Impact of intensified control strategies on incidence of visceral leishmaniasis in a highly endemic district of Bihar, India

An interrupted time series analysis to assess interventions as new WHO 2021–2030 elimination goals are agreed.

Vijay Kumar1†, Niyamat A Siddiqui1†, Timothy M Pollington2,3†, Rakesh Mandal1, Sushmita Das4, Shreekant Kesari1, Vidyanand R Das1, Krishna Pandey1, T Déirdre Hollingsworth3, Lloyd AC Chapman5,6 and Pradeep Das1,*

1Dept. of Health Research, Ministry of Health & Family Welfare, Govt. of India, Rajendra Memorial Research Institute of Medical Science (RMRIMS) (ICMR), Agam Kuan, Patna, 800007, Bihar, India. 2Mathematics Institute, University of Warwick, MathSys - Mathematics for Real-World Systems Centre, Coventry, CV4 7AL, Warwickshire, UK. 3Nuffield Dept. of Medicine, Li Ka Shing Centre for Health Information & Discovery, Big Data Institute, University of Oxford, Oxford, OX3 7LF, Oxon, UK. 4Dept. of Microbiology, All India Institute of Medical Science (AIIMS), Patna, 801507, Bihar, India. 5London School of Hygiene & Tropical Medicine (LSHTM), Centre for Mathematical Modelling of Infectious Diseases (CMMID), London, WC1H 9SH, UK. 6UCSF, School of Medicine, San Francisco, CA 94143-0410, USA.
†joint first authors, equal contribution.
*corresponding author: +91 (0) 612 263 1565, drpradeep.das@gmail.com

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5 figures, 1 table, 41 references.
Abstract

**Background:** Visceral leishmaniasis (VL) is declining in India, but persists in disadvantaged communities despite the World Health Organisation’s (WHO) impending 2020 ‘elimination as a public health problem’ target. Intensified combined interventions might help achieve elimination, but their impact has not been assessed. WHO’s Neglected Tropical Diseases draft 2021–2030 roadmap provides an opportunity for changing control strategies.

**Methods:** We estimated the combined effect from a district-wide pilot of intensified interventions in the highly-endemic Vaishali district, where cases fell from 3,598 in 2012–2014 to 762 in 2015–2017. The intensified control approach comprised indoor residual spraying with improved supervision; VL-specific training for accredited social health activists to reduce onset-to-diagnosis time; and increased Information Education and Communication activities in the community. We compared the rate of incidence decrease in Vaishali to other districts in Bihar via an interrupted time series analysis with a spatiotemporal model informed by previous VL epidemiological estimates.

**Results:** Changes in Vaishali’s rank among Bihar’s endemic districts in terms of monthly case numbers showed a change pre-pilot (3rd highest out of 33 reporting districts) vs. during the pilot (9th) ($P < 1 \times 10^{-9}$). The rate of decline in Vaishali’s cases was 26th highest pre-pilot and 19th during the pilot ($P < 1 \times 10^{-7}$). Counterfactual model simulations suggest an estimated median 96 cases (IQR-41–233) were averted by the Vaishali pilot between January 2015–December 2017.

**Conclusions:** Strengthening control strategies may have precipitated a faster decline in VL case numbers in Vaishali and suggests this approach should be piloted in other highly-endemic districts.

**Keywords:** kala azar, integrated control, distributed lag, regression discontinuity, elimination, NTD, neglected tropical disease, spatiotemporal, time series analysis

**Key messages**
- Here, we estimate the impact of intensified interventions in the highly-endemic district of Vaishali on the rate of decline in VL incidence using district-level surveillance data for Bihar state.
- We use a spatiotemporal statistical disease modelling framework to provide a rigorous analysis to estimate the additional impact of a pilot intervention study for visceral leishmaniasis, while accounting for existing declining incidence.
- This evaluation of integrated control activities suggests that visceral leishmaniasis (VL) incidence decreased faster in the pilot district than other districts, and that around 100 cases have been averted.
- This finding can help to inform future VL control policy and feed into WHO’s Neglected Tropical Diseases 2021–2030 draft roadmap.
- Since the contribution of individual interventions is hard to evaluate during a secular trend of declining incidence, we conservatively recommend conducting further pilots of combined interventions in highly-endemic districts, but with additional study covariates.
Introduction
Visceral leishmaniasis (VL) is a neglected tropical disease that persists in India despite large-scale concerted elimination efforts. India had an estimated 146,700–282,800 VL cases annually between 2004–2008, most of which were from Bihar state.1 VL cases have been declining since 2011 but have plateaued slightly in recent years.2,3 With WHO’s 2020 target for elimination of VL as a public health problem (< 1 case/10,000 people/year at block (subdistrict) level)4,5 fast approaching and 11% of endemic blocks still above the target in 2017,6 further insight into which combinations of interventions effectively reduce incidence is needed. Evidence-based research is urgently needed to guide VL control as new policies are set out in WHO’s Neglected Tropical Diseases 2021–2030 draft roadmap.7

Current interventions implemented by the National Vector Borne Disease Control Programme (NVBDCP) involve biannual indoor residual spraying (IRS) of insecticide at state level, passive case detection (PCD) at (block-level) by primary health centres and active case detection (ACD) by Accredited Social Health Activists (ASHAs); or via annual mobile camps (Supplementary information §S1).

An IRS review in Bangladesh, Nepal and India (BNI) showed IRS had an impact on sandfly densities when properly conducted but did not show a significant impact on VL case incidence.8 The only large-scale randomised control trial on the impact of a vector control intervention on infection incidence, the KALANET project,9 found no evidence that large-scale distribution of long-lasting insecticidal nets provided additional protection over existing control practices.10 A multi-site ACD screening intervention by ASHAs in highly-endemic districts of BNI discovered 6·7–17·1% more cases than PCD alone in Muzaffarpur and Saran districts (Bihar, India).11 Overall, there is a lack of robust evidence on intervention effectiveness from field trials. Nevertheless, we hypothesise that a combination of strengthening the ACD referral system through VL-specific training for ASHAs, higher quality IRS by well-trained and supervised spray teams, and Information, Education and Communication (IEC) community activities could produce measurable incidence reductions (§S2).

RMRIMS conducted an observational study on the impact of intensified VL control covering 1,569 villages in all 16 blocks in Vaishali district in late 2014–early 2015 (when 15 blocks were above the elimination threshold), while standard control by the NVBDCP continued in other districts (Figure 1 & §S1–S2).12 The triad of ongoing interventions, which began asynchronously, are specialised ASHA training (21–29 September 2014), IEC (19–21 February 2015) and improved IRS (from 15 February 2015)(Figure 1b & §S2). In this study we estimate: i) whether intensified control additionally contributed to the decline in VL cases in Vaishali, versus other districts, and ii) how many VL cases are were averted by the pilot.
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Figure 1 Study map and timeline. a) The pilot district of Vaishali is the hashed region. Shapefile source: GADM.\textsuperscript{13} b) Annotations indicate the start months of the intensified control elements and circular ticks mark the biannual accredited social health activist (ASHA) training; information, education and communication activities (IEC); and indoor residual spraying (IRS) training rounds. The hatched line marks the period of pilot scale-up when the combined methods would unlikely have reached full impact.

