Institution: Lancaster University

Unit of Assessment: 3 Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Multi-country risk-mapping leads to more efficient delivery of mass-treatment for the control of river blindness

1. Summary of the impact (123 words)

Onchocerciasis (river blindness) is a debilitating disease of major public health importance in the wet tropics. The African Programme for Onchocerciasis Control (APOC) seeks to control or eliminate the disease in 19 countries. Accurate mapping of Loiasis (eye-worm) was a requirement for implementation of APOC's mass-treatment prophylactic medication programme in order to mitigate against serious adverse reactions to the Onchocerciasis medication in areas also highly endemic for Loiasis. Model-based geostatistical methods developed at Lancaster were used to obtain the required maps and contributed to a change in practice of APOC in a major health programme in Africa. Our maps are used to plan the delivery of the mass-treatment programme to rural communities throughout the APOC countries, an estimated total population of 115 million.

2. Underpinning research (536 words)

Diggle (Distinguished Professor of Statistics) has been an academic at Lancaster throughout the period described in this impact case study and has been the lead researcher for the research underpinning this case study.

From 1995 onwards Diggle and colleagues were responsible for developing a novel model-based approach to geostatistical analysis and promoting its usage amongst epidemiologists, geographers and statisticians (Ref. 3.1). This model-based approach represents a major paradigm-shift from classical geostatistics, by importing efficient, principled methods of predictive inference rather than relying on the more ad hoc approaches used in classical geostatistics. Control efforts against onchocerciasis are co-ordinated by APOC (5.1) and include mass administration of drugs to kill *Onchocerca volvulus*, a worm parasite responsible for the severely debilitating condition river blindmess. The drug of choice for treatment is ivermectin (Mectizan® donated to APOC by Merck, 5.2), which kills the immature worms but due to the long-lived nature of the adults needs to be re-administered on an annual basis. However, a different parasitic worm, the eye-worm *Loa loa*, which has a partially overlapping distribution, is also killed by ivermectin, but treatment of individuals with heavy eye-worm infections can produce severe side effects.

Supported by grant-funding from WHO (3.6), Diggle and co-workers applied model-based geostatistical methods to produce a spatial risk map for Loaiasis prevalence in Cameroon and immediately surrounding areas, using parasitological (blood-sample) data from field-studies conducted by APOC field epidemiologists, in combination with remotely sensed data on environmental risk-factors (3.2). This provided key planning information for APOC to address this problem for the first time, putting in place precautionary measures and not providing mass administration in affected areas, but proceeding with confidence elsewhere. Further statistical research extended the methodology to include bivariate geostatistical modelling, enabling a more fine-grained mapping application to be developed and improving the precision of the drug administration programme (3.3). With MRC support (3.7) the bivariate model was then used to calibrate parasitological prevalence data against a safer, lower-cost, questionnaire-based instrument for estimating prevalence (3.4) thus potentially further improving the effectiveness of the APOC programme. This was realised in further research where the calibration relationship was extended to mapping all of the 19 participating APOC countries, using only questionnaire-based data (3.5). Following this research, the WHO policy for the prophylactic medication programme has now to put in place precautionary measures against serious adverse reactions to the medication in areas where Loiasis prevalence exceeds 40% as measured by the questionnaire-based instrument. The conventional mapping methods previously in use only give point estimates of prevalence and are ill-suited to this purpose. In contrast, model-based geostatistics enables the construction of probabilistic risk-maps. An example of the data produced is captured in the map 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 probability at least 0.9,

and a corridor of uncertainty where more data are needed to make an accurate prediction.

This case-study is only one of many examples of how model-based geostatistical methods are used for converting spatially sparse data into spatially continuous maps with associated estimates of precision. The methodology is well-suited to disease mapping applications in resource-poor settings where registry data are not available.

