Methods and approaches for Buruli ulcer surveillance in Africa: Lessons learnt and future directions

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i. Running Head

Buruli ulcer surveillance

ii. Summary/Abstract

Over 95% of the global burden of Buruli ulcer disease (BU) caused by *Mycobacterium ulcerans* occurs in equatorial Africa. National and sub-national programmes have implemented various approaches to improve detection and reporting of incident cases over recent decades. Regional incidence rates are currently in decline, however, surveillance targets outlined in 2012 by WHO have been missed and detection bias may contribute to these trends. In light of the new 2030 NTD roadmap and disease-specific targets, BU programmes are required to strengthen case detection and begin a transition towards integration with other skin-NTDs. This transition comes with new opportunities to enhance existing BU surveillance systems and develop novel approaches for implementation and evaluation

In this review, we present a breakdown and assessment of the methods and approaches that have been the pillars of BU surveillance systems in Africa i) Passive case detection ii) Data systems iii) Clinical training iv) Active case finding v) Burden estimation vi) Laboratory confirmation pathways. We discuss successes, challenges and relevant cases studies before highlighting opportunities for future development and evaluation including i) Novel data collection tools ii) Risk-based surveillance iii) Integrated skin-NTD surveillance. We draw on both experience and available literature to critically evaluate methods of BU surveillance in Africa and highlight new approaches to help achieve 2030 roadmap targets.

iii. Key Words

Surveillance, case finding, case detection, burden, Buruli ulcer, methods, methodology, *Mycobacterium ulcerans*, reporting, Africa

1. Introduction

Due to the environmental dependence of *Mycobacterium ulcerans,* Buruli ulcer (BU) disease exhibits marked spatial heterogeneity in both occurrence and incidence even at fine spatial scales, posing distinct challenges for surveillance[1]. The aim of any surveillance system is the systematic collection, analysis and interpretation of health outcome data in a timely manner to inform planning and decision-making[2]. For BU, surveillance systems should accurately track both disease occurrence and incidence, thus enabling limited resources to be efficiently targeted to affected communities. The system must also be designed with consideration of disease epidemiology and available resources. Human and logistical resource considerations have a significant impact on the design of BU surveillance systems in west and central Africa, where over 95% of the global burden occurred between 2010-2017[3]. Due to this concentration of cases, we will focus this review on implementation of BU surveillance systems in this region.

There are specific epidemiological, clinical and sociocultural challenges associated with the implementation of BU surveillance systems. Firstly, our understanding of BU epidemiology remains incomplete, and disease occurrence at local scales remains very difficult to predict[4]. From available data sources, we know that prevalence at population-level is low, cases can be focally distributed and disease burden falls disproportionately on disadvantaged rural communities[5]. For frontline healthcare providers tasked with identifying and recording cases, BU can be a challenging disease to diagnose and laboratory confirmation may not be available[6,7]. Such absence of laboratory confirmation has a detrimental impact on the sensitivity and specificity of cases reported within surveillance records. Patients may first seek treatment from traditional healers, rather than the formal health system, for varying reasons including perceived efficacy and economic cost[8]. BU can also be a hugely disabling and stigmatising condition, especially when treated late. Disfigurement, functional limitations and belief systems surrounding illness causation can contribute to social exclusion and affect health-seeking behaviour [9–11]. The target population of a BU surveillance system can,

therefore, be both difficult to access and may not preferentially engage with typical detection pathways of surveillance systems.

These inherent challenges that manifest for BU surveillance are apparent within data collected by WHO from national programmes between 2010-2017. Since 2010, worldwide annual incident cases of BU have declined from 4,906 to 2,217, although trends vary by country and the role of reporting bias is unclear[3]. Incomplete reporting remains common at both national and sub-national levels and PCR confirmation rates remain low at 58%[12]. These data also show that the proportion of patients presenting with ulcerative and category III lesions remain higher than programmatic targets set in 2014 (64% and 31% respectively)[3]. These data, therefore, highlight existing weaknesses in BU surveillance systems from a combination of incomplete reporting, low PCR confirmation rates and delayed identification of patients. This year WHO also launched the 2030 NTD roadmap[13]. This included targets to further reduce the proportion of BU cases presenting with category III ulcers (<10%) and increase the number of integrated skin-NTD programmes, a group that includes BU, by an order of magnitude. These ambitious targets will, therefore, require further strengthening and innovation within existing surveillance systems.

