Institution: University of Exeter		
Unit of Assessment: UoA 10 Mathematical Sciences		
Title of case study: Statistical model enables improved disease management in Brazil		
Period when the underpinning research was undertaken: September 2016 - present		
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:**
Dr Theo Economou Dr Oliver Stoner	Senior Lecturer in Statistics Research Fellow	2015 - present 2019 - present
Period when the claimed impact occurred: December 2017 to date		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Infectious diseases such as dengue and zika are a major problem in Brazil: effective management relies on being able to monitor cases accurately. Researchers at the University of Exeter have developed novel statistical methods that are being used by the Brazilian institute for public health, Fiocruz, for estimating the number of disease cases and correcting for reporting delays. The adoption of the Exeter model resulted in significant improvement to the regional disease warning system, InfoDengue which currently affects 788 Brazilian cities and the creation of a national influenza warning system, InfoGripe and has now been applied to the COVID-19 pandemic. Combined impact includes:

- Policy Change (mitigation strategies, immunization, health emergency contingencies)
- Reduced loss of life (between 6 – 171 pa)
- Significant financial savings ($300k - $2m pa)
- Improved operational efficiencies of regional and national health authorities, applicable to over 210m people
- More reliable early warnings
- Estimates of true Covid-19 burden across Brazil, informing international vaccine development stage III trials (Sinovac) and the Brazilian Ministry of Health.

2. Underpinning research (indicative maximum 500 words)

Predicting the spread of disease relies heavily on the availability of data on the number of cases **[3.1]**. Conventional data modelling approaches for estimating and predicting disease occurrence are designed for data at annual/seasonal time scales. Real-time warnings require shorter time scales, generally weeks, but this is difficult to achieve in practice as the disease data is invariably subject to reporting delay, caused by pending laboratory confirmation and logistic/infrastructure difficulties. As the reliability of public warnings and health resource allocation depends on accurate estimation of the number of cases, timely correction of the available information is vital, as is quantifying the associated uncertainty **[3.2]**.

In 2015, the warning system InfoDengue was launched, in an effort to mitigate the risk from dengue fever in Rio de Janeiro. However, the underlying method for correcting the delays in the data (i.e. estimating the yet-to-be-reported cases) was not providing sufficiently accurate estimates.

Research conducted between 2016 and 2020 led by Dr Theo Economou, lecturer in statistics at Exeter University in collaboration with Dr Leo Bastos, of the Oswaldo Cruz Foundation (Fiocruz), Brazil – resulted in the development of a novel statistical framework for real-time correction of delay in disease data **[3.3]**. The novelty of the framework is that it flexibly captures the spatio-temporal variability in the disease data, through a hierarchical structure, as well as the structure of the delay mechanism as an unknown function that varies with space and time. Despite its complexity and flexibility, the model is computationally fast (a necessary condition for an operational warning system), and its implementation in the Bayesian framework means full quantification of uncertainty in the form of posterior predictive distributions as the predictive quantity. Computational feasibility is ensured by assuming that spatio-temporal dependence is described by Markov random fields with sparse precision matrices. The proposed framework has pushed the boundaries of statistical correction of delays in disease data, and has already been adopted by practitioners globally (e.g. to correct dengue data in Thailand).

Application to historical disease data indicated substantial improvement in predictive performance compared to the original basic delay-correction method in InfoDengue. The improved InfoDengue went live in December 2017 and is currently being used to produce warnings for dengue, chikungunya and zika in 6 major Brazilian states: Rio de Janeiro, Paraná, São Paulo, Espírito Santo, Ceará and Minas Gerais.

The success of the improved InfoDengue led to a request by the Brazilian Ministry of Health for a similar warning system, but on a national scale, for severe acute respiratory infection (SARI). The ability of the statistical framework developed at Exeter, to capture spatial structure and dependence **[5.3]**, made this endeavour quite straightforward. This was demonstrated by application to weekly SARI count data in July 2016 - April 2017 across Brazil. It was shown (in **[3.3]**) that the statistical model was able to predict the exceedance of SARI counts above the epidemic threshold (of 65 cases per week), 2 weeks before the available data indicated this. The results were sufficiently compelling that Fiocruz with the backing of the Ministry of Health adopted the model to create a nationwide SARI warning system, InfoGripe, launched in 2018.