Answering these questions is complicated since incidence was already falling in Vaishali before the pilot started (Figure 2). Crude calculations indicate decreasing case numbers: 664 in January 2014–December 2014, falling by 38·1\% to 411 in January 2015–December 2015, and by 56·4\% to 179 in January 2016–December 2016.\textsuperscript{14} To estimate the impact of the pilot while accounting for the decreasing background secular trend, we compared Vaishali with other districts rather than analysing it in isolation. The model is informed by prior disease epidemiology and spatiotemporal features of the setting (§S7–S8).\textsuperscript{15} To estimate the number of cases averted, we fit the same model to a subset of pre-intervention months and make counterfactual predictions of case numbers with which observed case numbers can be compared (see Figure 5 & §S12).
Methods

Data
Monthly VL case numbers (by diagnosis date) for 33 out of the 38 districts of Bihar from January 2012 to December 2017 were provided by the State Vector Borne Disease Office. These case numbers included HIV-VL cases from January 2015 to December 2016 and HIV/TB-VL cases from January 2017 to December 2017, but excluded post–kala-azar dermal leishmaniasis (PKDL) cases (§S14). The 33 study districts formed a contiguous island of transmission without the five remaining districts (Aurangabad, Gaya, Jamui, Kaimur & Rohtas, which are considered non-endemic) (Figure 1a). Monthly district-level populations were estimated from 2001 and 2011 censuses.17 District shapefiles were used for maps and adjacency information.13 Analysis code is available at github.com/t-pollington/vaishali.

Descriptive analysis
Districts were compared by their ranked case number levels and year-on-year changes in monthly case numbers (§S4). Rank changes in absolute incidence/incidence rate rather than percentage change enabled us to crudely compare the relative changes of Vaishali to other districts, in the context of a state-wide medium-term decline in incidence. Using the two-sample two-tailed Wilcoxon test with continuity correction, we assessed if the ranks before and during the pilot were different. Evidence for global spatial correlation in incidence was assessed before and during the pilot with a Global Moran’s I statistic hypothesis test (§S5). The effective reproduction number $R_e$ for Vaishali and non-pilot districts was estimated to explore temporal patterns in transmission that may have been affected by interventions or seasonality (§S6).18,19

Interrupted time series analysis
Interrupted time series analysis (ITSA) is a subset of regression discontinuity analysis.20 We applied an ITSA to the district-level longitudinal case count data to assess the impact of the non-randomised pilot on incidence while adjusting for existing trends.21,22 The assignment variable in this ITSA is the calendar time of pilot implementation applied to a single district. We evaluated the dynamics of case numbers before and during the pilot using a spatiotemporal framework.23–27 The process producing observed cases $Y_{l,t}$ in a district $l$ in month $t$ is assumed to follow a Negative Binomial distribution with mean $\mu_{l,t}$ and variance $\sigma_{l,t}^2$ conditional on a weighted sum of cases from the previous 12 months $Y_{l,t-T, T \in [1,12]}$ (i.e. distributed-lag autoregression) (Equation 1 & §S8)

The distributed-lag represents the diagnosis-to-diagnosis (DD) distribution, i.e. the distribution of times between VL diagnoses of infector and infectee (§S7), akin to a ‘diagnosis’ serial interval distribution. It better represents the temporal correlation of diagnosis times than a naive lag-1 autoregression.24 The normalised DD distribution $D_T$ is informed by an estimated incubation period (mean = 6 mo) from previous work28 and in broad agreement with literature estimates,29 and an OT distribution (mean = 1.37 mo) from a Bihar study in 2012–2013.30
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\[
Y_{i,t} \big| \{Y_{i,t-12}, \ldots, Y_{i,t-1}\} \sim \text{NegBin}(\mu_{i,t}, \sigma^2_{i,t}),
\]

\[
\mu_{i,t} = e_{i,t} v_{i,t} + \lambda_i \sum_{T=1}^{T=12} D_T Y_{i,t-T} + \phi_i \sum_{j \neq i} (\omega_{ji} \sum_{T=1}^{T=12} D_T Y_{j,t-T})
\]

Equation 1 Base model: where \( t \) is time in units of months, \( e_{i,t} \) is the population offset term; \( \omega_{ji} = 1 \) if \( j \) neighbours \( i \) else 0; two overdispersion terms \( \psi_{\text{High}}, \psi_{\text{Low}} > 0 \) st. \( \sigma^2_{i,t} = \mu_{i,t} (1 + \psi_k \mu_{i,t}) \) for \( k \in \{\text{High}, \text{Low}\} \) endemic districts.

The base model of monthly district case numbers (Equation 1) represents ongoing direct transmission between cases while accounting for the typical VL DD interval (‘epidemic’ component, \( \lambda \)), hidden transmission from unobserved or asymptomatic cases (‘endemic’ component, \( \nu \)) with high/low endemic district stratification, neighbouring effects of directly-adjacent districts (‘neighbourhood’ component, \( \phi \)) (§S8), and changing district-level population effects (Figure S3).

We expanded the base model with the pilot effect (apriori primary variable, \( \alpha_{\text{pilot}} \)) and annual seasonality in the epidemic and endemic components (Equation 2:1/2:2, §S8–S9) to form the final model:

\[
\ln(\nu_{i,t}) = \alpha_{k}^{(\nu)} + A_{\text{END}} \sin\left(\frac{2\pi}{12} t + \Phi_{\text{END}}\right)
\]

\[
\ln(\lambda_{i,t}) = \alpha_{\text{other}}^{(\lambda)} + \mathbf{1}_{\{i=\text{Vaishali}\}} \left( \alpha_{\text{Vaishali}}^{(\lambda)} + \mathbf{1}_{\{t \geq \tau\}} c_t \cdot \alpha_{\text{pilot}}^{(\lambda)} \right)
+ A_{\text{AR}} \sin\left(\frac{2\pi}{12} t + \Phi_{\text{AR}}\right)
\]

\[
\ln(\phi_{i,t}) = \alpha_{i}^{(\phi)}
\]

Equation 2 Final model: with \( A_{(\cdot)} \) annual sinusoid amplitude and phase \( \Phi_{(\cdot)} \), fixed intercept means for the 32 districts \( \alpha_{\text{other}}^{(\lambda)} \), and Vaishali \( \alpha_{\text{Vaishali}}^{(\lambda)} \), and corrections \( c_t \) for the first 12 months of the pilot due to delayed lag effects (§S10).

Model selection was based on the lowest Akaike Information Criterion (AIC) of each candidate model versus the best-performing model from the previous selection step and also the change in parameter uncertainty, particularly for the primary variable. \(^{31}\) A range of possible pilot start months \( \tau \) were tested (September 2014 to September 2015 inclusive), and the most likely month chosen based on AIC. To assess the sensitivity of the final model’s parameters to the start month, we also report their range when the start month is varied. The fitted values of the final model were plotted against their residuals to assess heteroskedasticity (Figure S6).

Counterfactual model

A counterfactual model, formed by omitting the \( \mathbf{1}_{\{t \geq \tau\}} c_t \cdot \alpha_{\text{pilot}}^{(\lambda)} \) term in Equation 2:3, was used to predict the number of cases that would have occurred had there been no intensified control in Vaishali. Informed by the most likely start month we estimated the cases averted in Vaishali during January 2015 to December 2017 by summing the monthly differences between simulated case numbers from this counterfactual fitted on January 2013–December 2014, versus the final model (§S12). We calculated the cases averted as a percentage of those that would have occurred under the counterfactual model (see Figure 5:D).

For model validation the base, pilot and counterfactual’s goodness of fit were compared by AIC for the period January 2013–December 2017. The predictive
performance (§S10) of the base and final models for a shorter period January 2015–November 2017 was also compared.
Results

Trends in diagnoses
Case numbers have fallen in most districts, including Vaishali, since 2012 (Figure 2). During the pilot years 2015–2017, monthly cases in Vaishali declined substantially in absolute terms versus its highly-endemic neighbours and the district mean of the rest of the state (Figure 2).

