LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Supporting the Bihar VL Elimination Programme

Field team supervisors getting consent to do IQK tests in his house

Supporting the Bihar VL Elimination Programme

Background

Bihar IRS Programme
Overview

1 BIHAR IRS PROGRAMME OVERVIEW

Visceral leishmaniasis is a parasitic disease of public health importance in the Indian sub-continent, which is transmitted by *P.argentipes* sand flies. With an estimated 50% of cases across the region originating from Bihar, eliminating Kala-azar from the State has become a high priority. Since the inception of the elimination programme in the 1940s, the national programme has used indoor residual spraying with DDT as the main strategy used to eliminate the disease.

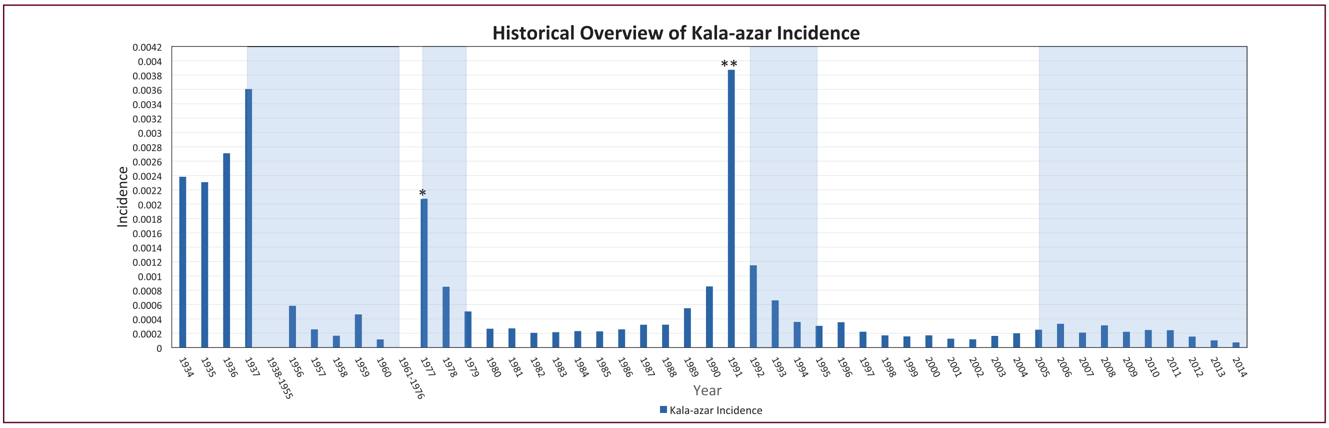


Figure 1: VL Incidence and IRS Programme

*Bars with * indicate years in which independent surveys to collect case numbers were performed (1977: National Institute of Communicable Diseases Delhi; 1991: Department of Malaria). These years probably indicate a more accurate representation of the number of cases than the numbers reported in other years.*

The Indian sub-continent target of elimination by 2015 was not met and a revised target of 2017 has been set. Concerted efforts by government and non-government organizations aim to improve intervention activities and case reporting.

Experience from other vector control and elimination programmes globally have highlighted the importance of effective monitoring and evaluation (M&E), particularly as the case burden falls and identifying the last few cases without strengthened systems can become problematic. In the absence of such enhanced M&E strategies, a programme can quickly regress back from an elimination phase to a control phase, requiring significant resource use to regain the lost ground.

To prevent this occurring, the implementation of innovative tools designed for public health programmes which provide improved data and promote informed decision making is crucial. LSTM have been implementing such tools in Bihar State since 2013.

