and follow-up surveys following every two rounds of treatment (WHO, 2011). This method assumes that changes in the prevalence and intensity of schistosomiasis and STH infections in a limited number of sentinel sites (schools) will provide sufficient information on the programme's progress in the entire area. However, sentinel sites for schistosomiasis are meant to reflect the situation of the foci rather than the situation of the disease in the overall country, and therefore can be used to monitor the programme in order to detect any problem such as low impact of the treatment, high reinfection, resurgence etc., and to correct these issues immediately. Therefore, more frequent surveys for instance annually are critical in not only detecting problems for corrections, but for also showing trends on the impact of MDA based on data from multiple timepoints within the 5-6 year period.

4. WHO, 2014: Guide for Mapping Neglected Tropical Diseases Targeted by Preventive Chemotherapy in the African Region

There is no mention of sentinel sites and the process of their selection in this 2014 guide for mapping. However, the mapping guide provides a graphical description of "ecological zones" to be considered for selection of sites to be used for mapping.

Appropriate sentinel site monitoring will contribute towards increased treatment coverage from year to year, and ensure that impact assessments or remapping after 5-6 years of MDA can lead to scaling down decisions. Therefore, while waiting for a more clarified guidance to countries on selecting these sentinels sites for schistosomiasis, countries that need to set up sentinel sites for continued monitoring and/or are due for impact assessments need to make localized decisions based on the resources available, the country technical capacity, and the areas of interest according to the distribution of the disease, and where the programme may anticipate problems.

The Kingdom of Eswatini is a small but scenic landlocked country in Southern Africa, enjoying a tropical to near-temperate climate and a rich culture, and on the right path to being in the top 10% of the human development group of countries, in line with the Kingdom's National Development Strategy vision 2022. There are 55[1] Tinkundla (districts) in the Kindgom. The Inkundla is the implementation unit (IU) in Eswatini. Both schistosomes (SCH) and soil-transmitted helminths (STH) are present in all the Tinkundla. The Eswatini SCH & STH control program is a school-based control programme which commenced mass drug administration in schools in 2016. So far, the program has conducted 3 annual rounds of MDA (2016, 2017 & 2018). Being a school-based control programme, the proposed system for the periodic collection of parasitological data for monitoring purposes is the use of sentinel sites. A sentinel site in this context is a school in which stool and urine specimens from approximately 50 children in the third-year class are investigated (WHO, 2011).

This protocol describes the process of selection of sentinel sites and implementing routine sentinel site monitoring. It is envisaged that this protocol will serve as a template to inform the design and selection of other sentinel sites in countries endemic for SCH

[1] *The number of Tinkhundla has increased to 59 but the data is yet to be updated*

that are conducting mass drug administration. However, it should be noted that countries will differ significantly in terms of sizes of Implementation units, disease transmission dynamics, resources etc all of which need to be taken into account when developing M&E plans.

CURRENT COUNTRY-CONTEXT INFORMATION

Geographical size and Population:
Eswatini is a small country (total area of 17,363 km^2), with a population of 1.1 million people, of which 23.6% are SAC.

IU geographical size and population density:
The IU geographical size is small and population is low, with a population density of approximately 57 persons per square kilometre.

Programmatic goal:
The current programmatic goal is morbidity reduction, 80% reduction of the prevalence of schistosome after five rounds of MDA.

Current Country prevalence:
Eswatini is a low endemicity country for both SCH (*S. mansoni* 0.3%, *S. haematobium* 16%) and STH 5.2%. *S. haematobium* is the predominant schistosome species. With this low prevalence, Eswatini represents one of the few countries where elimination of SCH is feasible.

Intervention:
Treatment with praziquantel every other year and annually with albendazole.
Our direct analysis of the baseline prevalence data shows Tinkhundlas stratified into the risk categories (see Table 1) according to WHO guidelines (WHO, 2006).

Table 1: Distribution of Tinkhundlas into different risk categories for SCH and STH MDA

Risk Category	Schistosomiasis	Soil transmitted helminthiasis
High risk	0	0
Moderate risk	38 (69.1%)	N/A
Low risk	17 (30.9%)	2
>0% but <20% for STH	-	50
None endemic	0	3
Total	**55**	**55**

Target:
School-age population (5-14 years old) in the entire country (approximately 258,004 children).