During the pilot, Vaishali had the 19th largest year-on-year percentage reduction in monthly VL cases out of 33 reporting districts (averaged over 36 monthly case ranks from 2015–2017) versus pre-pilot when it had the 26th largest reduction (averaged over 24 months from 2013–2014, $P < 1 \times 10^{-7}$ Wilcoxon test). It also had the 9th highest VL case numbers during the pilot period (averaged over 36 monthly case ranks from 2015–2017) versus pre-pilot when it had the 3rd highest number (averaged over 36 months from 2012–2014, $P < 1 \times 10^{-9}$).

![Figure 2 Visceral leishmaniasis time series for Vaishali and the rest of Bihar state. Monthly reported case numbers, with 95% Poisson confidence bands (§S3).](image)

*Note that HIV-VL cases are included from 2015–2016 and HIV/TB-VL from 2017. The state mean excludes the 5 districts of Aurangabad, Gaya, Jamui, Kaimur & Rohtas, as well as Vaishali.*

Seasonality and spatial correlation
Across Bihar an annual seasonality in case numbers was apparent, which was weakening in the context of decreasing endemicity (Figure 2). However, at district-level the strength of the seasonal signal varied and was only recognisable for some high-endemicity districts, e.g. Saran had a strong seasonal signal while others did not.
Spatial correlation in incidence between neighbouring districts was apparent both before and during the pilot; Global Moran’s $I = 0 \cdot 36$, $P = 0 \cdot 002$ (10,000 simulations) and $I = 0 \cdot 40$, $P = 8 \times 10^{-4}$, respectively. This supports the use of the between-district neighbourhood component in the model. Vaishali was surrounded by neighbours with a range of endemicities, which either remained constant (e.g. Saran) or declined. Although incidence was declining in Vaishali, it was also declining in many other districts, yet clustering remained among the other districts, while Vaishali was dissimilar to its neighbours.

**Effective reproduction number**

The estimated district-specific effective reproduction numbers $\hat{R}_e$ generally follow an annual seasonality (Figure 3b) which supports use of a seasonal trend in the models. Compared to the average trend of the other 32 districts, Vaishali saw sustained $\hat{R}_e < 1$ during 2012/3, with the next noticeable sustained reduction around the pilot start (Figure 3a). After summer 2015, Vaishali’s $\hat{R}_e$ did not return to a seasonal peak in January 2016 unlike the mean of the other 32 districts. However, this effect only lasted the 2015/6 season and Vaishali’s $\hat{R}_e$ resurfaced during 2017. Given 2017’s lower incidence, the impact of this above-one $\hat{R}_e$ in terms of new cases would have been less than if it had occurred at 2015’s case levels.

**Pilot effect estimation**

The final model selected consisted of a Negative Binomial distribution with population offset, annual sinusoid in epidemic component to account for seasonality and an otherwise constant high/low endemic component (for 15/18 districts, respectively), a distributed-lag epidemic component with change-of-intercept in Vaishali in January 2015, constant contribution from directly-adjacent districts in the neighbourhood component, fixed intercept means in the epidemic component (one for Vaishali and one for the other 32 districts), and overdispersion by high/low-endemicity districts (Equation 1, Equation 2, §S7–S10 & Figure S4). The final model fitted better than the base model ($\Delta AIC = -369.2$) and showed a reasonable fit to the observed case numbers for Vaishali (Figure S5), but tended to poorly estimate low/high incidences (Figure S6). As AIC varied little by pilot start month, we chose January 2015 as the start month.
Figure 3 Effective reproduction number $\hat{R}_e$ for Vaishali and the other 32 districts’ mean (a) or 32 separate districts (b). The x-axes inferred infection times were calculated by subtracting the mean incubation period and mean onset-to-treatment time. The dashed vertical line after the first 6 months indicates the length of the 6-month sliding window: all $\hat{R}_e$ estimates before this date will only include partial data within this sliding interval, so their estimates are unreliable.

Table 1 shows the parameter estimates for the pilot effect which can be interpreted as follows. For Vaishali pre-pilot, an estimated average 75.0% (95%CI 67.6–83.2%) of the weighted sum of the previous 12 months’ case counts contributed towards the current month’s case count, versus 84.5% (95%CI 82.1–86.9%) for other districts. This means a hypothetical same-sized epidemic in any of the other districts would take longer to die out than if it was to occur in Vaishali. During the pilot this 75.0% contribution was estimated to fall by 1.7%/month (95%CI -18.2–18.4%) to 73.7% (95%CI 63.5–85.5%) for January 2015 onwards, where the pilot effect confidence interval overlaps 0% c.f. -18.2–18.4%. The estimated endemic contribution was practically zero everywhere except highly endemic districts in their high season where an estimated 1 case/month occurred from endemic transmission since January 2012.
(based on a mean district population of 2.8 million). The seasonality term with its time-oscillating variation added up to an estimated 69.1% to the endemic component versus the minimum occurring in November. Each district received an estimated 0.4% average contribution of the immediate neighbour’s weighted sum of the previous 12 months' cases. The standard errors of all parameters were within reasonable bounds apart from the endemic component’s fixed mean and seasonality parameters. The parameter estimates were mostly insensitive to pilot start month, however the pilot effect on the epidemic component did differ by up to 14% versus its value for a January 2015 start.

The fit of the final model was superior (AIC = 10517.5) to the base model (AIC = 10886.7), but similar to the counterfactual (AIC = 10515.5). However, the final model was superior in its Ranked Probability Score (RPS = 2.58) to the base model (RPS = 3.04) in prediction for 2015–2017 ($P = 1 \times 10^{-5}$).

**Cases averted estimation**

The counterfactual model showed reasonable predictive performance (§S10) during the pre-pilot period (Figure S7). The final model (Figure S8b) produced forward predictions for 2015–2017 closer to the observed time series and smoother than those of the counterfactual model (Figure S8a). Predictions of the final model in 2017 were less robust to large departures from the mean trend, e.g. the unexpected July 2017 peak in observed cases (Figure S8b), as the epidemic component was diminished. There is poorer predictive performance at extreme incidences, especially at high counts as shown by the overdispersed Probability Integral Transform histogram (Figure S10). 32

Simulations comparing pilot and counterfactual models suggest a median 96 (IQR -41–233) cases were averted in Vaishali during the pilot from January 2015 (out of 100,000 simulations, 32% had estimated negative cases averted), which would have accounted for an estimated 10% of cases if there had been no intensified control (Figure 4).

Analysing the year-on-year incidence decreases that could have occurred anyway under the counterfactual model, the pilot was estimated to have averted additional cases, as a percentage of the total cases estimated under the counterfactual model, of 16.9% (IQR -10.8–57.1%) from 2015 to 2016 and 30.5% (IQR -13.4–102.2%) from 2016 to 2017 (Figure 4).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point estimate (adjusted for other listed covariates)</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilot effect (change-of-intercept), $\exp(\alpha_{\text{pilot}})$</td>
<td>0.983</td>
<td>0.093</td>
</tr>
<tr>
<td>Fixed intercept mean: Vaishali, $\exp\left(\lambda_{\text{other}} + \lambda_{\text{Vaishali}}\right)$</td>
<td>0.750</td>
<td>1.055</td>
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<tr>
<td>Fixed intercept mean: other 32 districts, $\exp(\lambda_{\text{other}})$</td>
<td>0.845</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Seasonality (epidemic component)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude, $A_{AR}$</td>
<td>0.265</td>
<td>0.015</td>
</tr>
<tr>
<td>Phase, $\Phi_{AR}$</td>
<td>-6.52</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Endemic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed intercept mean, $\exp(\alpha^{(\nu)})$:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 low-endemicity districts</td>
<td>$8 \cdot 43 \times 10^{-11}$</td>
<td>$3 \cdot 21 \times 10^{-10}$</td>
</tr>
<tr>
<td>15 high-endemicity districts (incl. Vaishali)</td>
<td>$3 \cdot 54 \times 10^{-10}$</td>
<td>3.852</td>
</tr>
<tr>
<td><strong>Seasonality (endemic component)</strong></td>
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<tr>
<td>Amplitude, $A_{END}$</td>
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<td>3.127</td>
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<tr>
<td>Phase, $\Phi_{END}$</td>
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<td><strong>Neighbourhood</strong></td>
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<tr>
<td>Fixed intercept mean, $\exp(\alpha^{(\phi)})$</td>
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<td>$1 \cdot 24 \times 10^{-3}$</td>
</tr>
<tr>
<td><strong>Overdispersion</strong></td>
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</tr>
<tr>
<td>Low-endemicity district, $\psi_{\text{Low}}$</td>
<td>0.226</td>
<td>0.025</td>
</tr>
<tr>
<td>High-endemicity district, $\psi_{\text{High}}$</td>
<td>0.059</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Table 1: Final model parameter estimates. Parameters also referred in the text are highlighted. Mathematical notation explained in Equation 1 & Equation 2 in the Methods section.
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Figure 4 Estimated cumulative cases averted since the pilot start
Discussion

