A Diagnostics Platform for the Integrated Mapping, Monitoring, and Surveillance of Neglected Tropical Diseases: Rationale and Target Product Profiles

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Background

Control and elimination strategies for trachoma, lymphatic filariasis, onchocerciasis, schistosomiasis, ascariasis, trichuriasis and hookworm infection have striking similarities, including the use of periodic mass drug administration (MDA). Because these diseases tend to be co-endemic in the poorest communities of the poorest countries, such that multiple NTDs are frequently found not just in the same populations but within the same individuals [1], it has been suggested that mapping, treatment, impact monitoring, and post-elimination surveillance could be coordinated to better utilise limited human and financial resources. Although many programmes now distribute multiple anthelmintics simultaneously, progress in integrating mapping [2,3,4], monitoring, and surveillance [5] activities has been slow [6]. Ideally, population sampling strategies, fieldwork protocols, and sample types (e.g., blood or urine) could all be harmonised between diseases to increase population compliance, simplify overall survey procedures, and decrease costs.

For each of these diseases, current diagnostic tools are imperfect (Table S1A), especially for areas with low prevalence. A cost-effective strategy for improved tool development would incorporate integration of diagnostic strategies from the outset [7,8].

To review available methods for population-based assessment of NTDs, develop target product profiles for tools to monitor infection burden, and consider how those tools would be used in the context of disease elimination programmes, the London School of Hygiene & Tropical Medicine (LSHTM), in collaboration with the World Health Organization, held a consultation at LSHTM from July 19–20, 2010. Participants included disease experts, laboratory and field scientists, authorities on diagnostics, control programme managers, mathematical modellers, and health economists. By bringing together, for the first time, individuals with such a broad spectrum of intersecting disease- and discipline-specific interests to consider issues surrounding integration of diagnostic systems, the consultation aimed to improve on the usual vertical approach to tropical diseases research, encouraging formulation of an innovative approach.

This article summarises that consultation’s outcomes, suggests target product profiles and a list of immediate research priorities, and drafts a roadmap for future efforts. We argue for development of a multiplex platform for NTD mapping, monitoring, and surveillance, and suggest changes to policy that might ensue if such a system were to become available.

Evolution of Diagnostic Needs with Successful Programme Implementation

We conceptualise four time points or periods at which disease elimination programmes require diagnostics:

1. Mapping to establish baseline disease prevalence, facilitating targeting of interventions.
2. Impact monitoring after interventions have commenced.
3. The stopping decision, which determines whether the pre-defined elimination target has been reached, allowing discontinuation of interventions.
4. Post-elimination surveillance after intervention has ceased.

Mapping and impact monitoring may require both qualitative and quantitative data from each individual sampled, in order to generate information about the prevalence and intensity of infection. As the prevalence falls with successful control interventions, the intensity of infection also

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monitoring prior to elimination, and a combination of assays detecting antigens (or nucleic acid) and antibodies (to assess prevalence of exposure in particular population subsets) for post-elimination surveillance. For the worm infections, reliance on detection of transmission stages (eggs, microfilariae) becomes more problematic as the elimination endpoint is approached, since (other than for ascariasis) this will only identify hosts infected with both male and female adults. Specific detection of IgG subtypes may be useful in some cases, particularly if applied at population level: for example, IgG4 responses are characteristic of chronic helminth infections, and titres decline following successful therapy in lymphatic filariasis, onchocerciasis, schistosomiasis, and strongyloidiasis. Monitoring vector, intermediate host, or non-human reservoir populations for the presence of parasites may be important in confirming elimination of infection.

Apart from performance characteristics, it is important to consider the operational characteristics of an assay. Large population-based surveys may require tests that can be batched for high throughput. Point of care tests, which generally detect antigen or antibody in dipstick or card format, are relatively cheap, require little formal operator training, and can be performed in the community [11]. They are of particular use when programme personnel need to make immediate decisions as to whether intervention is required. This is helpful when individual patients are being assessed. However, for MDA, where decisions are needed on whether or not to treat whole communities or districts, laboratory-based tests are probably adequate, provided samples are easy to collect (e.g., fingerprick) and transport (e.g., dried blood spots).

