Institution: Lancaster University		
Unit of Assessment: 3, Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Planning and delivering the control and elimination of neglected tropical diseases: the impact of model-based geostatistics		
Period when the underpinning research was undertaken: 2000 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Peter Diggle Emanuele Giorgi	Professor Senior Lecturer	1988–present 2015–present
Period when the claimed impact occurred: 2015 – 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Geospatial analysis techniques developed by Diggle and Giorgi have been used directly by public health agencies in planning and delivering interventions to treat neglected tropical diseases (NTDs) in some of the world's most adversely affected countries. This case study focuses on the impacts of Diggle and Giorgi's research in the control efforts for four diseases: onchocerciasis, malaria, trachoma and soil-transmitted helminths (STH). Public health mapping strategies have been adopted by governments at a continental scale, and the techniques have been used to plan treatment and resource allocation for over 100 million people, leading to the possibility of the elimination of some diseases in several resource-poor countries and enabling resource savings in some of those countries of an estimated USD100 million.

2. Underpinning research

In a 1998 paper, Diggle and two Lancaster colleagues introduced model-based geostatistics (MBG). Compared with classical geostatistics, MBG uses efficient, principled methods of predictive inference. It is particularly well suited to low-resource settings where, due to the lack of disease registries, monitoring of the disease burden is carried out through cross-sectional prevalence surveys. In these settings, MBG provides a way of combining empirical prevalence data with remotely sensed images of environmental variables to construct predictive maps that can be an order of magnitude more precise than predictions based on classical survey sampling methods [G5, R7]. Diggle and colleagues have since continued to develop MBG methods, especially for use in low-resources areas where the availability of comprehensive datasets is limited, and to promote their use amongst epidemiologists, geographers and statisticians. The 2016 article by Diggle and Giorgi [G1, R1] reviews methodological developments since the original 1998 paper, Giorgi and Diggle have also implemented the methodology in open-source software [R8] and have delivered training courses in its use.

With funding from the WHO in 2005 [G2, R2], Diggle proposed a method for identifying areas that did or did not meet the WHO requirements for safe mass distribution of ivermectin (Mectizan® donated for mass distribution by Merck) in control efforts against *onchocerciasis* (river blindness). Widespread administration of drugs such as ivermectin kills the immature worm parasites responsible for this severely debilitating condition, but the drug needs to be re-administered annually due to the long-lived nature of the adult worms. In addition, a different parasitic infection, *loiasis* (eye-worm), caused by the parasitic worm Loa loa, has a partially overlapping distribution with onchocerciasis; while ivermectin also kills immature Loa loa it can also produce severe, occasionally fatal, side effects in individuals with very severe eye-worm infections, which presents a major obstacle to safe ivermectin treatment for onchocerciasis control. Diggle and colleagues applied MBG methods to produce spatial risk maps for loiasis prevalence, initially in Cameroon in 2007 as a proof of concept [R2] and subsequently, in 2011 to delineate areas safe and unsafe for ivermectin treatment across the whole of Africa [R3] in line with the WHO's policy recommendation to put in place precautionary measures against serious adverse reactions to the medication in areas where loiasis prevalence, as estimated by

RAPLOA (Rapid Assessment Procedure for Loiasis), exceeds 40%. Unlike conventional mapping methods that provide only point estimates of prevalence, MBG has enabled the construction of probabilistic risk maps (as shown in Figure 1) which demarcates the study region into areas where the true prevalence is above (red) or below (bright blue) the 40% policy intervention threshold with a probability of at least 0.9 and a corridor of uncertainty where more data are needed to make an accurate prediction.