Agro-Ecological zones (Ecological zones):

Eswatini can be divided into four main agro-ecological zones[2] based on elevation, landforms, geology, soils and vegetation:

1. *Highveld in the west (approximate SAC population 76,072)*
2. *Middleveld in the centre (approximate SAC population 112,739)*
3. *Lowveld in the central east (approximate SAC population 55,858)*
4. *Lubombo Plateau in the far east (approximate SAC population 13,335)*

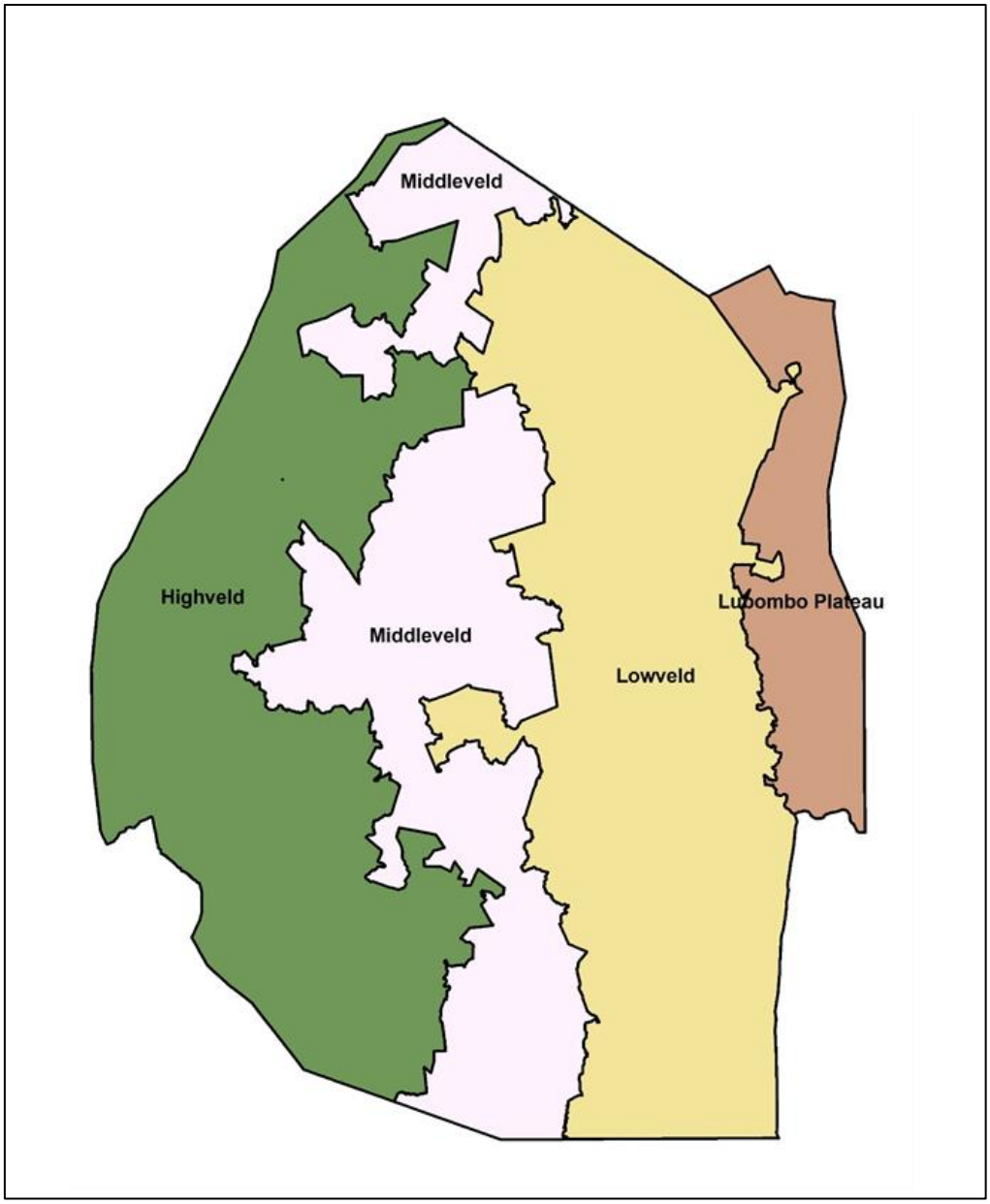

Figure 1. Ecological zones in Eswatini

[2] *The definition of an 'ecological zone' is still ambiguous*

In terms of size, the Highveld, Middleveld and Lowveld occupy about one-third of the country each, whereas Lubombo Plateau occupies less than one-tenth of the country. The climatic conditions range from sub-humid and temperate in the Highveld to semi-arid in the Lowveld. However, these zones are not strictly related to transmission of schistosomiasis, and risk of infection exists in all the 4 zones. Given that the classification of the agro-ecological zones closely mirror the proposed definition of an 'ecological zone' for schistosomiasis (*geographical area that is homogenous in terms of humidity, rainfall, vegetation, population density, and sanitation level*), there was a consensus with the country NTD team that the agro-ecological zones be reasonably used as ecological zones for Eswatini.