**Target Product Profiles and Immediate Research Priorities**

Target product profiles for lymphatic filariasis, trachoma, schistosomiasis, onchocerciasis, and soil-transmitted helminth infections are found in overlapping populations; are controlled through broadly similar, often complementary, strategies involving MDA; and are mapped and monitored by sampling individuals from the population-at-risk in the early part of the *Ascaris* life cycle, this may actually be helpful in interpreting test results at community level, since antigen detection will indicate the presence of ongoing transmission. Immediate research priorities are shown in Table 3.

**Discussion**

Trachoma, lymphatic filariasis, schistosomiasis, onchocerciasis, and soil-transmitted helminth infections are of particular use when programme personnel need to make immediate decisions as to whether intervention is required. This is helpful when individual patients are being assessed. However, for MDA, where decisions are needed on whether or not to treat whole communities or districts, laboratory-based tests are probably adequate, provided samples are easy to collect (e.g., fingerprick) and transport (e.g., dried blood spots).

Target product profiles for lymphatic filariasis, trachoma, schistosomiasis, onchocerciasis, and soil-transmitted helminths are shown for the mapping and impact monitoring phases in Table 1, and for the post-elimination surveillance phase (first four diseases only) in Table 2. The tables consider only the needs for diagnostic tools in mapping, monitoring, and surveillance of human infection because we see these as priorities for any first-generation integrated platform for NTD diagnostics; we have, for the moment, put aside programme requirements for monitoring MDA coverage; measures of morbidity; possible emergence of drug resistance; prevalence of infection in vectors, intermediate hosts, or reservoir animals; and force of transmission through environmental sampling.

The target product profiles that we set out here are aspirational. Some tests (e.g., antigen assay for *W. bancrofti* [Table 1] or Ov16 antibody assay in previously onchocerciasis-endemic areas [Table 2]) appear close to being validated for programme use, while for others, numerous technical hurdles remain. For this reason, we expect some of our target product profiles—particularly blood- or urine-based antigen detection tests for the soil-transmitted helminthiases—to be controversial. However, there is presently at least one commercially available ELISA kit to detect IgG directed against *Ascaris lumbricoides* in human serum: it should be possible to develop a test to detect the antigen driving that antibody response. If such antigens only circulate briefly in the early part of the *Ascaris* life cycle, this may actually be helpful in interpreting test results at community level, since antigen detection will indicate the presence of ongoing transmission. Immediate research priorities are shown in Table 3.

In many areas in which NTDs are highly endemic, basic health infrastructure is sparse or non-existent, and there are few trained personnel. Local laboratories may not have access to refrigeration, reliable power, or piped water; have highly variable capacity for performing diagnostic assays; and the capacity they do have is in general insufficient to meet existing diagnostic requirements of local clinical services. They are therefore ill-equipped to take on the extra burden of generating
**Table 1.** Proposed target product profiles for diagnostic tools for selected NTDs, mapping, and impact monitoring.

| Characteristic                              | Lymphatic Filariasis | Trachoma | Schistosomiasis | Onchocerciasis | Soil-Transmitted Helminths |
|---------------------------------------------|----------------------|----------|-----------------|----------------|---------------------------|
| Intended use                                | Mapping, monitoring, and stopping decision | Post-elimination incidence of infection | Post-elimination incidence of infection | Post-elimination incidence of infection | Post-elimination incidence of infection |
| Possible target population*                 | 6–15-year-old children | 1–9-year-old children (could be adjusted) | 6–15-year-old children plus occupational groups | 6–15-year-old children | 6–15-year-old children |
| Possible sample types                       | Blood spot           | Eye swab (other: mouth or nose swab, tears) | Blood spot or urine (avoid stool if possible) | Blood spot | Blood spot or urine (avoid stool if possible) |
| Ideal diagnostic marker                    | Parasite antigen     | C. trachomatis antigen | Species-specific antigen or pan-genus antigen | Parasite antigen | Parasite antigen |
| Ideal test format                           | POC or high throughput laboratory assay | POC or high throughput laboratory assay | POC assay | POC or high throughput laboratory assay | POC assay |
| Availability of ideal diagnostic marker     | Available but not right format, low reliability, high cost, and temperature sensitive | Available but not right format | Not yet available | Not yet available, IgG4 antibody may be a reasonable proxy | Not yet available |
| Required performance characteristics        | 95% sensitive; W. bancrofti-specific | >50% sensitive, 99.95% specific | >50% sensitive, 99.95% specific | >50% sensitive, 99.95% specific | >50% sensitive, 99.95% specific |
| Comparator assay (current reference standard) | Night blood micro-filaraemia | Quantitative PCR | Kato-Katz (multiple slides and multiple days) and/or urine filtration | Skin snips to detect micro-filariae | Kato-Katz (multiple slides and multiple days) |
| Possible sampling strategies                | PBPS/LQAS, school based, sentinel sites | PBPS/LQAS, home based, sentinel sites | PBPS/LQAS, school based, 50/school, increasing with control | PBPS/LQAS | PBPS/LQAS, school based |