3. References to the research (indicative maximum of six references)

3.1. Stoner OR, **Economou T**, Drummond G (2019). A Hierarchical Framework for Correcting Under- Reporting in Count Data, Journal of the American Statistical Association, DOI:10.1080/01621459.2019.1573732.

3.2. Economou T, Stephenson DB, Rougier JC, Neal RA, Mylne KR. (2016) On the use of Bayesian decision theory for issuing natural hazard warnings, Proceedings of the Royal Society of London, Series A. DOI:10.1098/rspa.2016.0295.

3.3. Bastos L, **Economou T**, Gomes M, Villela D, Coelho F, Cruz O, Stoner O, Bailey T, Codeço C (2019). A modelling approach for correcting reporting delays in disease surveillance data. Statistics in Medicine. https://doi.org/10.1002/sim.8303

4. Details of the impact (indicative maximum 750 words).

Infectious diseases are a major problem in Brazil: in 2019 more than 1.5 million probable cases of Dengue virus were reported in Brazil with 782 confirmed deaths from the disease **[5.1]**. The Fiocruz institute for public health in Brazil is responsible for developing effective warning systems to help mitigate the effects of disease. Researchers at the University of Exeter have helped Fiocruz to improve the data models used for estimating the number of disease cases and correcting for reporting delays. This has enabled more accurate forecasting of the spread of diseases and the likelihood of epidemics: the benefits arising from this work are detailed below.

InfoDengue

The improved Dengue regional warning system went live in December 2017 and is currently operating in 788 cities in Brazil. It has been successful because of its reliability in predicting accurate numbers of cases, allowing local authorities, hospitals, clinics and the general public to monitor the spread of the disease with greater confidence. Fiocruz described Dr Economou's research as being "instrumental in the success of InfoDengue" **[5.2]**.

InfoDengue is currently being used to create a colour coded warning system covering 6 large municipal states in Brazil with combined population of 108 million. The Health Surveillance Secretariat, responsible for the real-time monitoring of all diseases across Brazil, describe InfoDengue as being "extremely important" and that it is "currently used as part of activities to monitor the behaviour of arboviruses[1] in the City of Rio de Janeiro" and "keep on top of possible increases in the demands imposed on our Health Centres'. **[5.3]**.

Local Policy Change:

InfoDengue is already influencing policy and practice. For example, Parana state health authorities are rewriting their guidelines for how samples of dengue are collected at municipality level. In a change from previous policy, samples from mild cases and at ambulatory care will no longer be sent for laboratory testing if the municipality is already at a state of sustained transmission, as defined by corrected data from the statistical model in InfoDengue. This means that it will only be necessary to send samples of severe cases, thus saving resources.

InfoGripe

The accuracy of the corrected data from the statistical model in InfoDengue captured the interest of the Health Ministry and led to the decision to deploy a comprehensive influenza warning system similar to InfoDengue but on a national scale. Dr Economou of Exeter and Dr Bastos of Fiocruz extended the modelling framework to work on the national scale. This led to the launch of the SARI and influenza warning system, InfoGripe, in 2018. According to the Ministry of Health, "the InfoGripe project has demonstrated excellent results" and "has currently met all expectations" **[5.4]**. InfoGripe is applicable to the entire population of Brazil, currently over 210 million people.

National Policy Change

The Ministry of Health has commented how InfoGripe has "enabled effective influenza prevention and control activities to be set in place as necessary for each situation" **[5.4]**. It has influenced National Policy by enabling the Ministry to release a contingency plan for public

[1] Dengue is an arbovirus as it is transmitted by an arthropod vector

health emergencies **[5.5]**. This written policy from the Brazilian government mandates the use of InfoGripe's forecasting tool (the statistical model) to determine what actions should be taken.

Helping Local Authorities

InfoGripe has enabled local authorities to monitor likely demand on hospitals and services and manage resources accordingly. "The system enables, on a timely manner, the monitoring of cases especially by being the only influenza surveillance tool that estimates its time series behaviour, signalling the tendency and contributing for organizing surveillance and assistance actions." – Ms Leticia Garay Martins, responsible for influenza surveillance (Ministry of Health) in Rio Grande do Sul State **[5.6]**.