Middleveld and Lubombo plateau are the two zones where rivers flow slowly and stagnant pools form, and represent the zones with the highest risk of bilharzia infection. Swimming, washing and drinking are the main water contact activities along the rivers and streams, driven by the high temperatures and the lack of alternative water supply sources. Domestic animals use the same water and contaminate it, increasing the risk of transmitting infections to humans (http://www.fao.org/nr/water/aquastat/countries_regions/SWZ/SWZ-CP_eng.pdf).

Eswatini has four main river systems, namely:

- The Komati and Lomati systems, in the north of the country, both originate in South Africa and flow out of Eswatini back into South Africa, before entering Mozambique;
- The Mbuluzi River rises in Eswatini and flows into Mozambique;
- The Usuthu River, together with a number of major tributaries, originates in South Africa and flows out into Mozambique, forming the border between Mozambique and South Africa;
- The Ngwavuma, in the south of the country, rises in Eswatini and flows into South Africa before entering Mozambique.

The fifth river system contributing to the surface water resources of Eswatini is the Pongola River, which is found in South Africa, south of Eswatini. The Jozini dam, built on the South African side, floods some land on the Eswatini side and the water is available for use in Eswatini (http://www.fao.org/nr/water/aquastat/countries_regions/SWZ/SWZ-CP_eng.pdf).

There are nine major man-made dams with a height of more than 10 metres.

(http://waterwiki.net/index.php?title=Facing_Water_Challenges_in_Swaziland:_A_WWDR3_Case_Study)

Figure 2. The main river systems and dams in Eswatini

Objectives for Impact Monitoring & Evaluation using Sentinel sites

1. To determine the impact of MDA on prevalence and intensity of schistosomiasis & STH from periodic collection of parasitological data in selected foci for timely situational analyses.
2. To determine trends of prevalence and infection intensities for schistosomiasis following regular MDA through annual collection of parasitological data in sentinel sites.
3. To determine drug efficacy of praziquantel for schistosomiasis and albendazole for STH.

METHODOLOGY

Selection and location of sentinel sites

1. Number of sentinel sites:

The number of sentinel sites needed must be determined at the outset for each ecological zone based on the target population in that ecological zone.

The current WHO guidelines recommend that number of sentinel sites should be proportional to the number of target population (in this case school-age children) living in each zone. One sentinel site is recommended for every 200,000-300,000 children (WHO, 2011). The suggested ratio of sentinel sites to target population takes into consideration the fact that cluster sampling is used (50 children examined in each school) in several control programmes (Belizario et al., 2009; Koukounari et al., 2007) and offers several advantages (see WHO 2011).

However, for Eswatini baseline mapping, the selected schools/sites were at a ratio of one site/school for 4,000 population, and therefore represents already an advantageously high sampling frame.

To ensure that the control programme is adequately monitored, sentinel sites should be located in each homogeneous ecological zone. While the exact determination of each ecological zone can be ambiguous, such a zone normally covers several IUs in a country and can also be composed of non-contiguous IUs. To evaluate the national programme, sentinel schools do not have to be in every IU.

2. Method for selection of sentinel sites from the ecological zones:

According to the WHO 2011 guidance, a stratified sampling method should be used to select the schools that will serve as sentinel sites. For example, if 5 sentinel schools are needed in an ecological zone with a total of 20 IUs, a number should be assigned to each IU and a table of random numbers used to select 5 IUs.

Alternatively, a lottery method can be used: the names of all 20 IUs are written on separate pieces of paper which are placed in a container – 5 names are then drawn from the container. Once the 5 IUs are selected, one school in each IU can be randomly selected by the local team (using the list of schools that is normally available at district level).

However, the challenge with relying entirely on this approach is that it can leave out specific peculiarities that need to be determined purposively. For Eswatini, all sentinel sites were selected from the 275 schools that participated in the mapping in 2015. This will ensure that there is baseline data for comparison. Repeat cross-sectional surveys will then be conducted in a representative sample of sentinel sites. In order to take into consideration the small population size, the low prevalence of schistosomiasis and the need to select sentinel sites that address the focal nature of schistosomiasis, sentinel sites were selected as outlined below:

The representative sample of sentinel sites (schools) was selected from **sampling frames** [population in an ecological/geographical zone, endemicity categories (high, moderate or

low)] treatment coverage threshold and species representation), according to 4 main criteria, in a sequential manner:

1. The endemic areas were grouped according to the ecological zone based on mapping data and the population of the target population (SAC) was determined for each zone. One school from those involved in mapping, with the highest *S. haematobium* prevalence was **purposively selected** in each of the 4 ecological zones. Given that the sites used for mapping were at a ratio of one site/school for 4,000 population, and all the zones had <200,000 of the target SAC population, the single site per zone represents already an advantageously high sampling frame.