Figure 2: Bihar Spray Team - Samastipur district

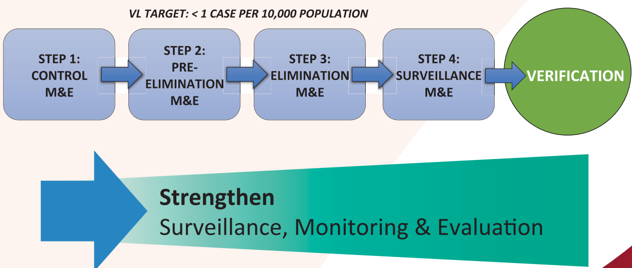


Figure 3: Public Health Control progamme phases

Activities to Date

2 Innovative Tools

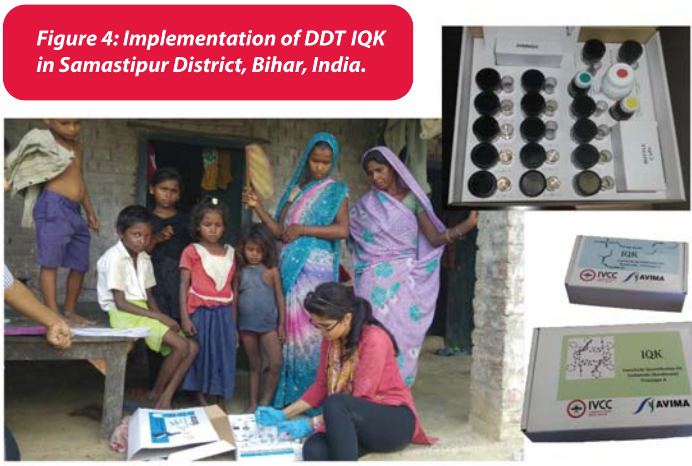
LSTM and IVCC have been involved in developing innovative tools to support vector control programmes and improve the quality of information on core programme performance and impact indicators that is available to decision makers. For the Indian context, two key tools have been developed or modified to suit the National Vector Borne Disease Control Programme (NVBDCP) needs: insecticide quantification kits and a decision support system.

2.1 Insecticide Quantification Kits (IQKs)

Quality assurance for insecticide programmes has until recently been dependent on pre-spray filter paper attachment and high performance liquid chromatography (HPLC) analysis – a method regarded as the gold standard by the World Health Organization. Given the complexity and cost of implementing this method, and the frequent lack of resources available to control programmes, quality assurance has assumed a low priority within disease programmes.

LSTM in partnership with IVCC and support from Bill and Melinda Gates Foundation and Wellcome Trust Foundation have been successful in developing a range of post-spray kits which carry a low cost and do not require specialist skills. Vector-borne disease control programmes globally have been eager to incorporate this technology as part of their M&E strategy and IQKs have been used in Equatorial Guinea, Vanuatu, Tanzania, Zanzibar, Ethiopia, Mozambique, South Africa and most recently India. IQKs are currently available for Pyrethroid, Carbamate and DDT insecticides and an organophosphate kit is currently under development.

Figure 4: Implementation of DDT IQK in Samastipur District, Bihar, India.



2.1.1 DDT Insecticide Quantification Kits

Prior to LSTM's involvement in India, the kala-azar elimination programme conducted no quality assurance of IRS, aside from basic visual inspections to determine whether a house had been sprayed. The simple point of use diagnostic to determine the actual amount of insecticide sprayed onto walls in houses targeted by IRS were implemented in 2014-15, with further use scheduled in 2016. The ease of use and limited resource requirements of the IQK post-spray method made quality assurance of IRS a practical possibility in Bihar.

Figure 5: The RMRI and LSTM IQK Team

2.1.2 Pyrethroid Insecticide Quantification Kits

The pyrethroid IQK kit has previously been implemented in several countries in Africa and 2015 saw the first use of this IQK in India. In order to confirm that the kit was suitable for use within the Indian context, 45 houses in Vaishali that were scheduled to receive IRS were visited. The houses were chosen to represent the three main house construction types in Bihar (15 mud, 15 thatch, 15 brick), and in each house a panel of tests was conducted, comprising pre-spray filter papers for processing by HPLC, post-spray IQK samples, and pooled samples to directly evaluate the IQK method against HPLC. This testing demonstrated that the pyrethroid IQK could be used on all surface types with the local pyrethroid IRS formulation and is suitable for QA of IRS in India. The implementation of the pyrethroid IQK as a post-spray QA system in Bihar is planned for February 2016.

2.2 Disease Data Management Systems (DDMS)

The disease data management system is the only free integrated platform currently available for public health programme use. The system was originally designed for malaria programmes, but implementation has subsequently been extended to dengue and visceral leishmaniasis. Included in the updated WHO Indoor Residual Spraying – An Operational Manual for Indoor Residual Spraying for Malaria Transmission Control and Elimination, the system includes support for programme managers for all stages of intervention planning and monitoring.