The objectives of this paper are to highlight the technical challenges of implementing BU surveillance and outline common approaches that have been applied to improve case detection and collection of accurate epidemiological data. This is with a view to providing realistic recommendations for improvement in recognition of complex ground-level realities. The focus is placed on three exemplar countries – Benin, Ghana and Cameroon – that represent high burden countries, although reference is made to other countries across the region. One important consideration to highlight is the lack of rigorous evaluation of measurable operational components that constitute BU surveillance systems, such as case finding approaches. Most BU surveillance-based activities are evaluated using quasi-experimental designs due to cost and feasibility issues associated with measuring rare

outcomes. Whilst understandable, this strongly limits the ability to make explicit recommendations of selected approaches. Historically, BU has been incorporated within leprosy and tuberculosis (TB) surveillance programmes. The importance of evidence-based strategies is emphasised by findings made among these other mycobacterial diseases. Systematic reviews of TB surveillance activities – including randomised controlled trials (RCTs) – have shown that even ostensibly beneficial approaches to active case finding can demonstrate limited benefit and are dependent on context and outcome measures[14–16]. In the absence of comparative effectiveness studies, therefore, the methods we present are considered best practise from accumulation of experience in diverse implementation settings, and we present examples from other mycobacterial diseases where appropriate.

2. Considerations of health system structure

The first consideration for implementation of a BU surveillance system is the structure of the health system[8]. Reliable case detection and reporting are dependent on interacting activities occurring simultaneously at different levels of the health system (Figure 1). Targeting individual components is unlikely to lead to sustainable success in isolation. For example, a new case finding strategy may initially refer a number of suspected incident cases, yet without adequate referral pathways and trained healthcare staff, patients won't receive adequate diagnosis or care thus disincentivising future health-seeking behaviour[11]. It is therefore essential to ensure planning stages to incorporate considerations across different components.

3. Passive surveillance, clinical diagnosis and data reporting

Passive surveillance is the process of detection and reporting of active BU cases presenting at health facilities for diagnosis. Within a strong surveillance system, passive detection allows reliable year-round reporting of these self-reporting cases. To date, most BU endemic countries have established passive surveillance systems directed by the Ministry of Health with Ghana having established a programme as early as 1993[17]. WHO has clearly defined

protocols for BU with set programmatic indicators for reporting and evaluation of data collected at health facilities. At the point of access to health services, all BU cases must be diagnosed clinically using WHO standardised case definitions[18] and cases should be confirmed using PCR-based tests wherever possible. Appropriately trained staff must enter patient data on a paper-based BU01 form followed by short summary data on a BU02 sheet[19]. The BU02 is sent to district-level health authorities and reported to national BU control programmes for aggregation[3]. Importantly, BU indicators can be included within district health information system 2 (DHIS2) platforms to facilitate reporting. National programmes are expected to report aggregated BU data to WHO on an annual basis where performance is assessed against four core indicators of early case detection and PCR confirmation rate. Benin represents an important case study of developing a reporting structure for passive BU surveillance system. Since 1997, a network of specialised centres have coordinated BU activities in endemic regions. Cases are referred to these centres where data collection is coordinated, findings are analysed and feedback is provided on a quarterly basis [8].

To maintain the function of a passive detection system, it is essential that regular training is provided to healthcare workers covering both data reporting and clinical diagnosis. Specialised clinicians can make reliable assessment of BU lesions[6,20] yet BU surveillance also relies on diagnosis by non-physician mid-level health workers (MLHWs), especially in locations without comprehensive BU programmes. In such places, PCR confirmation is also often unavailable. Cross-sectional surveys among frontline healthcare providers have demonstrated that knowledge of BU diagnosis and management can be low in endemic areas[21,22]. Studies on clinical diagnoses made at primary health centres also show that the majority of presumptive clinical diagnoses of BU without PCR have different aetiology[7,23]. With declining regional trends in BU incidence, it may become more difficult for MLHWs to make valid diagnoses, as prevalence scenarios affect diagnostic sensitivity and specificity in unpredictable ways[24]. Important lessons can be learnt from leprosy, where resource constraints following premature declaration of disease elimination saw widespread loss of

clinical expertise[25,26]. In addition to reinforcing MLHW skills, improving diagnostic training among this workforce has been shown to improve passive case detection rates in certain settings for TB[27]. One approach used to strengthen the passive detection of BU cases is the development of stakeholder referral networks within affected communities. These networks can identify potential cases and provide timely referral to locations where clinical expertise exist. A Stop Buruli Consortium programme in Cameroon demonstrated a large shift in the source of referrals using such an approach. Over 4-years of programme implementation, more than 90% of passively detected cases were referred by a network of community health workers (CHWs), former patients, traditional healers and household members[28,29].