**Table 2.** Proposed target product profiles for diagnostic tools for selected NTDs, post-elimination surveillance.*

| Characteristic                              | Lymphatic Filariasis | Trachoma | Schistosomiasis | Onchocerciasis |
|---------------------------------------------|----------------------|----------|-----------------|----------------|
| Intended use                                | Post-elimination incidence of infection | Post-elimination incidence of infection | Post-elimination incidence of infection | Post-elimination incidence of infection |
| Possible target population                  | Children born after transmission interruption | Children born after transmission interruption | Children born after transmission interruption | Children born after transmission interruption |
| Possible sample types                       | Blood spot           | Blood spot | Blood spot or urine (avoid stool if possible) | Blood spot |
| Ideal diagnostic marker                    | Antibody             | Antibody to a conserved species-specific epitope of MOMP | Antibody | Ov16 antibody |
| Availability of ideal diagnostic marker     | Not available        | Libraries available | In development | Available, but additional validation needed |
| Ideal test format                           | High throughput laboratory assay | High throughput laboratory assay | High throughput laboratory assay | High throughput laboratory assay |
| Population infection thresholds (for stopping MDA) | 1%                   | Not defined | 10% of school-aged children | 1/3,000 |
| Probable sampling strategy                  | PBPS                 | PBPS     | PBPS or school surveys (or sentinel occupations) | PBPS |

*Schistosomiasis is included in this table because several countries have programmes to eliminate this disease [18,19]. The soil-transmitted helminth infections are not included because (as for schistosomiasis in most endemic states) the current goal is prevention of morbidity in school-aged children through periodic high-coverage MDA.

ICT, immunochromatographic card test; LF, lymphatic filariasis; MDA, mass drug administration; MOMP, major outer membrane protein of C. trachomatis; NTDs, neglected tropical diseases; PBPS, population-based prevalence survey.

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data to feed into NTD elimination programmes without provision of additional money, staff, training, equipment, reagents, and utilities—or robust technologies that could perform well despite limitations to supply of these resources.

The ideal integrated system might therefore be a portable, self-contained diagnostics platform, capable of performing multiplex assays for several infections of interest on one or a small number of sample types. A system employing microfluidics (“lab-on-a-chip”) [12,13,14] technology could fulfill these requirements. The platform should be able to simultaneously undertake multiple roles in different NTD control programmes, each of which might be at various points of evolution within a given population. For example, in a district that had been hyperendemic at baseline for trachoma, soil-transmitted helminths, and lymphatic filariasis but in which interventions had already been in progress for a number of years, the platform would be capable of accurately detecting reductions in ocular C. trachomatis infection, whilst simultaneously measuring the prevalence of soil-transmitted helminth infection and monitoring for post-elimination re-emergence of lymphatic filariasis. Since diseases of potential interest will vary from one population to the next, a modular format would provide opportunities to swap diagnostic capacity for particular infections in and out of the platform according to global, regional, or local priority. For example, in onchocerciasis-endemic areas, the capacity to test for loiasis at the same time as measuring the prevalence of O. volvulus infection would benefit programmes [15]. Equally, the platform should be adaptable for the assessment of the community prevalence of HIV infection, malaria parasitaemia or anti-malaria antibody, and/or seroprevalence of antibodies to measles, rubella, or hepatitis B surface antigen following vaccination campaigns.