Modules in the Visceral Leishmaniasis DDMS include:

- Case Surveillance
- Entomological Surveillance
    - o Abundance
    - o Diagnostic Testing e.g. Insecticide susceptibility
- Quality Assurance
- IRS Monitoring
- IRS Planning
- Reports
- GIS

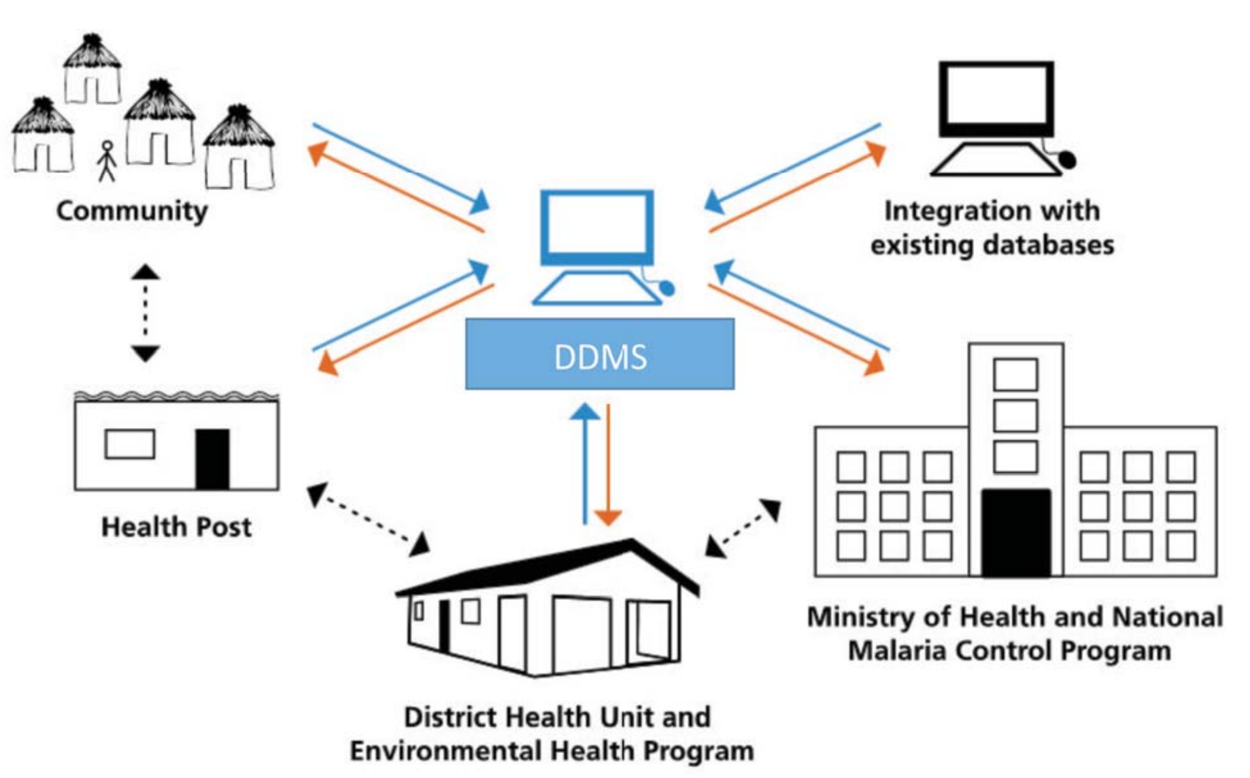


Figure 6: The DDMS System

The system was successfully implemented in conjunction with the Indian government research institute, Rajendra Memorial Research Institute (RMRI) in 2014. System set-up and training was provided for CARE – the non-governmental organization and Indian IRS implementation partner in 2015. Operational research conducted by RMRI and LSTM in 2016 will include the use of the system to monitor contemporaneous QA and IRS data once more.

3 PNAS 2014

3.1 Entomology Findings

The findings of RMRI and LSTM's initial work in 2014 were published in the Proceedings of the National Academy of Sciences USA (Coleman et al., 2015), and was highlighted as their paper of the month, due to the potential impact on policy change. The collections of *P.argentipes* sand flies from selected villages targeted by IRS (and corresponding control villages where no IRS was performed), showed that the IRS as performed in 2014 was only effective in reducing sand fly numbers for one month (see Table 1).

Significant IRS impact at 1 month post-IRS

At 3 months post-IRS, impact on sand flies is gone

Time point	Total sand flies collected		P
	IRS villages	Non-IRS villages	
Pre-IRS	0	0	1.0
1 month post-IRS	99	217	0.001
3 months post-IRS	122	123	1.0

Table 1. Entomology results from 2014

3.2 Quality Assurance Findings

The quality assurance testing performed in 2014 using the DDT IQK showed that IRS in India was poorly conducted, potentially influencing the limited effect that the control intervention had on sand fly numbers. The graph below shows the household graph from the PNAS paper with the QA upper and lower limits marked with yellow and red lines, respectively. The average level of DDT found on walls post-IRS was 0.37g ai/m^2, considerably below the 1g/m^2 target. Overall, only 7.4% of walls were within the target range; 84.9% of walls were under sprayed (below 80% of target dose of 1 g ai/m^2), and 7.6% of walls were over sprayed (above 1.2 g ai/m^2). This data emphasised the need for a proper quality assurance system for IRS with the VL programme.