2. Each of the four ecological zones was then sub-grouped into endemicity categories of high (≥50%), moderate (≥10 to ≤50%) or low (>0% but <10%) according to the current WHO preventive chemotherapy guidelines. One school was **randomly selected**[3] in each of the endemicity strata in each of the 4 zones. Given that *S. haematobium* is more prevalent than *S. mansoni* or STH in Eswatini, and schistosomiasis is more focal than STH with STH having a more homogenous distribution, the selection of sites based on endemicity categories was informed by prevalence of *S. haematobium*.

3. Each of the four ecological zones was then sub-grouped into treatment coverage thresholds of ≥75%[4] and below 75%. ***Treatment coverage is helpful in the selection of appropriate areas for this assessment (that is, if only high-coverage areas are included in the sampling, the parasitological survey would probably overestimate the impact of the control programme and vice versa.* Two sentinel sites were **randomly selected** from each of the 2 treatment coverage strata in each of the 4 ecological zones: one sentinel site that achieved ≥75% coverage and another sentinel site that had <75% coverage or in areas where there were significant logistical challenges in conducting MDA or where the programme anticipates problems). Treatment coverage was based on the most recent (2018) coverage data.

4. Criteria 1, 2 & 3 above were then checked for endemic species representation. Since Eswatini is co-endemic for *S. haematobium*, *S. mansoni* and STH, it was critical to select sentinel sites that contained a representation of SCH species (*S. haematobium* & *S. mansoni*) and STH in the ecological zones.
    a. *S. haematobium* + *S. mansoni* + STH
    b. *S. haematobium* + STH
    c. *S. mansoni* + STH

[3] *The purposive stratification prior to random selection ensured that the sites eventually selected were still reflective of schistosomiasis endemicity*
[4] 75% treatment coverage is the desired coverage to meet the 2020 global goal

The recommended random selection of Tinkhundlas per ecological zone was not considered as an initial step in selection of sites, but rather sites were selected directly from each ecological zone that was treated as one homogenous unit. This approach was informed by the following reasons:

i. the ecological zones in Eswatini are composed of non-contiguous districts (Tinkhundlas) without clear delineation of boundaries for some Tinkhundlas.
ii. the small size of the country (takes less than 3 hours to travel from any farthest point to the centre of the country)
iii. the fact that a maximum of only 3 sites was envisaged for each of the sampling frames (aforementioned in 1 to 3).

Note:

For criteria 2, 3 & 4 above, compile a sampling frame (a list of all primary schools) within each of the sub-groups. Then randomly select the required number of schools as sentinel sites.

Criteria 4 needs to be performed only when there is confirmation of lack of species representation among sites selected in the preceding criteria 1, 2, & 3 i.e. *criteria 4 need not to be mutually exclusive of 1, 2 & 3*, and may be performed only in the ecological zones where there is lack of species representation.

3. Random selection of schools from sampling frames to serve as sentinel sites (For steps 2, 3 & 4 only)

A sampling frame was compiled as a list of primary schools that participated in the baseline mapping survey within each sub-group area.

The required number of schools was then randomly selected within each sampling frame as sentinel sites as outlined in the steps below:

For Criteria 2:

a. Schools were sorted out into endemicity subgroups (high, moderate, low) for each ecological zone based on increasing prevalence of *S. haematobium* in an Excel worksheet. The list of schools contained school names and previously assigned unique codes that linked them to the ecological zones.
b. A number was assigned to each school within an endemicity sub-group in an ecological zone in increasing order.
c. A random number was then generated (based on the minimum and maximum range of numbers assigned in b above) to select one representative school from the list for each endemicity sub-group in each ecological zone using the online random number generator (https://www.random.org).
d. Once a random number was generated, it was then matched to the corresponding unique school code and the school was selected for each endemicity sub-group in an ecological zone.
    - Although the WHO 2011 guideline states that *"All schools in the district (IU), including private, religious and other special schools should be included in the sampling frame"*, this approach will likely not work where baseline data is

required for monitoring (in the event that a school that did not participate in mapping ends up being selected and hence no baseline information for that school would be available).

For Criteria 3:

a. Schools were sorted out into treatment coverage subgroups (>75% and <75%) for each ecological zone based on increasing coverage in an Excel worksheet. The list of schools contained school names and previously assigned unique codes that linked them to the ecological zones.
b. A number was assigned to each school within each treatment coverage sub-group in an ecological zone in increasing order.
c. A random number was then generated (based on the min and max range of numbers from numbers assigned in b above) to select one representative school from the list for each treatment coverage sub-group in each ecological zone using the online random number generator (https://www.random.org).
d. Once a random number was generated, it was then matched to the corresponding unique school code and the school was selected for each treatment coverage sub-group in an ecological zone.