Immunization planning policy change

The Department of Immunization and Transmissible Diseases is responsible for implementing vaccination programmes to mitigate cost from disease outbreak. They are currently adopting InfoGripe to create a protocol for pre-emptive emergency SARI vaccination. The statistical model predictions will be used to define cost-effective triggers specific to each outbreak. The current strategy relies on having a standard number of 2 million flu A shots available for outbreaks, but this sub-optimal figure may result in over- or worse under-estimation of the vaccination quantity needed. InfoGripe will change the response to SARI outbreaks and allow planning of the vaccination programme in the most efficient way. Specifically, it will enable planning when best to vaccinate people and what areas to target. Although this national policy has been approved, its implementation has been delayed by the Covid-19 pandemic.

Saving lives and healthcare resources

The following quantities have been estimated by Fiocruz and the University of Exeter **[5.7]**. They refer to a typical year of SARI epidemic and have been estimated using recent historical data. The statistical model in InfoGripe can identify (on average), 340 missed SARI cases on any given week during the outbreak period across the whole of Brazil. This means that for the period 2019-2020, the public health system saved resources in the range of 300K – 2million US dollars. Moreover, estimates for that year indicate that a reduction in SARI death count may be between 12 [6 - 29] and 68 [34 -171], where the numbers are median estimates and bracketed figures indicate a 95% prediction interval. It is important to note that these are conservative estimates in the sense that they should be considered a lower bound to the actual numbers. This is because the calculations use official data which are known to be under-reported, particularly in less affluent areas.

Covid-19

As of March 2020, InfoGripe is also being used to correct Covid-19 data and estimate the true burden of the pandemic in Brazil. The Ministry of Health cites InfoGripe as one of the official data sources it uses for dealing with Covid-19 **[5.8]**. The similarity of symptoms between SARI and Covid-19, and the fact that the cases must be confirmed by different labs, has the effect that Covid-19 reporting delays are not recorded. This is because the Covid-19 lab confirmation is not accompanied by the date of first symptoms, and thus the delay cannot be calculated. As such Dr Economou and Dr Bastos have developed a new statistical model (September 2020) to predict the proportion of all cases with SARI/Covid-19 like symptoms, that are actually Covid-19, from data during the early days of the pandemic (March 2020). The new model is applied on predictions from the model in InfoGripe (which corrects SARI data), to estimate the true current burden of Covid-19. This new statistical model is being used operationally to estimate Covid-19 incidence, with the corresponding data being provided to the Ministry of Health.

The ability to estimate the true (but unobserved) Covid-19 burden is already producing national impact. The Instituto Butantan in São Paulo -- the largest immunobiologicals and biopharmaceuticals producer in Latin America and one of the largest in the world -- is currently in phase III of trialling Sinovac, a Sars-Cov-2 (Covid-19) vaccine developed in China. In order to optimally target highly impacted municipalities to include in the trial, Instituto Butantan use our predictions to quantify the true burden of the disease at municipality level **[5.9]**. It is the existence of these predictions that make this targeting possible, as opposed to random selection or use of the very limited reported data that is available.

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

5.1. https://www.statista.com/statistics/797556/number-cases-dengue-fever-brazil-region/

5.2. Letter from Fundação Oswaldo Cruz (**Fiocruz**) stating Dr Economou's instrumental contributions to the InfoDengue and InfoGripe model

5.3. State Ministry of Health Surveillance Team, Rio de Janiero letter of support

5.4. Letter from Health Surveillance Advisor, Brazilian Ministry of Health letter of support

5.5. Copy of the Ministry of Health contingency plan for Public health emergencies

5Letter from official of the Influenza Surveillance team, State Ministry of Health, Rio Grande do Sul State

5.7. Fiocruz report on impact of the model

5.8. Brazilian Ministry of Health Special Covid-19 Report

5.9. Letter from the Clinical Research Medical Director of the Instituto Butantan, State Ministry of Health, Sao Paulo