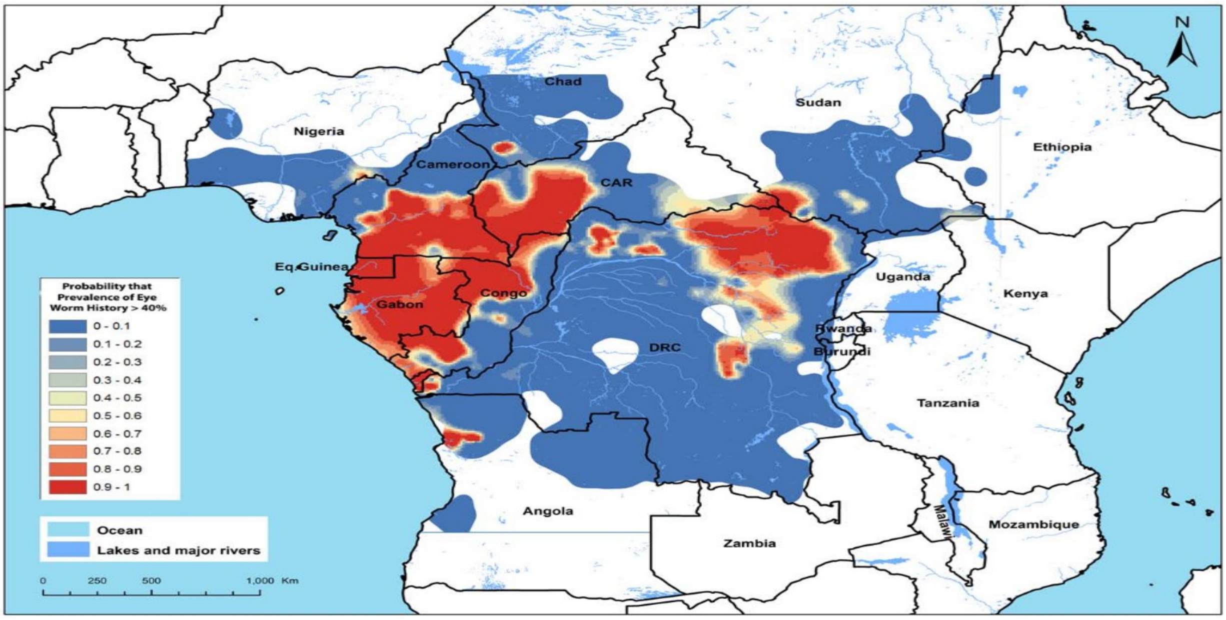

Figure 1. Predictive probability map showing the probability that Loiasis prevalence, as measured by a low-cost questionnaire instrument, RAPLOA, exceeds 40% [R3].

Other recent methodological developments by Diggle and Giorgi that are applicable to all NTDs include methods for the adaptive design of repeated cross-sectional surveys [G3, R4]; multivariate methods for combining data from randomised and convenience surveys [G1, R5] or from multiple diagnostic tools [G5, R6]; and a novel approach to the design and analysis of so-called elimination surveys, where the goal is to establish whether prevalence is low enough to meet the WHO requirement for the elimination of the disease in question as a public health problem [G4, R7].

3. References to the research

[R1] **Diggle, P. J., & Giorgi, E**. (2016). Model-based geostatistics for prevalence mapping in low-resource settings. *Journal of the American Statistical Association*, 111(515), 1096-1120. https://doi.org/10.1080/01621459.2015.1123158 (Google Scholar: cited by 38)

[R2] **Diggle, P. J.,** Thomson, M. C., Christensen, O. F., Rowlingson, B., Obsomer, V., Gardon, J., Wanji, S., Takougang, I., Enyong, P., Kamgno, J., Remme, H., Boussinesq, M., & Molyneux, D. H. (2007). Spatial modelling and prediction of Loa loa risk: decision making under uncertainty. *Annals of Tropical Medicine and Parasitology, 101*(6), 499-509 (Google Scholar: cited by 117)

[R3] Zoure, H. G. M., Wanji, S., Noma, M., Amazigo, U. V., **Diggle, P. J.,** Tekle, A. H., & Remme, J. H. F. (2011). The geographic distribution of loa loa in Africa: results of large-scale implementation of the Rapid Assessment Procedure for Loiasis (RAPLOA). *PLoS Neglected Tropical Diseases*, 5(6), -. [e1210]. https://doi.org/10.1371/journal.pntd.0001210 (Google Scholar: cited by 220, Altmetric score: 7)

[R4] Chipeta, M., Terlouw, D. J., Phiri, K. S., & **Diggle, P. J.** (2016). Adaptive geostatistical design and analysis for prevalence surveys. *Spatial Statistics,* 15, 70-84. https://doi.org/10.1016/j.spasta.2015.12.004

[R5] **Giorgi, E.,** Sesay, S. S. S., Terlouw, D. J., & **Diggle, P. J.** (2015). Combining data from multiple spatially-referenced prevalence surveys using generalized linear geostatistical models. *Journal of the Royal Statistical Society: Series A Statistics in Society,* 178(2), 445-464. https://doi.org/10.1111/rssa.12069 (Google Scholar: cited by 40, Altmetric score: 9)

[R6] Amoah, B., **Diggle, P., & Giorgi, E.** (2019). A geostatistical framework for combining spatially referenced disease prevalence data from multiple diagnostics. *Biometrics*, 76(1), 158-170. https://doi.org/10.1111/biom.13142 (Altmetric score: 6)

[R7] Fronterre, C., Amoah, B., **Giorgi, E.,** Stanton, M., **Diggle, P.J.** (2020). Design and analysis of elimination surveys for neglected tropical diseases. *Journal of Infectious Diseases,* 21(Supplement_5), S554–S560. https://doi.org/10.1093/infdis/jiz554 (Google Scholar: cited by 8, Altmetric score: 8)

[R8] **Giorgi, E., Diggle, P.J.** (2017). PrevMap: an R package for prevalence mapping. *Journal of Statistical Software*, 78 (8), 1-29. https://doi.org/10.18637/jss.v078.i08 (Google Scholar: cited by 48).