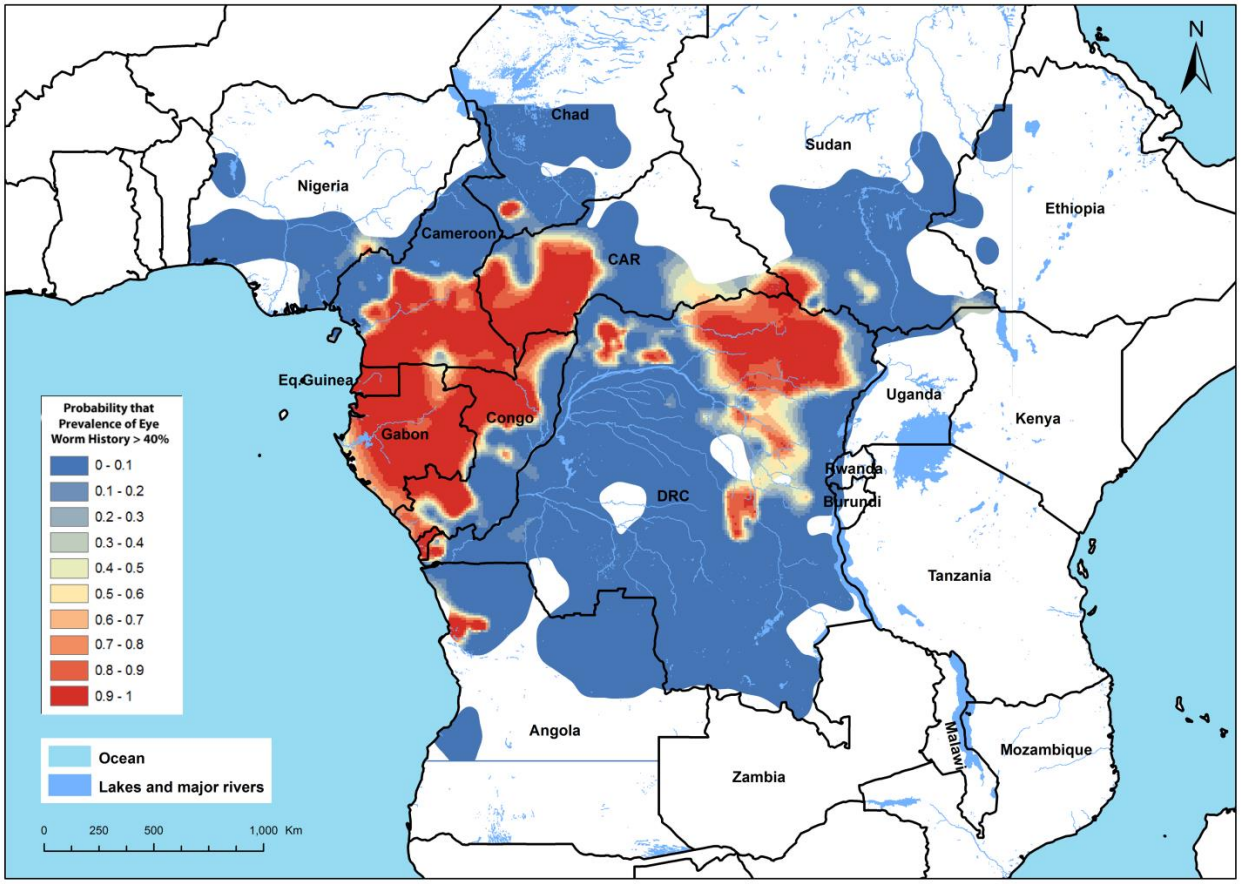

Figure 1. Loiasis (eye-worm) risk-map. The mapped variable is the predictive probability that Loiasis prevalence as determined by questionnaire exceeds 40%, defined by WHO to be “high risk.” Areas coloured red have high probability (>0.9) of the true prevalence exceeding 40%, areas coloured bright blue a low probability (<0.1). Pink, cream and light blue areas denote intermediate probabilities as indicated on the legend. (From reference 3.5).

3. References to the research

Publications

3.1 Diggle, P.J., Moyeed, R.A. and Tawn, J.A. (1998). Model-based geostatistics (with Discussion). *Applied Statistics*, **47**, 299-350. doi: 10.1111/1467-9876.00113. On 27/10/2013, Google scholar listed 957 citations.

3.2 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. And Molyneux, D.H. (2007). Spatial modelling and prediction of Loa loa risk: decision making under uncertainty. *Annals of Tropical Medicine and Parasitology*, **101**, 499-509. doi: 10.1179/136485907X229121.

3.3 Crainiceanu, CM, Diggle, PJ and Rowlingson, B (2008) Bivariate binomial spatial modelling of *Loa loa* prevalence in tropical Africa (with Discussion). *Journal of the American Statistical Association*, **103**, 21-43. doi: 10.1198/016214507000001409. Submitted in REF2.

3.4 Wanji, S., Akotshi, D.O., Kankou, J.M., Mutro, M.N., Tepage, F., Ukety, T.O., Diggle, P.J. and Remme, J.H. (2012). Validation of the rapid assessment procedures for loiasis (RAPLOA) in the Democratic Republic of Congo: health policy implications. *Parasites and Vectors* **5**, 25 doi:10.1186/1756-3305-5-25.