The same sentinel schools will be used to monitor the impact of the programme over the years.
The number of schools do not have to be the same in the sub-groups or ecological zones.

Note:
Repeating the data collection in the same schools may result in increasing awareness in those schools and therefore in a reduction in transmission that does not reflect the situation in the other (unsampled) schools. To avoid this bias, 50% of the sentinel schools can remain the same over the years while the location of the remaining 50% can be changed every year.
For Eswatini, since the Sentinel site surveys are commencing post mid-term with only 2 more rounds of MDA to go for this current 5 year round, the same sentinel sites can be used for the remaining 2 years. The approach to change 50% annually can then be employed after end-term evaluation/Impact assessment.

Schematic of M&E Programme based on Sentinel site surveys for Eswatini

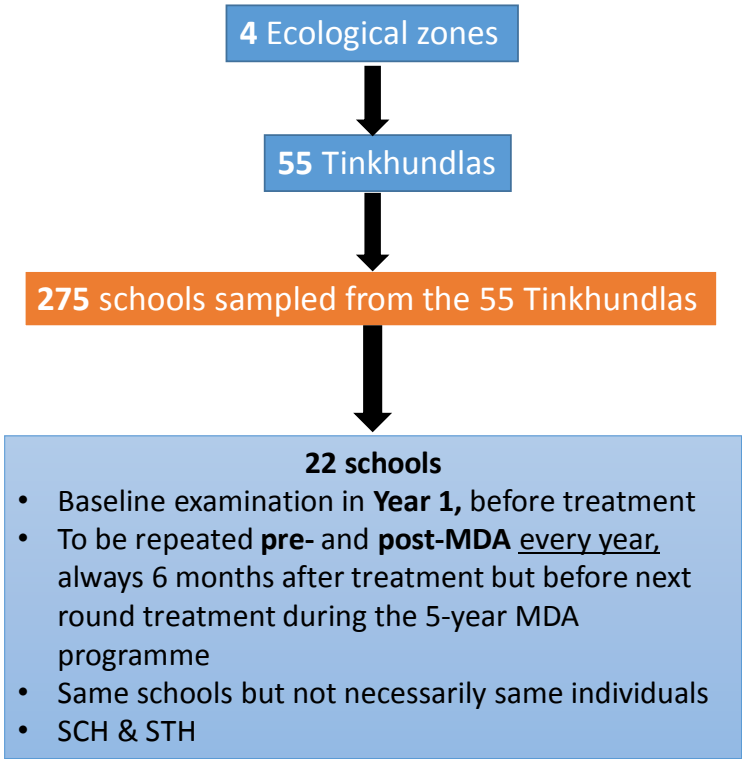

Table 2: A summary of the number of sites selected as sentinels based on the above criteria

	Criteria							
Ecological zone	**Population**[5]	**Endemnicity**			**Treatment coverage**		**Endemic Species representation**[6]	**Total number of sentinel sites**
		High	**Moderate**	**Low**	**Desired (≥75%)**	**Low (<75%)**		
Highveld	1	0	1	1	1	2[7]	0	6
Middleveld	1	1	1	1	1	1	0	6
Lowveld	1	1	1	1	1	1	0	6
Lubombo Plateau	1	0	1	1	1	0	0	4
Total	4	2	4	4	4	4	0	22

Additional characteristics for each of the sentinel sites selected is provided in **Annex 1.**

[5] *One school with the highest S. haematobium prevalence was purposively selected from each population strata*

[6] *There was adequate species representation in the sentinel sites that were selected, therefore no additional sites were selected based on Criteria # 4.*

[7] *One additional site was selected since it had the lowest treatment coverage of 16.5% and the program wished to include this as a site where problems may be anticipated*