An important addition to ensure reliability of routine data is implementation of regular data system audits. These processes support monitoring and evaluation, and help in identifying factors causing bottlenecks that affect the quality of data input. Assessments of routine information systems in African health systems have highlighted poor data quality in health programmes and their mechanisms, including maternal health and routine immunisation[30,31]. Standardised tools have been used for assessment of BU information systems, although general reporting trends suggest these approaches are not widely implemented[32]. A comprehensive tool for evaluation of health information systems is the PRISM toolkit established by the MEASURE evaluation project[33,34], which can be readily adapted for programme-specific questions.

4. **Community outreach, mobilisation and stigma reduction**

Even with a strong passive surveillance system in place, a large proportion of incident cases can fail to be detected. Qualitative investigations in BU endemic communities have repeatedly shown that community beliefs around disease causality, stigma, economic cost and treatment likely impose negative impacts upon health-seeking behaviour[9–11]. Due to the natural history of BU disease, it is also important to identify patients at the earliest stages of disease to prevent the debilitating impact of more advanced forms[35]. BU surveillance systems therefore

typically require outreach activities to overcome these barriers and are often used in combination with case finding drives to enhance detection of community-based cases.[36]

During implementation, it is crucial to empower locally trusted authorities to disseminate information and raise awareness; these may include community leaders, women's groups, youth organizations, religious leaders, village elders, teachers and traditional healers[37]. In Zou District, Benin in 1997 (population 1.7m), a BU programme was launched with a wide-reaching community education campaigns to counter public misconceptions about the disease[38]. In a 5-year cohort of 1,700 cases, new case detection rates increased to a peak of 21.5 per 100,000, and median delay to diagnosis reduced from 73 to 30-days relative to historical cohorts. Importantly, awareness campaigns in neighbouring districts saw increasing numbers of cases detected from these locations. A recent large-scale example led by the Stop Buruli Consortium saw the development of innovative outreach programmes in Benin, Cameroon and Ghana delivered to approximately 75,000 people[37]. Multiple years of anthropological investigations facilitated adaptation of culturally sensitive education materials[28]. Emphasis was placed on avoiding photos of severe stages and explaining how treatment could lead to complete healing. Mobile events used presentations and utilised key stakeholders to address questions from participants with answers informed by formative research[28]. In Benin, the focus was on task-shifting passive detection to peripheral centres and resulted in an almost seven-fold increase (14 to 96 over 2-years) in confirmed cases detected at peripheral level relative to a historical control group. This included a high proportion of early-stage ulcers (71%) that were treated without referral[39], although pre-implementation proportions are not reported. Ghanaian programmes implemented an outreach programme using video-based events in the 1990s[40] and also report improvements in detection of earlier stages of disease. Between 2011-2012, the Togolese National Buruli Ulcer Control Programme scaled up an existing community education campaigns over five-fold to reach over 1,000 target communities on a quarterly schedule[41]. This was combined with regular CHW screening events and establishment of a reference laboratory to reduce diagnostic delays. This example did not result in increased

case detection but reduced delay to clinical diagnosis relative to historical trends. Programmes in Cameroon[29], Nigeria[42] and the Democratic Republic of Congo (DRC)[43] also provide further examples of similar outreach approaches within BU programmes.

During outreach education for BU, it remains important to address stigma to mitigate negative perceptions of disease often found in communities. BU is a disease that is strongly associated with perceived, internalised and enacted stigma[9,44,45]. Both BU and leprosy control programmes have long-standing experience of involving former patients in outreach activities[28,39,46]. Recent contact-based interventions in leprosy have provided some quantifiable evidence of stigma reduction in communities following interactions with former patients[47]. Similar evaluation and implementation of standardised and validated scales will help evaluate the most effective approaches to stigma reduction for BU. Useful lessons may be learnt from the field of HIV where significant research has been applied to methods and evaluation of stigma reduction[48].