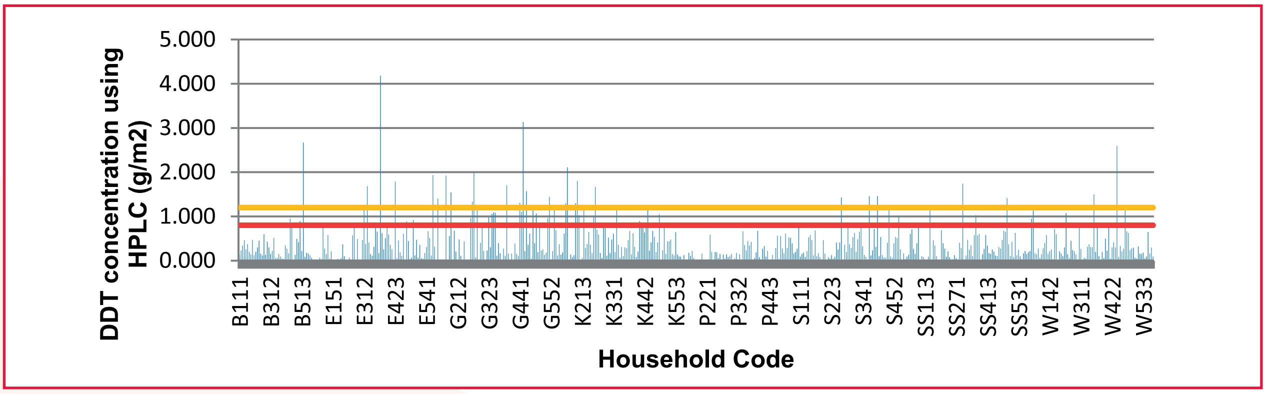


Figure 7: Average household results from 2014 DDT IRS

3.3 Key Impact from Research

In October 2014, LSTM in conjunction with RMRI hosted a symposium titled "Tools to Improve Quality of Indoor Residual Spraying" in Delhi. The meeting invited stakeholders from VL and malaria programmes across India to initiate discussions on innovative tools and how they could be used to better inform programme decision makers. This also provided a platform for LSTM and RMRI to share their findings, published in PNAS, with government officials and to advise on key programmatic steps required to ensure Kala-azar elimination targets can be met.

The paper attracted attention from several Indian papers, calling for government to improve the status of the programme and namely phase out the use of DDT. In 2015, 23 years after the first reporting of DDT resistance, the national vector borne programme piloted use of alternative insecticides in Bihar – implementing the pyrethroid insecticide alpha-cypermethrin across seven districts. Use of alpha-cypermethrin for IRS in Bihar is scheduled to expand to 15 districts in early 2016.

Despite initial resistance to the implementation of hand-compression pumps within Bihar, the national programme accepted that stirrup pumps were problematic and were willing to explore the potential for switching to a more widely used alternative.

4 Which is the Best Insecticide - DDT or a Pyrethroid?

In light of the key findings from the 2014 surveys, the suitability of continuing vector control with DDT for VL elimination was questioned. Although the National Vector Borne Disease Control Programme identified alpha-cypermethrin as the pyrethroid alternative suitable for piloting in Bihar, the absence of baseline data meant that there was no clear idea of the impact that such a switch might have.

4.1 Insecticide Susceptibility Overview

Historical field data on *P.argentipes* sand fly susceptibility status in Bihar demonstrated a rapid decline in mortality, which can be equated to reduced effectiveness to DDT as a suitable insecticide for vector control. Updated to include 2015 data, Figure 8 continues to indicate that pyrethroid and organophosphate insecticides are suitable alternatives to DDT for the VL elimination programme.