This study comes at a critical point in VL elimination, where high-endemicity districts are predicted to be the hardest in which to reach the elimination target. Our analysis of the Vaishali pilot study suggests that existing interventions when applied in combination and with special attention to quality might contribute to additional reductions in VL incidence.

Descriptive analysis suggests a faster rate of decline in case numbers in Vaishali for the first two pilot years than other districts (Figure 2 & Figure 3), which is supported by our detailed spatiotemporal analysis that accounts for decreasing trends in cases pre-pilot and neighbouring district effects.

Model simulations characterising the pilot period suggest around a hundred cases have been averted since 2015, but with an IQR overlapping zero. ‘Single-world’ matching of counterfactual simulations to their corresponding pilot simulations could produce similar point estimates for cases averted but with lower stochastic variation, such that the averted estimate would have a narrower uncertainty interval (c.f. Figure 4), but is beyond scope.

We cannot conclusively attribute the additional decline in case numbers in Vaishali from 2015 to the intensified control programme because this is an observational study. For internal validity of an ITSA it is important that the continuity assumption is met so that one is reasonably confident that “no other interventions or confounding covariates than the treatment of interest in analyses changed” at the intervention start month. As pilot and initial decline were concurrent and because no other district-wide interventions are known, we conclude that this is the most likely explanation.

Limitations

We do not know the treatment information of some Vaishali cases that chose nearby district hospitals nor other districts’ cases migrating into Vaishali. It is also unclear how drug supply may have impacted incidence since the national programme introduced single-dose liposomal amphotericin B in 2015–2016. Some of the largest differences among the 32 non-Vaishali districts are the VL endemicity and mean OT, however, our model does not account for these heterogeneities. If ASHA training reduced OD times and thus infectious durations and subsequent incidence, this would have also shortened the DD distribution, meaning that our inferences and prediction are biased. However, we expect any large reductions in the infectious duration would only marginally affect
the OD distribution as the mean infectious period was only 6% of the mean DD. This study does not apportion how much each of the pilot triad contributed to the decline nor does it include covariates that describe the time-varying susceptibility of sandflies to the deployed insecticides. A recent study in two highly-endemic districts suggests IRS, as implemented under the national control programme, has a negligible impact on sandfly abundance. Vector abundance, insecticide susceptibility and IRS coverage and quality data from Vaishali and other districts would allow an investigation.

Underreporting of cases, estimated at 15–18% in Vaishali in 2012–2013, with a non-uniform age distribution, may have affected our results. However, NVBDCP introduced mandatory VL and PKDL reporting state-wide for the public sector on 7 January 2016. Although HIV/TB-VL co-infection data is included in the monthly cases, we have been unable to stratify their status in the model due to this data only being available since 2015. In a Vaishali hospital in 2011–2013, VL admissions with unknown HIV had OD times on average 3 weeks longer; their underdiagnosed HIV-VL status accounted for 2.4% of admissions, rising to 5% in middle-aged men. This may also be important if HIV-VL co-infected individuals contribute disproportionately to transmission. If they do, then the pilot effect for Vaishali, a district with a rising proportion of HIV-VL co-infections (Figure S9), in 2017 may be underestimated. Furthermore PKDL cases have not been incorporated in the analysis as the elements of the pilot did not specifically address them, but recent studies suggest they contribute significantly to transmission.

This study lacks a control group as the 32 comparison districts could have unobserved confounders distributed heterogeneously across districts, which limits its external validity. Along with the overlap of the pilot effect uncertainty interval with 0%, this is why we recommend further pilot studies but with more study covariates collected.

When the study started, 15 out of 16 blocks in Vaishali were above the elimination target of 1/10,000 people/year, but all blocks apart from Raghopur (where flooding interrupted the pilot in August 2017) are now below the target.

Nevertheless, we recommend further pilots in high-endemicity districts since results in a single district may not generalise elsewhere. Prior to rolling out intensified interventions to all highly endemic districts, cost effectiveness should be assessed against other disease control measures.
Conclusion

This study has assessed if intensified control can reduce VL incidence more quickly in a highly endemic district in India. Our robust analysis supports the view that reported VL case numbers fell more quickly in Vaishali than other districts, in line with previous crude analyses.\textsuperscript{14} We believe there is justification to continue piloting this approach in other highly-endemic districts provided that the suggested improvements to study design and analysis are made.
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India is fast approaching the WHO 2020 deadline for eliminating visceral leishmaniasis, a deadly vector-borne disease, as a public health problem, but better understanding of intervention impact is needed. We estimate that combined intensified interventions can lead to faster reductions in incidence via a rigorous spatiotemporal analysis of the impact of a pilot study in Vaishali district, Bihar.

**Figure 5 Summary of the modelling framework**

The pilot effect (C) estimates the additional contribution intensified control made amidst the declining state-wide incidence.

Model composed of epidemic, endemic and neighbourhood infection processes (B & C)

A counterfactual model predicts the cases that would have happened if no pilot had occurred to estimate the cases averted (D).

India is fast approaching the WHO 2020 deadline for eliminating visceral leishmaniasis, a deadly vector-borne disease, as a public health problem, but better understanding of intervention impact is needed. We estimate that combined intensified interventions can lead to faster reductions in incidence via a rigorous spatiotemporal analysis of the impact of a pilot study in Vaishali district, Bihar.

**Figure 5 Summary of the modelling framework**
Supplementary information
Please see appendix for detailed information on study design and modelling.

Ethics approval
The Institutional Ethical Committee of RMRIMS (03/RMRI/EC/2018) approved the intensified control programme. University of Warwick’s Biomedical & Scientific Research Ethics Committee (REGO-2018-2231) approved this analysis.

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**Author contributions**

*Pilot conception & design:* VK RM SK PD; *Pilot implementation:* RM SK; *Secondary data collection:* VK NAS SD; *Pilot supervision & resources:* PD KP VNRD SD; *Analysis conception & design:* TMP TDH LACC; *Data analysis & interpretation:* TMP NAS RM LACC TDH; *Analysis supervision & resources:* TDH LACC; *Manuscript drafting:* TMP LACC TDH NAS VK RM KP SK SD PD; *Literature search:* TMP LACC TDH NAS RM; *Figures & tables:* TMP; *Supplementary information:* TMP RM NAS LACC VK; *Critical revision of the article:* LACC TDH TMP NAS RM PD SD VNRD KP; *Guarantor of the article:* PD; *Final approval of the version to be published:* VK NAS TMP RM SD SK VNRD KP TDH LACC PD.