3.5 Zoure, H., Wanji, S., Noma, M., Amazigo, U., Diggle, P.J., Tekle, A. and Remme, J.H. (2011). The geographic distribution of Loa loa in Africa: results of large-scale implementation of the Rapid Assessment Procedure for Loiasis (RAPLOA). *Public Library of Science: Neglected Tropical Diseases,* **5**, (6): e1210. doi:10.1371/journal.pntd.0001210.

Grants

3.6 2005, $80,000 from WHO to Prof Peter J Diggle, for "*Calibration and Mapping of Parasitological and RAPLOA estimates of Loa loa Prevalence*".

3.7 2010-2013, £484,968 (FEC) from MRC to Prof Peter J Diggle and Mr Barry Rowlingson for "*Statistical modelling for real-time spatial surveillance and forecasting*".

Evidence of the quality of the research

All the underpinning research is original and has been published in peer-reviewed journals. As a measure of the significance of the research, total funding since 2005 amounts to some £500,000 and was obtained in open competition.

4. Details of the impact (601 words)

Following the original methodological work (3.1), Diggle led the development of an open-source R package (geoR, http://cran.freestatistics.org/) to implement model-based geostatistical methods so as to facilitate their adoption by applied scientists. This led to a collaborative project with the Liverpool School of Tropical Medicine, which in turn led to Diggle being invited to join an international oversight group (the Mectizan Expert Committee) advising the African Programme of Onchocerciasis Control (APOC) in the roll-out of a multi-country mass-distribution programme of prophylactic medication against onchocerciasis (river blindness), and subsequently to working directly with APOC scientists in Burkina Faso and at WHO Tropical Diseases Research in Geneva (5.1,5.2,5.3).

The APOC programme has been running since 1995, spans 19 African countries and has generally been very successful, having administered approximately 70 million treatments to date, with a target of reaching 90 million treatments by 2015 (5.4, 5.5). However, the programme encountered a problem when it was discovered that people heavily co-infected with *Onchocerca* and *Loa* parasites were at risk of a severe (occasionally fatal) adverse reaction to the prophylactic medication. As a result, the programme needed to obtain an accurate map of Loiasis prevalence across the 19 APOC countries. In the absence of reliable census information, this required a major effort in the collection of prevalence data from field surveys and its integration with remotely sensed proxies for environmental risk-factors, using model-based geostatistical methods. The modelling problem was further complicated by the need to combine two different survey instruments: a "gold standard" parasitological (blood-sample-based) instrument available at several hundred locations, and a questionnaire-based instrument that could be collected at several thousand locations throughout the 19-country target region. This required an extension of the original methodology, reported in references 3.3 and 3.4. This methodology was then used to map prevalence throughout the APOC region (3.5). Dissemination of these ideas to the user-community was achieved by Diggle making successive presentations to annual meetings of APOC's Technical Consultative Committee in Burkina Faso, attended by scientific and administrative representatives of the participating countries (5.6). As a result, model-based geostatistical methods have now been adopted for decision making and prevalence mapping throughout the region covered by the APOC member-countries, for example, the map below from "Fifteen Years of APOC" (Fig. 2, 5.7). Specifically, APOC has adopted a policy of putting in place appropriate precautionary measures before implementing mass-treatment in areas where questionnaire-based Loiasis prevalence is thought to exceed 40%. The model-based approach delivers maps that show, at each location, the predictive probability that local prevalence exceeds this 40% threshold, conditional on all of the available data.

The research has changed APOC's practice with regard to implementation of the mass-treatment programme in areas highly endemic for Loiasis (5.8) and, through this, has been of indirect benefit to all rural communities throughout the 19 APOC countries, an estimated total population of around 115 million (5.4). Prior to implementation of the APOC programme in some areas up to 50% of adults suffered from blindness, but by 2005 the number of disability-adjusted life years (DALYs)

lost to onchocerciasis had been reduced by 50%. With the help of Prof Diggle's research and continued efforts on the ground further reductions in DALYs are occurring, the prediction is that this will be reduced by 86% by 2015 (5.4), As the current Director of APOC states "*Prof Diggle's input, using his model-based geostatistical methodology, has been an essential contribution to the APOC programme*" (5.8). The impact is continuing, since publication of the first prevalence maps in reference 3.2. Prof Diggle's work has also been cited by HEFCE as an effective use of QR funding in delivering impact (5.9).