5. Active case finding and the role of community health workers

Active case finding (ACF) is used as a tool to enhance the number of cases reported to BU surveillance systems through activities conducted away from health facilities. Typically, ACF for BU follows community outreach and involves central-point screening or systematic case searches. Screening events utilise mobile teams composed of healthcare providers, community health workers (CHWs) and logisticians. Teams setup central stations located within the community[28,39,49], or educational institutions like schools[17,41] where residents can have suspicious skin lesions assessed by team members. The alternative strategy of case searches involves periodic assessment of catchment populations for clinical signs of BU through systematic visitation of households, schools or other meeting places. In many settings, ACF is often led by CHWs due to their knowledge and trusted position within affected communities. To support this workforce, the WHO has produced guides specifically to support CHWs in the identification of clinical forms of BU[50,51]. In Ghana, 44 CHWs undertook regular

training in identifying clinical forms of disease, followed by regular case searches in households, schools and religious centres. Observational data from this catchment population over 4-years showed the largest proportion of referrals among 451 PCR confirmed cases from CHWs (45%; versus health workers, former patients and self-referral), and CHWs also identified earlier, nodular forms of disease. Comprehensive review of 1,965 BU01 referral forms in Benin showed that across all endemic regions, CHWs referred the highest proportion of all cases (26.5%) but also highlighted similar contributions from former patients (22.0%) and health workers (20.0%)[52]. Initiation of a multi-faceted BU programme in Songololo Territory in the Democratic Republic of Congo, including ACF, saw large magnitude shifts in male-female gender ratios among referrals from 2.4 to 1.0 over comparative 3-year periods[43]. Similar effects on gender equity have been observe in TB ACF programmes, and this highlights how ACF can improve the equity of surveillance systems[53]. A particularly exhaustive approach was recently piloted in Ghana, with CHWs conducting monthly physical examination of all residents in a population of 3,255[54]. CHWs were able to achieve impressive coverage (94%; 11.1 mean visits per person per year) and detected a substantial incidence of PCR confirmed disease (3.0 per 10,000 per year) with high confirmation rates (70.6%). Despite widespread involvement of CHWs in ACF for BU in Africa, the majority of studies have not rigorously assessed their relative impact on case detection[55]. This is important as examples exist, both within BU and other mycobacterial diseases, where ACF approaches has failed to improve case detection[14,38]. Further studies evaluating the effectiveness and sensitivity of different ACF mechanisms would be of particular benefit to guide implementation.

The examples we have used describe the individual components of an effective BU surveillance system, including community outreach, ACF, clinical training and data management. Due to their co-dependence, many of these activities are typically implemented simultaneously within a programmatic implementation period. Important studies have evaluated the impact of such programmes implementing combinations of these measures. Examples include quasi-experimental before-after evaluations of large BU programmes in

DRC, Cameroon and Ghana. The example from DRC demonstrated a 3-fold increase in annual case detection rates over 3-years following case management, education campaigns and ACF. A similar process evaluation of Cameroon's BU programme saw national detection rates steadily rise from 0.99 per 100,000 to 3.99 per 100,000 after four years[29]. A comprehensive programme review of Ga West District, Ghana following expanded communication, ACF and case management strategy[17] resulted in a more moderate increase in mean annual case detection from 3.5 per 10,000 to 4.9 per 10,000. Whilst understanding the contribution of individual activities is not possible in these studies, they do support the beneficial effect of combined implementation of surveillance activities on BU case detection.

6. Survey-based approaches and burden estimation

Targeted surveys are used in various NTD programmes to formally assess the burden and distribution of diseases towards planning service provision. Unlike some NTDs[56], standardised protocols for BU burden estimation are not available, but different approaches have been used as springboards for planning when available epidemiological data were insufficient. Careful choice of sampling design is required using survey-based approaches for BU due to the typical low population prevalence and focal distribution of disease. BU surveys also often use communities as sampling units and therefore possess a hierarchical design. Together these factors result in large sample size requirements and the use of analysis methods that account for complex survey designs. Due to the rare and spatially heterogeneous nature of disease, data may violate distributional assumptions and lack precision, adding complexity to analysis and interpretation.