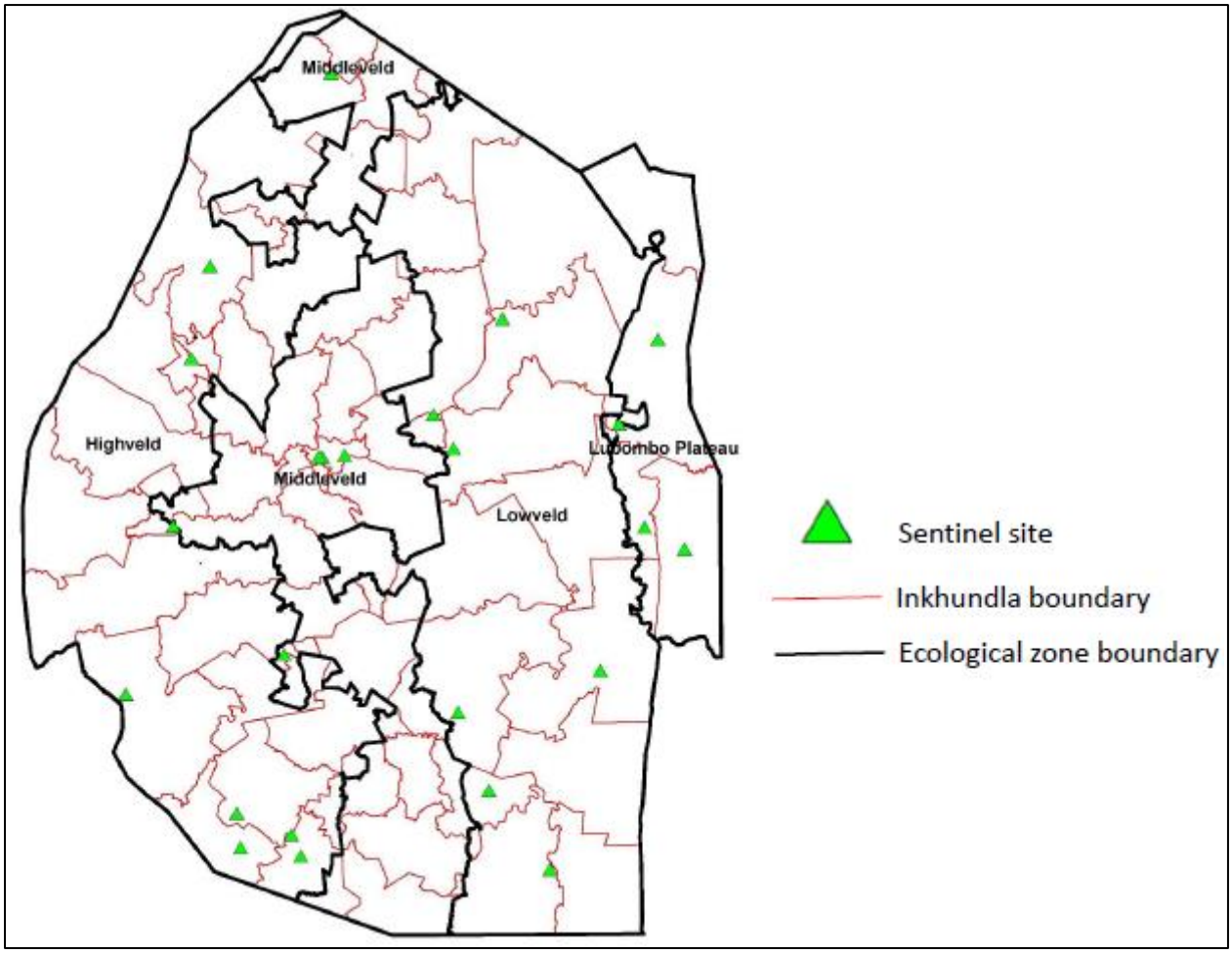

Figure 3. Distribution of the 22 sentinel sites selected for Eswatini

4. Selection of children for sentinel site surveys

To facilitate the comparison of data from different countries, it is recommended to collect data in children of the same age; children in their third year of school are suggested. Approximately 50 children, balanced by gender in the third-year class will be surveyed.
In each sentinel school, a lottery method should be used to select 50 children. If the number of children in the third year is less than 50, another class of an older age group should be selected to give a total of at least 50 children.

5. Mobilization for Sentinel site surveys

Once the number and location of the sentinel sites have been selected, health and education authorities - at regional, district and village levels – and the relevant community authorities should be contacted for permission to visit the schools and collect the stool and/or urine specimens. There should be meetings with those involved to explain the purpose of the deworming programme and of the survey, and the expected benefits for the children and the community.

6. Frequency of sentinel site surveys

Although the current guideline indicates that sentinel sites are to be used for baseline data collection and after every 2 years due to resource constraints, sentinel surveys will be conducted in all sentinel sites annually subject to availability of funds[8], beginning at baseline. This will help to reflect the situation of the foci and for monitoring the programme in order to detect any problem such as low impact of the treatment, high reinfection, resurgence etc., and to correct these issues immediately. The more frequent annual surveys will also be useful in showing trends on the impact of MDA based on data from multiple timepoints within the 5-6 year period (within the 5 rounds of MDA).