Our vision can be conceptualised as the delivery of two linked components: a hardware module, on which samples will be processed, and various elements of software, including both the assays themselves and the algorithms to guide their use in the field. To ensure that any new technologies are ready for both registration and end use, field personnel, programme managers, regulatory agencies, ministries of health, and other key stakeholders should be involved in platform development and evaluation.

In addition to the potential savings to existing vertical control programmes that would become possible through integration of diagnostic tools, this approach has several other potential advantages. First, it makes conducting surveys to rule out specific diseases easier and more cost-effective. This can occasionally yield surprising results. In Burundi in 2007, examination for trachoma was included in a school-based survey protocol (need threshold minimum school attendance) [16] able to maintain specificity at high temperatures and low humidity [23], with accompanying standardised survey methodologies.

### Table 3. Immediate research priorities.

| Disease                  | Research Goal                                                                 | Feasibility (0–10*: 0, Impossible; 10, Inevitable) | Impact if Achieved (0–10*: 0, None; 10, Massive) |
|--------------------------|-------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------|
| Lymphatic filariasis     | Development of antigen tests to usable/reliable format                         | 9                                                | 8 if =USD 0.50                                  |
|                         | Development and validation of tests (e.g., IgG4-subclass antibody detection tests using recombinant Bm14, BmR1, WbSXP, and W. bancrofti-specific antigens [20] or PCR-based detection of parasite DNA in homogenised mosquitoes [21]) useful for post-elimination surveillance, with accompanying standardised survey methodologies | 9                                                | 8 if =USD 0.50                                  |
| Trachoma                 | Development of a test for ocular C. trachomatis infection [22] able to maintain specificity at high temperatures and low humidity [23] | 9                                                | 8 if =USD 0.50                                  |
|                         | Development of eye/nose swab-, saliva-, or blood-based anti-C. trachomatis antibody test and exploration of the impact of successful trachoma control on antibody profiles in endemic populations | 3                                                | 5                                               |
| Schistosomiasis          | Development of antigen [24] or antibody [25] isotype combination(s) useful in high and low transmission intensity environments, able to distinguish current from past infection | 8                                                | 9                                               |
| Soil-transmitted helminthiases | Development of antigen isotype combination(s) useful in high and low transmission intensity environments, able to distinguish current from past infection | 8                                                | 4                                               |
| Onchocerciasis           | Development of a quantitative antigen test for use in endemic areas in Africa and validation of Ov16 antibody test for demonstrating interruption of transmission in Africa | 5                                                | 8                                               |
|                         | Development of a test for loiasis                                           | 5                                                | 9                                               |

* Determined by expert consensus.

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progome planning for other infections for which control strategies are in the early stages of development. An October 2009 WHO expert consultation discussed recent work piloting taeniasis elimination in Peru and possible MDA approaches for food-borne trematode infections. These diseases may have global control initiatives developed in the foreseeable future.

Third, establishing capacity for reliable diagnosis of what have hitherto been the most neglected diseases could catalyse a frame-shift in the global health community’s vision of developing world laboratory science. A diagnostics platform that could be configured to generate community- or individual-level data for any of the infections already mentioned as well as perform tests for (for example) sexually transmitted infections, human African trypanosomiasis, or leishmaniasis would represent a game-changing advance in the fight against infectious diseases.

World Health Assembly Resolution 60.29 on Health Technologies recognizes that medical devices are indispensable tools for prevention, diagnosis, treatment, and rehabilitation in health care [16]. It is widely accepted that the availability of, and access to, appropriate and affordable health technologies in low- and middle-income countries remain inadequate. In 2010, WHO held the first Global Forum on Medical Devices [17], which featured selected technological innovations that could improve global health. The innovators identified financing, manufacturing partners, and distribution channels as their top three challenges in getting their technologies into resource-limited settings.

WHO undertook to continue to interact with industry, funding agencies, academia, and international organizations to raise awareness of the need to design, produce, and commercialize innovative, accessible, and robust technologies which address the needs of health systems particularly in low-resource settings. The development, evaluation, and deployment of an integrated platform to monitor progress towards NTD elimination would be consistent with this WHO vision.

Supporting information

Table S1 Performance against the Assurance criteria [11] of existing diagnostic tools for the neglected tropical diseases employing mass drug administration. (DOC)

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