**Conflicts of interest**

VK, NAS, SK, VNRD, KP & PD were the permanent employees of RMRIMS, Patna, and RM was a PhD student under its Dept. of Vector Biology. They initiated this institutional study on the instruction of the Directorate General of Health Services, Ministry of Health & Family Welfare, Govt. of India. PD had full access to the data and final responsibility for the decision to submit for publication. TDH, LACC & TMP report no conflicts of interest.
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Impact of intensified control strategies on incidence of visceral leishmaniasis in a highly endemic district of Bihar, India

Vijay Kumar, Niyamat A Siddiqui, Timothy M Pollington, Rakesh Mandal, Sushmita Das, Shreekant Kesari, Vidyanand R Das, Krishna Pandey, T Déirdre Hollingsworth, Lloyd AC Chapman, Pradeep Das

Corresponding author: Pradeep Das. drpradeep.das@gmail.com

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Pilot description

We describe in detail the implementation and the regional visceral leishmaniasis (VL) control context at the time.

S1. Visceral leishmaniasis control under the national programme

1) Routine control activities

- Early case detection and management, mostly as passive surveillance followed by annual active case detection with a ‘camp approach’ which is less sensitive and uses a weak referral system. Liposomal amphotericin B in a single dose of 10mg/kg was the first-line VL treatment, and combination therapy (paromomycin-miltefosine injection for 10 days) as the second-line treatment followed by other regimens e.g. amphotericin B emulsion, miltefosine (28 days) and amphotericin B deoxycholate in multiple doses as per availability; this was also the case for Vaishali district under the pilot study.

- Indoor Residual Spraying (IRS) using DDT (dichlorodiphenyltrichloroethane) in earlier rounds (50% wettable powder applied at 1g/m²) and then alpha-cypermethrin (a synthetic pyrethroid: 5% wettable powder at 25mg/m²) was introduced at different times across Bihar in 2015 once DDT resistance in sandflies was detected. During a calendar year, the two IRS rounds were conducted in human dwellings and cattle sheds up to 1.8m height. Usually the first IRS round started February–March and then May–June for the second round. Village selection was based on passive case reports, i.e. any village or hamlet reporting VL in the past 3 years qualified for 100% IRS coverage in that round). Districts of Bihar typically received varying levels of supervised IRS since there was no squad-level supervision, only at a block level.
• Unstandardised Information Education and Communication (IEC) activities with low coverage.

Neither pilot nor comparison districts were known to have been supplied insecticide treated nets by RMRIMS (Rajendra Memorial Research Institute of Medical Sciences), National Vector Borne Disease Control Programme (NVBDCP) or by others. However, the WHO TDR programme did provide logistical support across Bihar.

2) Management hierarchy
At district level, IRS was monitored by one District Vector Borne Disease Control Officer and one District Vector Borne Disease Consultant. However, at the block (Public Health Centre or PHC, subdistrict) level, IRS activity was managed by one Kala-azar Technical Supervisor, with at most one roving camp for active case detection (ACD) at any time.

3) Early case management and detection
There has previously been Accredited Social Health Activist (ASHA) training in Bihar state since 2012. A Grand Challenges Canada®-funded project in March–April 2012 and October–December 2013, conducted ASHA training in Paroo (Muzaffarpur district) and Marhoura (Saran district) blocks; whereas Sahebganj (Muzaffarpur) and Baniyapur (Saran) blocks received single training in October–December 2013; but as the training was not implemented comprehensively in these districts, it has not been included in the model herein. From these four blocks approximately 1,000 ASHAs were trained in groups of 100–150 by RMRIMS in VL/post–kala-azar dermal leishmaniasis (PKDL) identification, transmission, treatment and IRS. In 2014 the following districts’ blocks also received two rounds of ASHA training ending in September 2014: Muzaffarpur (1/16), Saran (1/20), Siwan (1/19), Khagaria (1/7), Saharsa (7/10) and Vaishali (1/16) (blocks trained/total in parentheses); the single Vaishali block of Raghopur received two more rounds of ASHA training in September 2014 as part of this pilot study’s intensified intervention for all 16 Vaishali blocks as described in §S2.

![Figure S2 Annotations indicate the start months of the intensified control elements and circular ticks mark the biannual accredited social health activist (ASHA) training; information, education and communication activities; and indoor residual spraying (IRS) training rounds. The hatched line marks the period of pilot scale-up when the combined methods would unlikely have reached full impact.](image)

**S2. Intensified control for Vaishali district under this pilot**
Vaishali is composed of 16 blocks with their own VL control programme supervisor. Additionally, under intensified control, block-level supervisors were selected by and originated from RMRIMS based in Patna or from their respective block. However, all spraying squads were recruited from each block. Similarly, insecticide and pump equipment were delivered through the District Vector Borne Disease Control Office, Vaishali to blocks and then to villages—in 2015 RMRIMS provided equipment in seven Vaishali blocks out of 16, but from 2016 it was given to all blocks by the District Vector Borne Disease Control Office. Vaishali district had a total population of 3·50 million in 2011 and this
pilot covered all of its 1,569 villages. RMRIMS staff supervised the pilot which was composed of three elements:

1) Early case detection and management
The case referral system was strengthened through ASHA training in a variety of ACD approaches. A total of 2,431 new and existing ASHAs across all 16 blocks received two training rounds between 21–29 September 2014. Each trained ASHA worked exclusively on VL and PKDL case detection covering 200 households and was linked by name to the village’s microplan; so they were separate from other ASHAs in Vaishali who were outside of this study and monitored other diseases.

This training programme was repeated 15 days before each IRS round during the study. Complicated cases of VL were referred to the Samrat Ashoka Tropical Disease Research Centre Hospital (RMRIMS), Patna.

The particular ACD approach used was context dependent: house-to-house screening (blanket approach) in villages with five or more VL cases; or for newly-detected VL villages, the index case approach where 50m surrounding a newly detected VL case is actively surveilled throughout the year; furthermore when high incidence was recorded in a focal area then temporary mobile roving teams (camp approach) would intervene using four camps over an interval of 3–4 months, starting on the same months as IRS (Table S1). In the absence of cases the standard passive surveillance was followed.

2) Improved indoor residual spraying
In Vaishali district the IRS insecticides, their concentration, mode of application and village selection were identical to the national programme (§S1) apart from the additions detailed here.

To conduct IRS activities in Vaishali, 24 block supervisors were selected and trained (as per WHO IRS monitoring and supervision criteria) by RMRIMS and assigned to blocks. For IRS monitoring, monitors were also selected and trained by RMRIMS and assigned to each squad for each block. All block supervisors had their own motorbike with daily fuel provision from RMRIMS. Monitors were selected from the locality for spraying, whereas squads were still recruited from the national IRS programme at the district level by the Vector Borne Disease Control Office (VBDCO), Hajipur. Insecticide, spray pumps and other equipment were delivered through VBDCO to blocks and then to villages. The total IRS coverage during the study was 1,145 villages, however this varied between rounds as villages’ endemic status changed. IRS coverages by round were as follows: 1,144 villages (Round I 2015); 1,078 (Round II 2015); 995 (Round I 2016); 1,001 (Round II 2016); 1,046 (Round I 2017); 1,067 (Round II 2017).

Initially, supervised IRS with DDT was conducted at 90% household coverage within a block. Later, alpha-cypermethrin was introduced with quality checks, as earlier insecticide sensitivity tests had found DDT resistance. During the DDT era the usual reason for not reaching full coverage was refusal or locked households, as the residents were away working in their fields. Urban/peri-urban properties had higher refusal rates as people with lower socioeconomic status were worried of the effect on their retail goods while people with a higher socioeconomic status did not think that it affected them or their concrete-walled properties. This indicates how supervision is key to IRS coverage.