Sentinel sites will be a sub-set of the schools selected from those used for mapping (baseline survey – just before initiation of 1st round of MDA), mid-term evaluation and end-term evaluation (Re-assessment mapping/Impact assessment).

Types of samples to be collected in sentinel sites

Urine and stool samples[9] will be collected from children. On the morning of sample collection, each participant will be issued with empty stool and urine cups and other sanitary necessities such as tissue paper and a scoop-stick, and the procedure for safe stool and urine collection will be explained. The survey team are trained in sterile techniques of collection of samples to minimize any chances of contamination and infection. Children will also be asked to wash hands with medicated soap (provided by the study) after providing samples. Stool and urine sample collection will take place in the school and will be supervised by technicians with the help of a health teacher. The teachers will help in organizing the children and to ensure the process is conducted in an orderly manner. The technicians will obtain assent from the children whose parents gave consent, they will explain and demonstrate hygienic sample collection procedures and provide children with coded stool and urine cups. Once the children return from the restroom, the technicians will verify the sample code against the child's name. The staff collecting the samples will not know the infection status of the children at the time of sample collection and all testing will be recorded according to the sample codes, with no names. Urine and stool samples will then be processed in designated space assigned to the survey team by the school.

Diagnostic tests to be conducted

- Kato-Katz
- Point-of-care Circulating cathodic antigen test (POC-CCA)
- Urine filtration
- Urine dipstick/hemastix test
- Visual observation of urine for macrohematuria (visible blood in urine)
- Fingerstick for anaemia[10]

[8] *Collection of data from sentinel sites after every 2 years may be used where resource constraints and other logistical challenges present.*

[9] *Fingerstick blood may be added if testing for anaemia is included.*

[10] *The National program to decide whether to include testing for anaemia as a marker for morbidity*

Assessment of drug efficacy as part of the M&E

Egg reduction rate (ERR) will be determined 14-21 days[11] after PZQ administration as an indicator of drug efficacy in a sub-set of children aged 9-12 years from 5 schools selected from the sentinel schools.

The drug efficacy assessment will be undertaken under 2 main scenarios:

a. In any sites where the program suspects reduced treatment performance, despite satisfactory treatment coverage (≥75%) and compliance. Specifically, in case of:
    i. Unexpected persistence of parasite-attributable morbidity (e.g. haematuria or anaemia)
    ii. Unexpected persistence of high proportion of heavy intensity schistosome and/or STH infections in the SAC population.
    iii. An insufficient drop in prevalence and intensity of infections in the SAC
b. After 4 or more years of MDA, independent of whether drug failure is suspected (WHO, 2013).

50 children positive for each of the parasites targeted to be investigated, from third year of school will be selected per school (WHO, 2013). The initial number of schoolchildren to sample will depend on the point prevalence of the SCH in the 'study region'[12] and borrows from estimated sample size for assessing drug efficacy for STH (Vercruysse *et al.* 2011) where a minimum of 250 infected children is recommended per region for drug efficacy evaluation[13]. Therefore, for Eswatini, it is proposed that Drug efficacy assessment be conducted in any 5 sites that meet criteria (a) and/or (b) above.

Frequency of drug efficacy assessment will be twice i.e. after 3 rounds of MDA (mid-term) in areas where the program suspects reduced treatment performance and after 5 rounds (end-term) either in areas of suspected reduced treatment performance and/or in select areas independent of suspected drug failure. For (i), (ii) and (iii) of Scenario (a) above, morbidity and prevalence data will need to be obtained immediately after the mid-term

[11] *An interval of 14–21 days between the treatment and the collection of follow-up data increases data standardization and avoids the risk that eggs identified in a specimen are from parasites that infected the individual after drug administration.*

[12] *Study region used in this context to refer to the entire country of Eswatini as one geographically disparate region of the world.*

[13] *Statistical power analyses, based on random simulations of correlated overdispersed FEC data reflecting the variance-covariance structure in a selection of real FEC data sets, suggest that a sample size of up to 200 individuals (α = 0.05, power = 80%) is required to detect a 10 percentage point drop from a null efficacy of ~ 80% (mean percentage FEC Δ per individual) over a wide range of infection scenarios. Standard power analyses for proportions also indicate that the detection of a ~10 percentage point drop from a null cure rate requires sample sizes ranging up to 200 (the largest samples being required to detect departures from null efficacies around 50%). Given an anticipated non-compliance rate of 25%, a sample of 250 individuals pre-treatment should therefore be followed up for post-treatment FEC data at each study locality (Vercruysse et al. 2011).*

and end-term surveys (atleast within 2 weeks) to enable the identification of the sites for the longitudinal drug efficacy follow-up within the 14-21 day period.