Grants

G1. Geostatistical methods for disease risk mapping. 2015–18, PI: Giorgi.	GBP256,631	MRC
G2. Calibration and Mapping of Parasitological and RAPLOA estimates of Loa Loa Prevalence. 2005, PI: Diggle.	USD80,000	WHO
G3. Statistical modelling for real-time spatial surveillance and forecasting. 2010–14, PI: Diggle.	GBP402,328	MRC
G4. NTD Modelling Consortium: moving towards elimination. 2017–21, Diggle and Giorgi.	USD423,720.	Gates Foundation
G5. Loa loa geospatial and post-validation surveillance. 2019–21, Diggle and Giorgi	USD142,871	TFGH

Awards

- Royal Statistical Society Research Prize 2018: awarded to Giorgi for [R8].
- Royal Statistical Society Barnett Award 2018: awarded to Diggle for his complete body of work on geospatial statistical methods for environmental epidemiology.

4. Details of the impact

4.1 Malaria

In collaboration with partners in Africa such as the Somalian Ministry of Health and epidemiologists and geographic information system (GIS) experts from the KEMRI Wellcome Trust in Nairobi, Giorgi developed novel MBG methods and applied them for malaria mapping in sub-Saharan Africa which has subsequently informed malaria control policies [S1, S2]. For example, in 2017, Somalia launched a 5-year malaria strategic plan with the aim of sustaining malaria prevalence levels below 1% in the north and increasing access to treatment and vector control in the south. Giorgi drew on [R1] to fit spatio-temporal MBG models to cross-sectional prevalence survey data collected between 2005 and 2015 to identify regions highly likely to have malaria prevalence above or below 1% (Figure 2, left-hand panel). Giorgi also ran the analysis for Sudan [S2] using data from cross-sectional surveys conducted between 2000 and 2016 (Figure 2, right-hand panel).

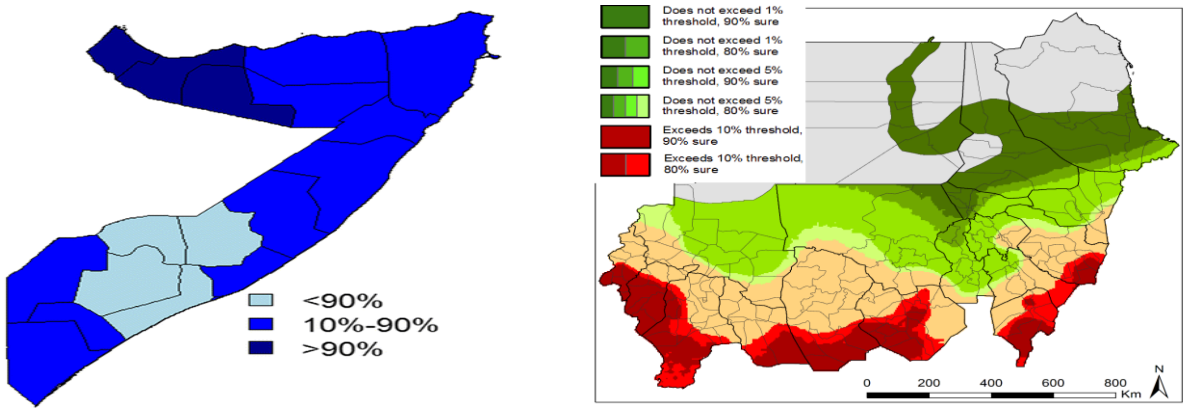

Figure 2. *Left-hand panel:* classification of the 18 regions in Somalia based on their estimated probability of malaria prevalence below the 1% threshold, as indicated by the legend. *Right-hand panel:* classification of areas of Sudan according to their probability of low prevalence (northern Sudan, shades of green) or high prevalence (southern Sudan, shades of red), as indicated by the legend.

The maps shown in Figure 2 allowed the distinction of areas highly likely to have achieved public health policy targets and areas that require additional sampling effort to be classified correctly, which triggered a significant shift in the decision-making process, which was previous informed by maps of predicted malaria prevalence that did not acknowledge the inherent uncertainty. This provided evidence for public health policy decisions in Somalia, Kenya and other countries. In the words of the Head of the Strategic Information Unit at the Global Malaria Programme, World Health Organization, "*Professor Peter Diggle and Dr Emanuele Giorgi's work has not only been extremely helpful to analysing the spatial and temporal changes of malaria in Somalia and Kenya as well other African countries, but it has also been instrumental in changing policy and practice through the development of national strategic plans for malaria for these countries. This is a clear demonstration of how research evidence can immediately translate in policies and action in countries to reduce the burden of malaria."* [S3].