<table>
<thead>
<tr>
<th>Date</th>
<th>IRS round</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>February–April</td>
<td>2015</td>
<td>DDT. IQK for 8 blocks. All districts: use stirrup pump except Vaishali where 7 blocks use</td>
</tr>
</tbody>
</table>
Two IRS rounds were conducted annually with the help of 166 spray squads. DDT was used in the first round of 2015 for all districts and in the second round DDT for the first 15 days for Saran, Vaishali and Muzaffarpur districts then alpha-cypermethrin thereafter. All districts received alpha-cypermethrin from 2016 onwards.

In Vaishali district, IRS was performed using stirrup and compression pumps. In the first and second rounds of 2015, seven blocks used the compression pump while nine continued with the stirrup pump. From the first round of 2016 onwards, all 16 blocks used Hudson® X-Pert® compression pumps. To monitor the quality and coverage of the spraying activity there were 166 monitors; in 2015 one monitor was assigned to each squad whereas in 2016 a monitor covered two squads. A programme supervisor at the block level oversaw the work of the monitors.

Each squad comprised six members: five Field Workers and a Senior Field Worker. In the teams with stirrup pumps, two pairs operated a pump each, one person mixed the insecticide, and a Senior Field Worker maintained the register and marked stencils onto the entrance of the sprayed house. Spraying with the compression pump enabled three people to spray with three pumps, while a pair made the solution, and another acted as the Senior Field Worker.

Village selection in Vaishali district used GIS-based mapping of endemic and non-endemic villages for VL trends and hotspot analysis to prepare the microplans. In addition to endemic villages of the last three years, periphery villages of hotspot villages within 500m of the endemic village boundary that had had a case in the previous year were also included. This algorithm provided a list of villages for the spray team. NVBDCP decided the start of the first round according to the timing of the first seasonal surge in *P. argentipes* sandfly densities. The start of the second round was often dictated by the end of the first round plus a gap of twelve weeks, and by access, e.g. if flooding risk from the monsoon rains had diminished; conversely it could not be too late due to people’s reluctance to allow spraying before they re-decorated interior walls for October/November festivals.

During the study period the existing stirrup pump was trialled against a compression pump and the latter found to deliver more uniform results.

A summary of the IRS schedule is described in Table S1. To assess the quality of spraying, four methods were employed:

i. Visual checks by the senior field worker on the same or next day following spraying, and re-spraying as necessary.

ii. Random samples by the squad monitor of one in every 10 of the 60–80 households in each village sprayed (i.e. \( n = 6 \)) by a squad; they were re-sprayed if the spray quality was deemed poor, on an individual basis. If the spraying quality in more than 50% of households was poor, then the whole village was re-sprayed.

iii. An indirect measure was sandfly density tests performed in 6 households in 1 village/block (i.e. 16 villages \( \times \) 6 households = 96 households). One of each of three dwelling types was
recorded: ‘human only’, ‘human + cattle in same dwelling’ or ‘human only + adjacent cowshed’. Samples were taken during a single night at 15 days before IRS, and {2, 4 & 12} weeks afterwards. Sandfly densities by \textit{P. papatasi}, \textit{Sergentomyia spp.} or \textit{P. argentipes} were later determined.

iv. IQKs (insecticide quantification kits) were used to take 3,000 samples from four interior walls of one sleeping room of a household at three different heights (1·8m, 1·1m and 0·3m) from eight districts during the first round of 2015. Previous research has shown the IQK’s performance as comparable to High Performance Liquid Chromatography—the gold standard.\textsuperscript{9}

3) Information, education and communication activities
Advice on how to prepare for the forthcoming IRS was first conducted during 19–21 February 2015 using audio broadcasts from auto rickshaws. It was conducted at 1,196 locations including marketplaces, private hospitals, block- and panchayat-level health centres, rural childcare centres (anganwadis), schools, state and central governmental offices, and households covered down to the ward level. Supporting literature over the course of the study covered banners (block level \(n = 44\); village \(n = 495\)), hoardings (marketplaces and government offices \(n = 52\)), posters (\(n = 47840\)), leaflets (\(n = 95680\)) and stickers (\(n = 47840\)). These activities continued 2–3 days before every spray round.

Descriptive analysis methods
These crude analyses provided essential information prior to spatiotemporal model development.

S3. Poisson confidence bands
These were computed using the \texttt{poisson.test} function in the \texttt{R stats} package\textsuperscript{10} for Figure 2.

S4. Year-on-year comparisons of monthly case numbers before and during the pilot
Ranked analyses were used as some differences are not visually discernible in time-series graphs that plot multiple districts. For each month, the year-on-year comparison of case numbers was computed, then a rank was given to the districts according to which had a) the most absolute cases (most = 1\textsuperscript{st} rank) and b) the largest negative change in its cases (largest negative change = 1\textsuperscript{st} rank). Comparisons before and during the pilot were then made by taking the rounded mean rank of each district for each period.

S5. Global Moran’s \(I\)
Alongside choropleth maps, Global Moran’s \(I\) statistic was used to assess the evidence for global spatial correlation in case numbers, for which a positive value (\(I > 0\)) indicates clustering of similar case numbers; a negative value indicates clustering dissimilarity in case numbers; and a zero value indicates no correlation.

S6. Effective reproduction number \(\hat{R}_e\)
The \texttt{epiEstim} \texttt{R} package estimated the effective reproduction number\textsuperscript{11,12} \(\hat{R}_e\) using an estimated \textit{diagnosis-to-diagnosis} (DD) distribution (§S7). To smooth the estimate a 6-month sliding window was used that matched the mean DD. As the time of the estimate was still in the diagnosis time domain they were shifted by a fixed single 7 months back in time (mean of incubation period + onset-to-diagnosis distribution) to show the results in the infection time domain.
Inputs into the spatiotemporal model

The spatiotemporal model is parametric in the Negative Binomial and seasonality distributions used, and regional endemicity levels (§S9). However, it was also informed by previous epidemiological parameters in the disease-specific diagnosis-to-diagnosis distribution (§S8).

S7. Obtaining the diagnosis-to-diagnosis distribution

The sum of normalised weights of 12-month lagged data accounts for the diagnosis-to-diagnosis (DD) distribution for VL as $D_T$, which was estimated as $\{0.08 \text{ [1st lag at } t-1], 0.11, 0.13, 0.13, 0.12, 0.10, 0.09, 0.07, 0.06, 0.05, 0.04, 0.03 [12th lag at } t-12]\}$. This is simulated from:

i. previous incubation period (IP) model estimate from a Bangladesh study using a zero-truncated Negative Binomial distribution with shape parameter $= 3$ and probability of success $= 0.35^{13}$ and maximum time 24 months, that produces a sample distribution with mean 6 months.

ii. onset-to-diagnosis (OD) time estimate$^{14}$ from Bihar in 2012–2013 using a Lognormal distribution with log mean $= 3.5$ and log standard deviation $= 0.7$ and maximum time 281 days, that produces a sample distribution with mean 1.3 months. We assumed that diagnosis and treatment occurred at the same time as field studies suggest they are only separated by 1–2 days anyway.$^{14}$

From these simulated distributions the diagnosis-to-diagnosis distribution, $D_T$, can be generated (Equation S1). Note that the OD distribution was randomly drawn twice for the independent time intervals of case 2 and case 1. By truncating the DD below 1 month and above 12 months, only $\sim 9\cdot 7\%$ of intervals are outside of this range.