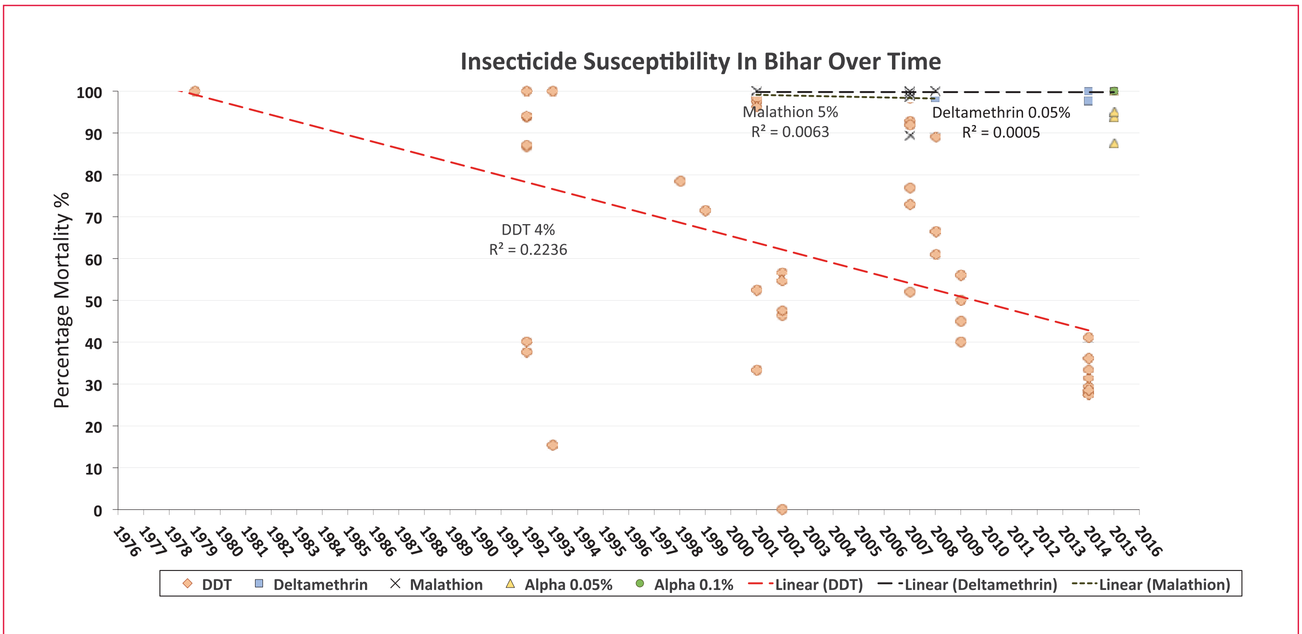


Figure 8: P.argentipes Susceptibility Status in Bihar

4.2 Establishing a Baseline Standard

The insecticide resistance testing performed in 2014 indicated that pyrethroid insecticides such as deltamethrin and alpha-cypermethrin were viable alternatives to DDT IRS. Following the NVBDCP decision to switch to alpha-cypermethrin IRS in a limited number of areas in 2015, we established a susceptibility baseline for alpha-cypermethrin and deltamethrin for the local sand fly population. As there is currently neither a susceptible laboratory colony or defined discriminating dosages for sand fly susceptibility to pyrethroid insecticides, we used wild caught sand flies collected from six different districts and tested them against both the defined discriminating dosage for mosquitoes (alpha-cypermethrin and deltamethrin) and 50% of the defined mosquito dosage (alpha-cypermethrin). The results showed that the mosquito dosages of deltamethrin and alpha-cypermethrin was effective against *P.argentipes* sand flies in all six districts, and that 50% of the mosquito dosage for alpha-cypermethrin was fully effective in 2 of the 6 districts and left few survivors in the remaining 4.