To limit some of these common statistical issues, BU surveys have often employed total population strategies. This involves selecting a fixed population and assessing the prevalence of BU among all individuals. Exhaustive household searches have identified prevalence of PCR confirmed BU cases of a 2.1 per 10,000 in Bankim, Cameroon (48,692 individuals) [57], 1.5 per 10,000 cases in Offin River, Ghana (20,390 individuals)[58] and 1.1 per 10,000 in

Songololo, DRC (39,044 households)[59]. Some programmes have even previously attempted this at national scale using exhaustive case searches[60]. Spatially stratified sampling techniques have also been used in Cameroon, which can reduce analytical complexity and can help account for a degree of spatial heterogeneity inherent to BU epidemiology[61].

Independent of the choice of design, the success of BU burden estimation will depend on coverage and implementation of survey methods. Case finding strategies often utilised in the examples discussed, such as door-to-door case searches by CHWs, cannot be assumed to produce an exhaustive sample[62]. To ensure rigorous implementation, quality control should also be embedded to assess coverage and sensitivity of case detection methods. This can include capture re-capture as part of quality control surveys, or collection of GPS coordinates to validate coverage against reliable satellite imagery[63]. Such thorough quality control may be unfeasible in some settings, but a minimum level of supervision can still promote reliable estimates.

7. Improved targeting and evaluation of surveillance

Recent technical advances in the field of geospatial epidemiology have provided new strategies that can support BU surveillance[64]. Although the transmission of BU in Africa remains unclear, the environmental dependence of *Mycobacterium ulcerans* bacteria make both pathogen and disease amenable to geospatial models that predict disease occurence[1]. These models use environmental variables to predict the presence of disease, producing maps that highlight where the risk of disease is high or where our knowledge is uncertain. A continent-scale risk map of *M. ulcerans* occurrence and possible entomological BU vectors (*Hemiptera*) in Africa have been recently developed in support of this[65,66]. Survey efficiency can also be increased in areas with previous BU survey data using spatially-optimised sampling strategies, an approach currently being refined and implemented across various rare NTDs[67].

The use of electronic data collection tools can support surveillance activities by improving validity, timeliness or providing spatial reference to datasets. One use of simple mobile technology has been implemented for the management of morbidity associated with lymphatic filariasis (LF). In multiple countries, a simple text-based system was successfully developed for case-based reporting of LF morbidity by CHWs[68,69]. This approach may be adaptable to facilitate BU case-reporting, especially in remote areas where regular reporting by CHWs or MLHWs may be limited by logistical constraints. With increasing availability and low cost of smartphones, these tools can also be used in support of more rigorous stand-alone activities such as surveys or ACF[70]. Their added functionality can be used to help validate household coverage via GPS, improve reliability of longitudinal activities using capture re-capture methods or even support telemedicine[71]. Open-access toolkits, such as Open Data Kit (ODK)[72] use excel-based templates that can be uploaded to any Android-based smartphones and secure, encrypted open-access servers are increasing available and user-friendly, making these approaches further simplified and low-cost[73]. Where feasible, electronic tools can strengthen reporting and monitoring of surveillance activities, particularly in remote settings where data collection and supervision are challenging.

8. Laboratory confirmation in surveillance programmes

WHO recommends that all new cases of BU are confirmed by PCR, with confirmation rates of clinically diagnosed cases included as one of four core reportable indicators. Within a surveillance programme, there are a number of considerations needed to ensure collection and delivery of viable samples for PCR. Samples are collected using a swab for undermined ulcers, or through fine needle aspiration (FNA) for pre-ulcerative forms or indurated ulcers[74]. These can be collected even in remote setting but staff must be appropriately trained in both methods. During swab sampling, clinical material must be collected from multiple points of the lesion. DNA material will most likely to be found at the distal edges of undermined ulcers, while FNA samples are best collected from the centre of pre-ulcerative lesions. Incorrect collection

can produce false negative results and may impact on patients' access to anti-microbial therapy[6,75].

The location and accessibility of sites where BU samples are collected can also affect surveillance protocols. If samples cannot be processed within 24 hours, then both FNA and swab samples require transport media and storage at 4°C[74]. If refrigerator systems are not available, then a temperature stable transport medium is required, with a cell lysis solution manufactured by Qiagen maintains viability at ambient temperature for up to 6 months[41,76]. Once collected, all samples should be sent to reference laboratories with a BU03 request form[19] specifying the test required. Examples of developing and running reference laboratories are available in the literature from Ghana and Togo[7,41], whilst the WHO has published comprehensive guidelines for laboratory protocols for BU sample collection and analysis[74].