$$D_T := \text{diagnosis-to-diagnosis interval}_{1\rightarrow 2} \sim \text{IP}_{\text{case 2}} + \text{OD}_{\text{case 2}} - 1/2 \text{OD}_{\text{case 1}}$$

Equation S1 Diagnosis-to-diagnosis interval definition

S8. Concept behind the three components of the base spatiotemporal model

There is a process producing the observed cases $Y_{i,t}$ in a district $i$ for a certain month $t$ given the cases seen in the previous 12 months $Y_{i,t-\tau}$, (for a lag-12 autoregression). This process is assumed to follow a Negative Binomial distribution with conditional mean $\mu_{i,t}$ and variance $\sigma_{i,t}^2$ (Equation S2).

$$\ln(\lambda_{i,t}) = \ln(\nu_{i,t}) + \lambda_i \sum_{\tau=1}^{T=12} D_T Y_{i,t-\tau} + \phi_i \sum_{J \neq i} \omega_{ji} \sum_{T=1}^{T=12} D_T Y_{J,t-\tau}$$

where: $\ln(\nu_{i,t}) = \alpha_i^{(\nu)}(\text{endemic}), \ln(\phi_i) = \alpha_i^{(\phi)}(\text{neighbourhood}),$

$$\ln(\lambda_{i,t}) = \alpha_i^{(\lambda)}_{\text{other}} + 1_{(i=Vaishali)} \alpha_i^{(\lambda)}_{\text{Vaishali}} (\text{epidemic})$$

$$D_T := \text{diagnosis-to-diagnosis interval distribution weightings (normalised)}$$

Equation S2 Base model

The cases observed in the previous 12 months cannot fully account for those observed in the current month because of noise in the temporal correlation of a district’s cases with itself or its immediate (first-order) neighbours. In using Held et al.’s framework$^{15}$ we assume there is a directly-observed process of autoregressive effects from the same district or its neighbours (epidemic and neighbourhood components, respectively) and an indirectly-observed process of background cases (endemic component) which are unobserved symptomatics or asymptomatics; these three
components sum to give the conditional mean \( \mu_{i,t} \) and the full process we observe (Figure S3). A directly-observed process can be inferred from spatiotemporally-local information of the case numbers in the last 12 months in the district and its immediate neighbours; whereas an indirectly-observed process is inferred by fitting a trend to the global time series to estimate a time-averaged, district-averaged monthly contribution.

**Figure S3** Model composition. The respective component triad of the Held et al. spatiotemporal model framework.\(^ {15} \) \( Y_{i,t} \) is the cases in district \( i \) at month number \( t \).

**Base model:** Negative Binomial with three components (Equation S2):

- **‘endemic’** \( (e_{i,t} v_{i,t}) \): cases in the same district caused by a constant background unobserved transmission, with a population offset \( e_{i,t} \) to account for the higher case numbers expected in districts with larger populations.

- **‘epidemic’** \( (\lambda_i \sum_{j=1}^{T-1} D_T y_{i,t-j}) \): cases correlated with a weighted sum of the last 12 months’ cases in the same district \( i \). This component was represented by two fixed intercepts: one for other districts \( \alpha_{\text{other}}^{(i)} \) and one for Vaishali, \( \alpha_{\text{other}}^{(i)} + \alpha_{\text{Vaishali}}^{(i)} \). The offset term was not included here since the study’s cases occur in a minority subset of the district so are assumed to be dependent on the cases arising in the epidemic process rather than the wider population.

- **‘neighbourhood’** \( (\phi_i \sum_{j\neq i} (\omega_{ji} \sum_{j=1}^{T-1} D_T y_{j,t-j})) \): recent case importation from adjacent districts \( j \) \( (\omega_{ji} = 1, \text{ else } 0) \). District differences encapsulated control effectiveness (epidemic component), two high/low endemcity level (endemic), strength of transportation links and human flow between districts (neighbourhood).

**S9. Overdispersion cut-off choice**

The Negative Binomial distribution produces non-negative predictions and can account for overdispersion arising from increased variability due to unobserved covariates or time-aggregated incidence.\(^ {16} \) As the endemicity distribution of districts (histogram of district cases during the study) resembles a two-component mixture model (Figure S4), the overdispersion term was dichotomised, \( (\psi_{\text{high}}, \psi_{\text{low}}) \), for high and low endemicity districts at a cutoff of 1,000 total cases during the study. This parsimonious approach was preferred rather than introducing a separate overdispersion parameter \( (\psi_{i}) \) for each district.
Model development

We desired a single model to both infer the pilot effect and to use to generate counterfactual predictions (by omitting the pilot effect from the pilot model). When developing a model for both inferential and predictive purposes it is unclear how to weight the importance of AIC and predictive performance (§S10) for these respective purposes. So pragmatically, we optimised for fit first; and then optimised for prediction, working from the pilot model.

S10. Model building

Each fit used all the districts’ data for the whole time series (unless indicated) to ensure a good fit to Vaishali’s neighbours; sometimes we extracted Vaishali-specific information from the output for further calculation or graphs. Parameters were inferred using an iterative scheme built into the surveillance and hhh4addon packages that minimised the model’s likelihood using Nelder-Mead optimisation. Starting from the base model (Equation S2) the model fit was sequential to reach the final (pilot) model. We evaluated the relative contributions of the time-varying components through a plot of the fitted components alongside the observed cases (Figure S5).

Figure S4 Overdispersion classification. District frequency by total VL cases to decide cut-off for high/low overdispersion assignment. $\psi_H, \psi_L$=high/low overdispersion parameters, respectively.
Model development can be summarised as follows:

**Base model**

+ **pilot effect**: impact was modelled via a step-change in the intercept in the epidemic component for Vaishali only, to capture changes in the time series of cases when the pilot began (epidemic component). This answered the first research question (*Has intensified control additionally contributed to the decline in VL cases in Vaishali, versus other districts?*).

+ **pilot start month**: due to the uncertainty of when each of the three control elements may have started to have an impact on diagnosed cases, we treated them as having a single combined effect, assumed on January 2015 (Figure S2). Thirteen possible pilot start months (September 2014–September 2015 inclusive) were tested and the best model chosen that minimised the AIC. To assess the sensitivity of the pilot model parameters to the start time we also report their range when the start month is varied. September 2014 was the lower bound as ASHA training had started by then, while September 2015 was the upper bound as if IRS in the first half of 2015 had failed due to DDT resistance, the second round may still have become effective after insecticide change (Figure S2).

+ **seasonality**: annual sinusoid in epidemic and/or endemic components.

The final pilot model is featured in Equation S3.

Selection of the predictive model was based on predictive performance. Firstly, we compared the predictive performance of the pilot model against the base model to establish that the pilot model was a relative advancement. Probability Integral Transform (PIT) histograms also indicated if the pilot model had a constant predictive performance throughout the predicted range.\(^{21}\)
We then compared the predictive performance of simulations of the (pilot) null model and alternative models with alternative parametric functional forms to the diagnosis-to-diagnosis distribution (they were linear, Geometric or Poisson) by summing ‘one-step-ahead’ sequential model scores; however the DD distribution was shown to have the lowest RPS value. The ‘one-step-ahead’ approach fits up to and including month $t$ and predicts the cases in the next month $t+1$; it uses the difference between observed and predicted cases to form a model score; the model was then refitted with the extra observed data at $t+1$ and the next month’s cases predicted, and so on. This approach thus sequentially trials the two models repeatedly, and takes the mean of these scores, then compares the pair’s scores. We used the ranked probability score for comparison, since it gives less weight to extreme departures from the trend of the observed.