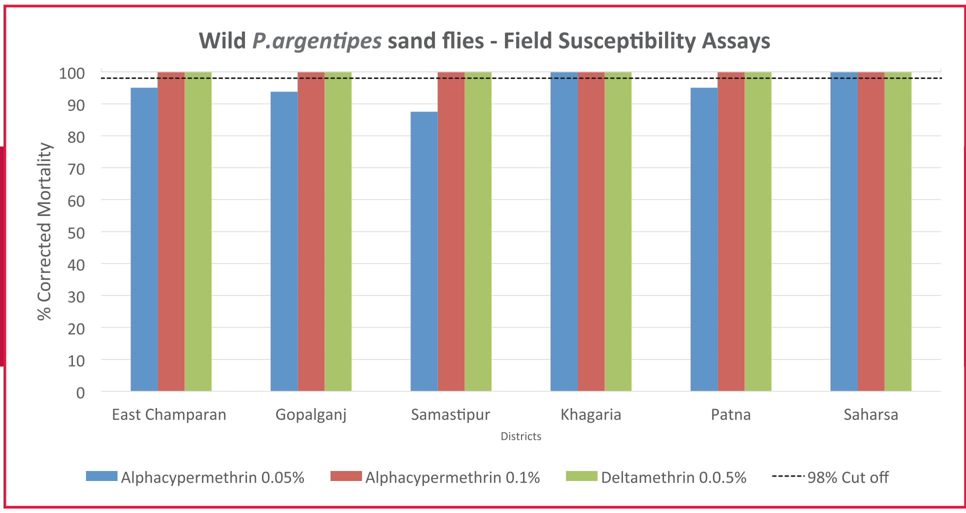


Figure 9: Baseline field susceptibility results

As the diagnostic dosage assays are only an indication of a potential problem, not a diagnostic of operational failure, we went on to assess whether DDT might still be operationally effective if actually sprayed correctly. This required assessment of the intensity of the resistance and the survival on sprayed houses.

4.3 Intensity of DDT Resistance

To understand the intensity of DDT resistance witnessed in the field, CDC bottle bioassays, exposing *P.argentipes* sand flies to DDT, were conducted under laboratory conditions. In order to control for potential variations caused by age, 1 day old F1 generation female sand flies reared from wild *P.argentipes* originating from the Patna/Samastipur area, were only used for the test.

Under normal programmatic situations a baseline, using a true susceptible colony of sand flies, would be established to determine the diagnostic dose for the *P.argentipes* population in that region. In the absence of a species- and region-specific diagnostic dose, the diagnostic time and dose for Anopheles mosquitoes (100µg/bottle, 45 minutes), was used as a proxy.

As demonstrated in Figure 10, at 45 minutes of exposure at the diagnostic dose, only 30% of *P.argentipes* sand flies were killed, rising to 35% at 2x the diagnostic dose, 42% at 5x the dose and 69% at 10x the dose. Mortality breaching the 98% WHO limit for susceptibility was only found at 10x the diagnostic dose after 75 minutes and 5x the diagnostic dose after 150 minutes. We would expect this level of resistance intensity to have an operational impact.

The experiment will be repeated in 2016 to determine the alpha-cypermethrin resistance intensity profile for sand flies in Bihar.

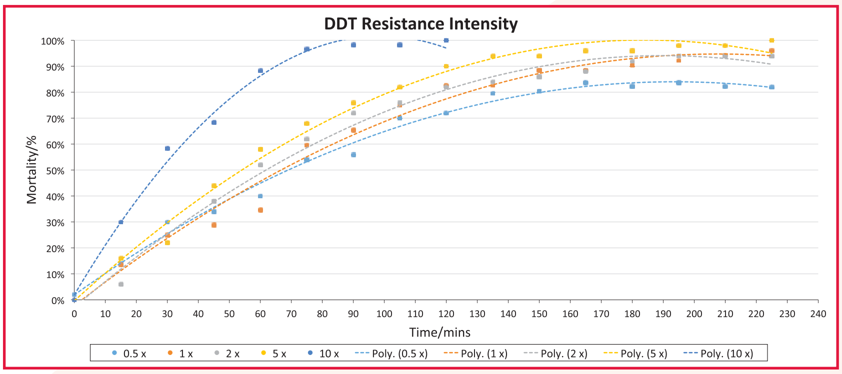


Figure 10: P.argentipes DDT resistance intensity

4.4 Assessing the Operational Impact of Insectiside Resistance

Taken together, the results from the 2014 studies, the field susceptibility baseline testing and the DDT resistance intensity indicated the following:

- *DDT IRS as currently performed is not effective;*
- *There is widespread resistance to DDT in P.argentipes sand flies, at an intensity that would be expected to have an operational impact;*
- *Alpha-cypermethrin used at the discriminating mosquito dosage appears to be effective against wild caught P.argentipes from 6 districts across Bihar.*

However, the possibility existed that correctly performed DDT IRS might be effective against *P.argentipes*. To answer this operational question, we assessed the actual operational impact of DDT resistance in two ways: by creating 'perfect' laboratory conditions using accurately treated tile surfaces of mud, brick and lime wash, and by accurately spraying mud, brick and lime wash walls in houses to assess the 'real world' effect of accurate DDT IRS. We took the opportunity of the house (hut) trial to also spray a number of houses with alpha-cypermethrin to assess the operational impact of this insecticide on local sand fly populations.