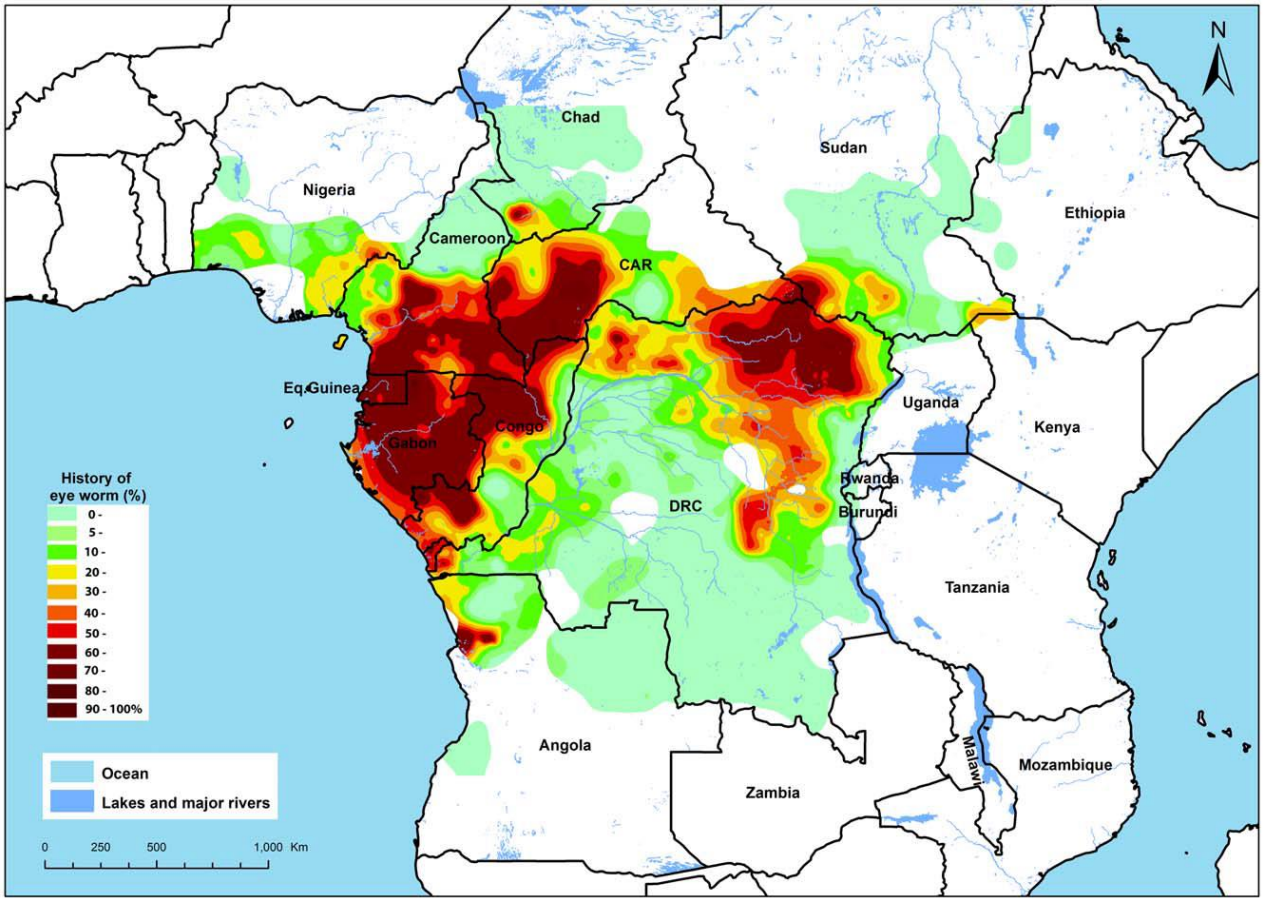

Figure 2. Map of the estimated prevalence of eye worm history in Africa. Map reproduced in "Fifteen Years of APOC" (5.7) from reference 3.5.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 Professor of Tropical Health Sciences, Liverpool School of Tropical Medicine
5.2 WHO Scientist, WHO Tropical Disease Research
5.3 Former Director, African Programme for Onchocerciasis Control
5.4 African Programme for Onchocerciasis Control
http://www.who.int/blindness/partnerships/APOC/en/
5.5 Mectizan Donation Program http://www.mectizan.org/
5.6 Report of the 29th session of the Technical Consultative Committee (TCC) Ouagadougou, 14-19 September 2009
http://www.who.int/apoc/about/structure/tcc/TCC29_FINAL_REPORT_Eng.pdf (page 16, para 69)
5.7 Fifteen years of APOC, 1995-2010
http://www.who.int/apoc/magazine_final_du_01_juillet_2011.pdf, (page 21)
5.8 Letter from Director of APOC
Collaborative work between APOC and Prof Diggle Statement.pdf
5.9 Securing world-class research in UK universities: Exploring the impact of block grant funding. HEFCE publication (case-study, page 6)
http://www.hefce.ac.uk/media/hefce/content/whatwedo/research/howwefundresearch/QR.pdf