9. Integration of BU with other skin-NTDs

The pillars of early case detection, referral and timely treatment that are at the forefront of BU surveillance systems are also measures shared with other NTDs that manifest with skin symptoms (skin-NTDs). Since many skin-NTDs also exhibit similar geographical distribution, there is currently a move towards integrated strategies to improve programme efficiency[77]. Other skin-NTDs that prevail in BU endemic setting include leprosy, yaws, scabies (and other ectoparasites), lymphatic filariasis, mycetoma and possibly cutaneous leishmaniasis[78]. This presents an opportunity for surveillance activities to be combined across diseases. Examples of integration of BU-specific surveillance activities with other skin-NTDs including combined outreach ACF components are now emerging[79]. Recent surveys in West Africa have also used integrated school-based sampling designs to understand disease burden given the skewed age distribution of many skin-NTDs, including BU[80,81]. Although not intended to provide a population-level burden estimate, other NTD programmes also use school surveys as fast and efficient approaches to identify priority areas for programmes[82]. This may represent a strategy

to identify skin-NTD hotspots, although comparative epidemiological data will be needed to justify this approach.

With the current move towards skin-NTD surveillance, it is important to highlight some of the challenges that have emerged from early attempts at integration. A consistent issue is the large burden of common skin diseases that are encountered when using broad case definitions for integrated screening or diagnosis. This burden outweighs skin-NTD diseases and can add significant workload for healthcare staff or on to specific activities[80]. Treatment of common skin diseases must be considered to promote skin health and improve acceptability within target communities. Secondly, integration also necessitates a more demanding training programme for clinical decision-makers. Health workers tasked with the responsibility of diagnosis must be able to reliably identify a broad array of disease presentations among both skin-NTDs and common skin diseases. Towards development of integrated training programmes, it is important to tailor clinical content to different cadres of worker. The ideal staff cadre and methods for integrated training have yet to be formally evaluated and remains a priority area of research. The length of any training must be considered to minimise disruption of routine activities and prevent overloading participants with new information. From our experiences, two to three-day training programmes are required to cover three to six diseases. For common skin diseases, the use of simplified, easy-to-understand algorithms may minimise the burden on health workers[83,84]. Recently a training manual to support diagnosis of skin-NTDs was developed by WHO in English, French, Spanish, and Portuguese [Accessible at: https://www.who.int/neglected_diseases/resources/9789241513531/en/]. For implementation of either, however, context-specific adaption is recommended including the use of local photos and information on local guidelines for prescriptions and management.

With new emphasis on the integrated surveillance of skin-NTDs, there will also be opportunities to evaluate the effectiveness of novel approaches. Some of the statistical and

economic challenges associated with measuring the impact of BU case detection may be offset through assessment of integrated interventions. Even in the absence of gold-standard randomised controlled trials, quasi-experimental approaches or process evaluations can provide important evidence towards identifying consistently effective mechanisms for programmatic implementation. An often-lacking addition would also be the application of economic analyses to surveillance programmes, principally costings or cost effectiveness approaches. As the skin-NTD surveillance model evolves, new opportunities for improved evaluation should be seized and readily enacted to improve the evidence base for this transition.

10. Conclusion

In the face of changing epidemiology, BU surveillance should remain prioritised in endemic countries due to the devastating impact of delays in case detection and treatment for patients affected by the disease. There are many building blocks that constitute a functional BU surveillance system and it is important to consider all components during design and implementation. Neglecting individual components can impact on the performance and responsiveness of the system as a whole. We have outlined examples of common approaches and successful examples, emphasising how success is typically coupled to strong cooperation and understanding with target communities. As surveillance moves towards an integrated skin-NTD approach, new evidence is required to support best practise guidelines and achieve 2030 NTD roadmap targets. Lessons learned from successful BU programmes can be taken forward and applied to integrated skin-NTD programmes. It will remain crucial, however, to ensure rigorous evaluation of new approaches to address unforeseen challenges and provide a reliable evidence base for skin-NTD surveillance systems.

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