All of the testing was performed following standard WHO Cone bioassay protocols with 1 day old female F1 *P.argentipes* reared from field caught females.

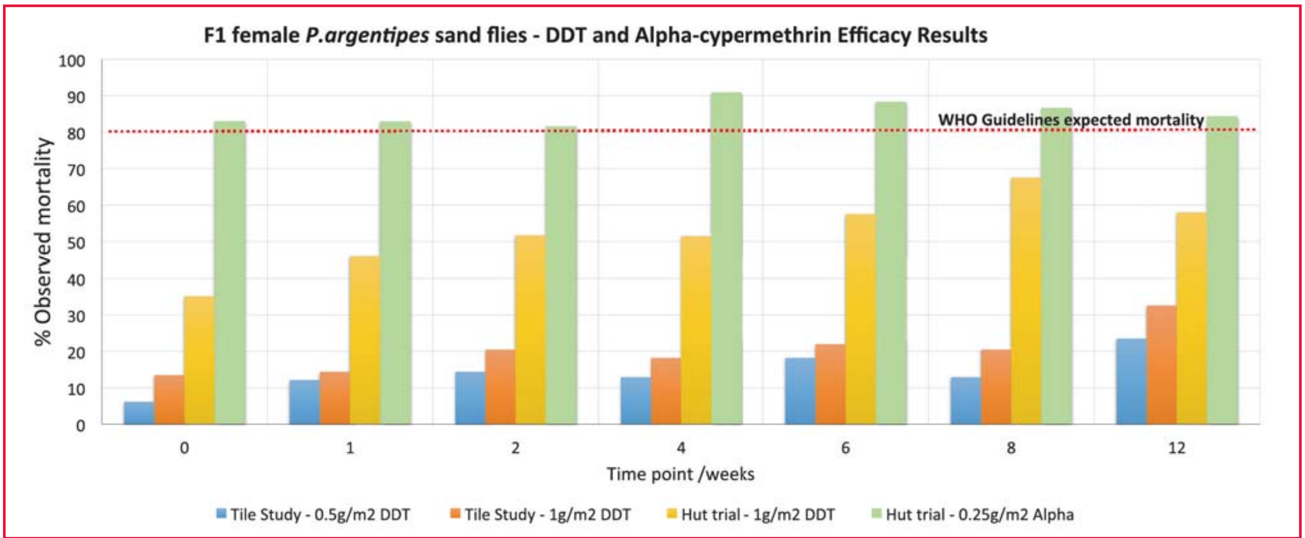


Figure 11: Efficacy of DDT and Alpha-cypermethrin against female P.argentipes

- Under laboratory conditions that mimic the DDT concentration delivered in the field in 2014 (Tile Study 0.5g/m^2 DDT), the observed mortality for sand flies on three different surface types (mud, un-plastered brick, lime wash) was never more than 23% over the 12 weeks of the study;

- The observed mortality for DDT at the recommended dosage (1g/m^2) was well below the WHO expected mortality under both laboratory conditions (Tile Study 1g/m^2 DDT) and house spraying (Hut trial 1g/m^2 DDT), indicated that, even if the correct dose was delivered during IRS, the insecticide would not be efficacious;

- The observed mortality of sand flies after exposure to walls sprayed with alpha-cypermethrin over the 12 weeks of the study (Hut trial 0.25g/m^2 Alpha), show a minimum of 80% mortality at each time point. This is fully in line with the WHO expected mortality for effective alpha-cypermethrin IRS.

5 Turning Research Into Impact

Indoor residual spraying IRS using DDT and stirrup pumps has been the main intervention adopted by the visceral leishmaniasis (VL) elimination programme. However, according to the Stockholm Convention and the India's national plan, DDT should be phased out of vector control programmes in India and replaced with alternative insecticides. Stirrup pumps have largely become redundant within vector control programmes globally and have been replaced with hand compression pumps. These pumps improve programme efficiency by:

- *Improving spray team make-up by using one pump per operator;*
- *Compression in the pump and the use of a constant-flow valve means that the flow rate of insecticide is controlled, reducing some of the operator error associated with stirrup pumps.*

To build the body of evidence required to influence change in strategy and policy in India, a cluster randomized trial (CRT) comparing the impact of alternative insecticides (alpha-cypermethrin) and pumps (hand compression pumps) to standard practices will be conducted by RMRI and LSTM in 2016. The study is fully integrated with government activities and will be composed of four IRS arms to determine the optimal strategy for effective vector control in Bihar.