As the histograms of the distribution of score differences were non-Normal, the non-parametric Permutation Test (using 10,000 simulations) was used to assess the significance of the difference. A $p$-value less than 0.05 was considered to indicate the alternative model had reasonably better predictive performance. It turned out that the model we reached through AIC selection (pilot model) was also optimal for predictive performance. Therefore, the counterfactual model stayed the same as the pilot model apart from omitting the pilot effect.

\[
Y_{i,t} \sim \text{NegBin}(\mu_{i,t}, \sigma_{i,t}^2), \text{ for cases } Y_{i,t}, \text{ districts } i \text{ at month } t \text{ with conditional mean } \mu_{i,t} \text{ & variance } \sigma_{i,t}^2 :
\]

\[
\mu_{i,t} = e_{i,t} \nu_{i,t} + \lambda_{i,t} \sum_{T=1}^{T=12} D_T Y_{i,T-T} + \phi_i \sum_{j \neq i}^{T=12} \omega_{ji} \sum_{T=1}^{T=12} D_T Y_{j,T-T}
\]

where $t$ is in month time units, $e_{i,t}$ is the population offset term, $\omega_{ji} = 1$ (if $j$ neighbours $i$) else 0, with two overdispersion terms $\psi_{\text{High}}, \psi_{\text{Low}} > 0$, st. $\sigma_{i,t}^2 = \mu_{i,t} \left( 1 + \psi k \mu_{i,t} \right)$ for $k \in \{ \text{High, Low} \}$ endemic districts.

The three components were formulated as:

\[
\ln(v_{k,t}) = \alpha_k^{(v)} + A_{\text{END}} \sin \left( \frac{2\pi}{12} t + \Phi_{\text{END}} \right) \quad (\text{endemic}),
\]

\[
\ln(\lambda_{t}) = \alpha_{\text{other}}^{(\lambda)} + 1_{(i=Vaishali)} \left( \alpha_{\text{Vaishali}}^{(\lambda)} + 1_{(t \geq \tau)} c_t \cdot \alpha_{\text{pilot}}^{(\lambda)} \right) + A_{\text{AR}} \sin \left( \frac{2\pi}{12} t + \Phi_{\text{AR}} \right) \quad (\text{epidemic}),
\]

\[
\ln(\phi_i) = \alpha_i^{(\phi)} \quad (\text{neighbourhood});
\]

with $\tau$ starting pilot month, $A_{(\cdot)}$ annual sinusoid amplitude and phase $\Phi_{(\cdot)}$, fixed intercepts for the 32 districts $\alpha_{\text{other}}^{(\lambda)}$ and Vaishali $\alpha_{\text{Vaishali}}^{(\lambda)}$, and $c_t = \begin{cases} 0, & \text{if } t < \tau \\ \frac{1}{\sum_{p=1}^{12} Y_{t-p}} \sum_{p=1}^{12} Y_{t-p}, & \tau \leq t < \tau + 11 \\ 1, & t \geq 12 \end{cases}$

\textit{Equation S3 Pilot model}. The counterfactual model was the same but omitted the $1_{(t \geq \tau)} c_t \cdot \alpha_{\text{pilot}}^{(\lambda)}$ term. The $c_t$ term corrects for the first 12 months of the pilot due to delayed effects of the distributed lag.
S11. Model validation

Heteroskedasticity was present in the pilot model since high variance of model residuals was present when the model was fitted to low or high numbers of cases (Figure S6). The final counterfactual model made reasonable ‘one-step-ahead’ sequential forecasts of the monthly case numbers in Vaishali in 2014 based on a fit to the 2013 data, as assessed visually (Figure S7), suggesting that the model captured the essential features of the process giving rise to the case counts and could be relied upon to make counterfactual predictions from 2015, based on the 2013–2014 status quo.

Time series plots were used to visually assess the difference between the pilot and counterfactual models versus the observed cases time series; and fanplots of the distribution of simulations from sequential ‘one-step-ahead’ forecasts of January 2016–December 2017 (Figure S8). The distributed-lag model responds to the July 2017 in Figure S8b like real-life transmission and shares the impact of this incidence peak over latter months.

Figure S6 Pilot model heteroskedasticity.
Figure S7 **Counterfactual pre-intervention goodness of fit and predictive performance.** The counterfactual model was fitted to the observed data (black line) during 2013 (on the left-hand side of the vertical grey line) to produce the initial fit (red line) for that time series. ‘One-step-ahead’ forecasts were then sequentially made for progressing months (dashed red line) according to the complete observed time series for the 12 previous months (further details in §S9). 17

Figure S8 **Fanplots**—sequential probability distributions for a) counterfactual model and b) pilot model. The connected black line represents observed cases, and the red gradient band indicates sample quantiles about each month’s predicted values.
Figure S9 HIV-VL case proportions. Vaishali and the mean of the other 32 districts.

Figure S10 Probability Integral Transform (PIT) histogram for the pilot model.
S12. Estimating cases averted
To answer *how many VL cases are expected to have been averted by the pilot?*, we took the difference in monthly ‘one-step-ahead’ January 2015 to December 2017 forecasts for pairs of i) simulated cases from the counterfactual model fitted to all data from January 2013 to December 2014, initialised with the Mersenne-Twister random number generator seed; and ii) simulated cases from the pilot model. The paired difference was summed for all forecast months to obtain the estimated case numbers averted. We simulated 100,000 pairs to produce an estimated median and IQR quantiles.

S13. Further model developments
Introducing a time-varying overdispersion term to account for districts like Vaishali whose endemicities change over the course of the study would improve the model fit; as would weighting the neighbourhood adjacency term \( \omega_{ij} \) in Equation S3 by the proportion of the shared edge to the perimeter of district \( i \).

The selected island of 33 districts could underestimate the full neighbourhood effects for two reasons: firstly, the five unsurveyed districts in south-west Bihar may have had unreported cases. Secondly the absence of the effect of neighbouring states like Uttar Pradesh, Jharkhand and West Bengal or the Nepalese border which are low-endemicity zones.\(^{23,24}\) The latter could be addressed within the surveillance framework by modelling entire neighbouring states as additional ‘district’ units.

Given that the disease has a relatively long and varied incubation period it was reasonable to expect that cases are temporally-related through the months. As we use case diagnosis dates, it is unclear how this correlation is obscured by changes in the unobserved OD time distribution. It is likely that environmental attributes (temperature, rainfall and humidity) affect sandfly populations district-wide on a faster timescale, which has a stronger influence on new cases than the epidemic component. This model should not be applied when there is a wide range of endemicities within a single spatial unit, as heteroskedasticity would hamper model fitting and simulations at low or high case counts.

For a decreasing epidemic the mean of the (backward) diagnosis-to-diagnosis distribution \( D_f \), like a (onset) serial interval distribution, is expected to increase\(^{25}\) however under the existing hhh framework we can only use a static profile. This will result in the later lags (e.g. months 9–12) in later study years contributing less to the autoregressive component than they should and thus \( \lambda_i \) (Equation S2 & Equation S3) may be overestimated.

S14. Source of the data and open access
This routine data originated from the Kala-azar Notification Registry as part of the National Public Health Reporting System maintained by the Office of the Additional Director-cum-State Programme Officer, NVBDCP (Patna). The raw data was inputted electronically and checked for completeness, consistency and data entry errors. Any errors were resolved by the State Programme Office and Nodal Officer of the NVBDCP. The cleaned data was also cross-validated with the NVBDCP’s national data repository. This anonymised data aggregated by month and district (admin level 2) was shared with RMRRIMS and so was non-personal and non-identifiable since age, sex and location of village was not provided. New cases continued to be reported through the usual health system and collated by the NVBDCP; thus this was a secondary data analysis.
References

1. GADM. Global Administrative Areas: India level 2 shapefiles v2·8 [Internet]. 2015 [cited 2018 Feb 6]. Available from: gadm.org