In addition to the research being directly adopted by national programmes for malaria in the worst affected countries in Africa, Giorgi and Diggle's research and outreach has also supported capacity-building within resource-constrained countries in tackling other public health priorities, leading in particular to impact in Kenya where vaccination policies have been shaped by work on infant mortality undertaken by African statisticians [S3].

4.2 Onchocerciasis

Since 2015, the focus of Lancaster research on onchocerciasis control has been to develop methods for the optimal combination of mobile microscopy and a rapid diagnostic test to determine which areas are and are not safe for mass drug administration. In 2015, Diggle began a formal collaboration with the NTD Centre of the Task Force for Global Health (TFGH). Predictions from geospatial statistical models were validated by in-country data from Nigeria, Cameroon and Gabon As a result, the prediction algorithm has been incorporated into the LoaScope devices procured by the Gates Foundation and has been considered a viable strategy that the TFGH and its partners are interested in piloting in other global NTD-affected areas [S4]. In January 2020, the TFGH NTD Centre Director of Research stated that Diggle and Giorgi's work has been "*instrumental in developing a comprehensive Loa loa mapping strategy at the continental scale*" [S4]. The theoretical contributions [R1] have been used to develop new analytic tools that avoid the need to test every individual with the LoaScope diagnostic, enabling an estimated resource savings of USD100 million [S4]. In addition, according to the Director of Research, TFGH NTD Centre, due to Diggle and Giorgi's contributions to the development of these analytic tools, "*onchocerciasis may be possible to eliminate in areas where Loa Loa is co-endemic (a 10 country region with over 85 million individuals)*" [S4].

4.3 Trachoma

In 2018, Diggle and Giorgi began working with the WHO's Global Trachoma Elimination Programme and used their MBG methods and software [R1, R8], to provide estimates of the burden and fine-scale spatial distribution of Trachomatous trichiasis cases throughout Ethiopia. The importance of this work was summarised by the Trachoma Medical Officer of the Department of Control of Neglected Tropical Diseases (DCNTD) in 2019, "*It will allow highly resource-restricted national trachoma programmes, currently active in more than 50 countries, to better target services to deliver sight-saving operations. These operations are needed by 2.5 million of the world's poorest and more marginalized individuals"* [S5].

The Ethiopian analysis provides an example of the direct use of Diggle and Giorgi's developed analytical approaches for trachoma control, as confirmed in 2020 by the Trachoma Medical Officer, who stated, "*Geostatistical approaches have been applied to all available current data on trichiasis in Ethiopia, the world's most heavily trachoma-affected country. They were used to calculate the probability that the TT component of trachoma's elimination as a public health problem has already been achieved, for each of 482 evaluation units, finding that it had been* *with probability 0.9 or more in only eight of those evaluation units. In other words, continuing heavy investment in trichiasis surgery programmes is needed in that country*" [S5].

4.4 Soil-transmitted helminths (STH)

In 2017, Diggle began working with the Sri Lankan Ministry of Health to provide research techniques to inform their de-worming strategy. The Senior Professor of Parasitology at the University of Kelaniya, responsible for the oversight of the Ministry's de-worming programme, stated in 2020, "*As a result of using the geostatistical modelling techniques that Prof Diggle have equipped us with, the Ministry of Health in Sri Lanka has revised its approach to deworming for STH infections in the entire country. The design of this new strategy would not have been possible without using the modelling techniques developed by Prof Diggle, and without his input, the revised strategy would have resulted in either overtreatment (with unnecessary use of anthelmintics) or undertreatment, resulting in rebound in the prevalence of STH infections in Sri Lanka*" [S6].

All the software developed for these analyses is publicly available as an open source R package, PrevMap, with associated tutorial material [G1, R8]. Between January 2016 and December 2020 the package was downloaded 25,965 times [S7].

5. Sources to corroborate the impact

[S1] Giorgi E et al. (2018) Using non-exceedance probabilities of policy-relevant malaria prevalence thresholds to identify areas of low transmission in Somalia. Malar J, 17: 88. https://doi.org/10.1186/s12936-018-2238-0. NOTE: Key members of the Ministries of Health of the Somalian Federation are also the co-authors of this publication.

[S2] Updating the malaria risk profile of the Republic of Sudan. LINK Project Technical Report, 2018.

[S3] Testimonial from the WHO Head of the Strategic Information Unit at the Global Malaria Programme on the policy changes and impact from the adoption of Lancaster methodologies, 2020.

[S4] Testimonial and email from the Task Force for Global Health NTD Centre Director, 2020.

[S5] Emails from Trachoma Medical Officer of the Department of Control of Neglected Tropical Diseases, WHO, 2020.

[S6] Testimonial from Senior Professor of Parasitology at the University of Kelaniya, Sri Lanka, 2020.

[S7] PrevMap download statistics.