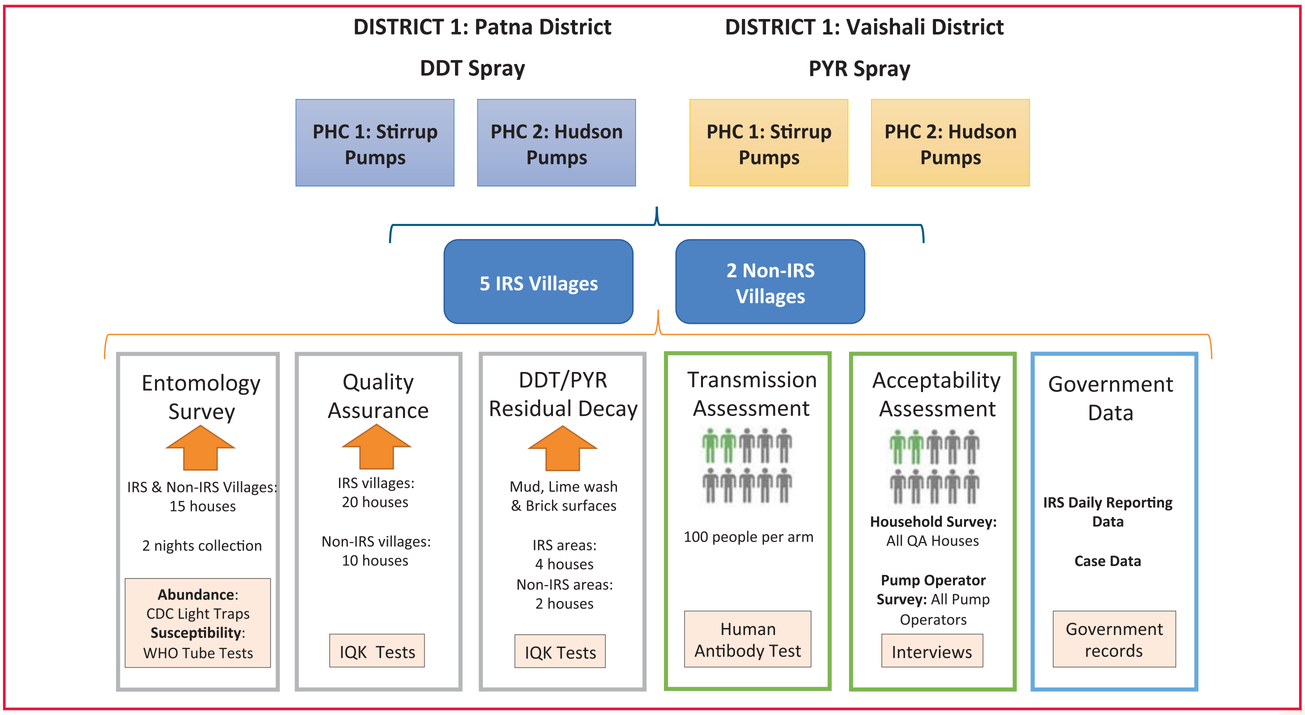


Figure 12: Cluster Randomised Trial Study Design

Evidence generated from the activities will aim to address the following key operational questions:

- **Entomology:**
  - **What is the sand fly population density trends over 12 months?** – collections will include from human dwellings, mixed dwellings, cattle sheds and outside near where villagers sleep during warmer months
  - **What is the susceptibility status of sand flies to all classes of insecticide?** – carbamates, organophosphates, organochlorines and pyrethroids
- **Quality Assurance and Residual Decay:**
  - **What is the quality of spray in the various study arms?** – implementation of DDT and Pyrethroid IQKs
  - **What is the residual effect of insecticide sprayed on to walls, up to three months after IRS?**
- **Transmission:**
  - **Are humans still getting bitten by sand flies after IRS?** – new information on transmission
- **Acceptability:**
  - **What are the household owner's viewpoints on the IRS in the various study arms?** – household owner acceptability
  - **What are the views of the IRS teams of the pumps?** – pump operator acceptability

To support implementation of hand compression pumps LSTM have procured a total of 4,500 Hudson X-Pert brand sprayers and personal protection equipment that is in alignment with World Health Organization guidelines. In addition spray teams involved in the CRT will receive supplementary IRS training from IRS experts Abt Associates and pocket reference guides.
In addition to conducting the study design, the study aims to improving current practices and operationalise official national guidelines for the disposal of insecticides, cleaning of PPE and maintenance of pumps.

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