Note: *If one parasite is present at a low prevalence (e.g. less than 10%) in a site, it is not considered to be of public health importance, and assessment of drug efficacy against this parasite is probably unnecessary.*

Depending on the 2 main efficacy assessment criteria outlined above, the 5 schools for Drug efficacy assessment may or may not be drawn from the 22 sentinel sites.

Only children who were infected and who actually injested the medicine, and only one anthelmintic (no combination of anthelmintic drugs) (WHO, 2013) will be enrolled (longitudinal cohort) in the efficacy survey.

Only children that had a positive specimen at baseline will be requested to provide a second specimen after 14-21 days.

It is essential that the drugs administered are within the expiry date and are properly stored.

Drug efficacy will be calculated based on egg reduction rate (ERR). ERR will be calculated using the formula below:

$$ERR\ (\%) = 1 - \left\{ \frac{1 - \text{arithmetic mean egg counts at follow-up}}{1 - \text{arithmetic mean egg counts at baseline}} \right\} \text{X } 100$$

The efficacy of PZQ will be evaluated against the standard WHO reference of drug efficacy (WHO, 2013).

It is recommended that a pooled sample be prepared of the positive samples at follow-up by mixing a standard quantity of each positive faecal specimen in a single container and adding a standard quantity of fixative. This sample can be stored at room temperature and will be useful for future reference.

If reduced efficacy is observed, it is mandatory to contact WHO to discuss further action. It is also important inform the National drug authority about the reduced drug efficacy and any further investigation or corrective measure established in collaboration with WHO (WHO, 2013).

Vector snail-related aspects of transmission

- Focal snail control – Molluscicding
- Testing of infection in snails[14].

[14] *Technical support for testing of infection in snails could be requested from ESPEN*

Recommendations on monitoring in Sentinel sites after Impact assessment

Sentinel site monitoring activities will be conducted annually from the onset of intervention and after the reduction in the frequency of drug administration.

If sentinel site monitoring shows that the prevalence remains low for 4 years despite the reduction in frequency of drug administration, a further reduction could be applied.

If monitoring indicates that prevalence tends to return to the original levels (recrudescence of the infections), reintroduction of the original treatment schedules will be warranted.

Use of POC-CCA as an additional diagnostic is recommended due to the low prevalence of *S. mansoni* and the inherent limitations associated with Kato-Katz in such low prevalence.

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ANNEXES

Annexe 1: List of the 22 Schools selected as Sentinel sites for Eswatini

		School name	School code	Region	Inkhundla	Ecological zone	*S. mansoni*	*S. haematobium*	*T. trichiura*	*A. lumbricoides*	Hookworm
Criteria 1: Population		Entuthukweni	1		Mbabane West	Highveld	No	Yes	No	No	No
		Dumisa Metropolitan	1001			Lowveld	No	Yes	No	No	No
		Loyiwe	1007			Lubombo Plateau	Yes	Yes	No	No	Yes
		Manzini Infant	311			Middleveld	No	Yes	No	No	No
Criteria 2: Endemicity	**Moderate**										
		Mafutseni Nazarene	339		Mafutseni	Middleveld	Yes	Yes	No	Yes	No
		Nkhaba Anglican	509		Nkhaba	Highveld	Yes	No	No	No	No
		New Thulwane	1028			Lowveld	No	Yes	No	No	No
		St. Johns	945			Lubombo Plateau	No	Yes	No	No	No
	Low										
		Othandweni	718			Middleveld	No	Yes	No	Yes	No
		Enjabulweni	951			Lowveld	No	Yes	No	Yes	No
		Nyamane	701			Highveld	No	Yes	No	No	No
		Mhlumeni	927		Lugongolweni	Lubombo Plateau	Yes	Yes	No	Yes	Yes
	High										
		Dlalsile	1004		Hlane	Lowveld	No	Yes	No	Yes	No
		Mbasheni	101		Ntfonjeni	Middleveld	No	Yes	No	No	No

Criteria 3: Treatment	**High (>75%)**										
		Magubheleni	750		Gege	Highveld	No	Yes	No	Yes	No
		Nkonjwa	1021			Lowveld	No	Yes	No	No	No
		St. Paul's Methodist	349			Middleveld	Yes	Yes	No	No	No
		Mlindazwe	1065		Lugongolweni	Lubombo Plateau	Yes	Yes	No	No	No
	Low (<75%)										
		Nhlangano Central	63		Shiselweni 2	Highveld	Yes	Yes	No	No	No
		Mkhondvo	721		Shiselweni 2	Middleveld	No	Yes	No	Yes	No
		Ekuthuleni	713			Highveld	No	Yes	No	No	No
		Langolotjeni	795			Lowveld	No	Yes	Yes	No	Yes