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Time-series modelling of dengue incidence in the Mekong Delta region of Viet Nam using remote sensing data

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Objective: This study aims to enhance the capacity of dengue prediction by investigating the relationship of dengue incidence with climate and environmental factors in the Mekong Delta region (MDR) of Viet Nam by using remote sensing data.

Methods: To produce monthly data sets for each province, we extracted and aggregated precipitation data from the Global Satellite Mapping of Precipitation project and land surface temperatures and normalized difference vegetation indexes from the Moderate Resolution Imaging Spectroradiometer satellite observations. Monthly data sets from 2000 to 2016 were used to construct autoregressive integrated moving average (ARIMA) models to predict dengue incidence for 12 provinces across the study region.

Results: The final models were able to predict dengue incidence from January to December 2016 that concurred with the observation that dengue epidemics occur mostly in rainy seasons. As a result, the obtained model presents a good fit at a regional level with the correlation value of 0.65 between predicted and reported dengue cases; nevertheless, its performance declines at the subregional scale.

Conclusion: We demonstrated the use of remote sensing data in time-series to develop a model of dengue incidence in the MDR of Viet Nam. Results indicated that this approach could be an effective method to predict regional dengue incidence and its trends.

According to the World Health Organization (WHO),[1] Viet Nam is among the top 10 countries with the highest reported number of dengue cases in the world (91 321 cases in 2012). Studies have shown that dengue epidemics in Viet Nam occurred cyclically every 3–5 years and peaked approximately every 10 years.[2] These cycles are thought to be influenced by the circulating viral serotypes, host immunity and climate oscillations.[3] Dengue transmission occurs throughout the year in Viet Nam with peak numbers of cases reported in the rainy season from May to October.[4] Since 2007, dengue has been recorded in 55 of the 63 provinces in Viet Nam, increasing from north to south with the Mekong Delta region (MDR) experiencing the highest incidence recorded during the years 2000 to 2016.

Several recent studies have aimed to better understand the dynamics of dengue and the influences of environmental factors on the disease and to better predict outbreaks. Climate factors, in addition to multiple human, biological and ecological determinants, influence the emergence and re-emergence of infectious diseases, including dengue,[5] which is transmitted by both the primary vector *Aedes aegypti* and the secondary vector *Aedes albopictus.*[6,7] Studies have found a significant correlation between rain and dengue incidence in Metropolitan Manila, Philippines from 1996 to 2005,[8] and a correlation between temperature, rain and dengue incidence in southern Thailand by multiple regression analysis.[9] On a regional scale, a review of the impacts of climate change on human health provided more evidence of the burden of climate change–attributable diseases and emphasized the uncertainty in attributing diseases to climate change, owing to a lack of long-term, high-quality data.[10] Climate change is likely to affect the seasonal and geographical distribution of dengue fever in

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the Asia–Pacific region, but more studies are needed that adjust for regional and subregional socio-environmental factors in the assessment of climate effects on dengue transmission.[5] Climate is only one of many environmental factors; changes in land cover by human settlements, the presence of water bodies, and vegetation type also affect dengue transmission processes.[11]

A range of approaches, including statistical modelling, mathematical modelling and spatial analysis, have been applied to demonstrate relationships between dengue and climate variables and to predict dengue cases and outbreaks.[12, 13] Statistical models that are commonly constructed to predict dengue incidence cannot precisely predict the time and place of a dengue outbreak. However, they are able to quantitatively associate climactic factors such as rain, temperature and humidity with dengue epidemics at certain geographic areas with specific time lags.[14]

We assumed that there was a strong association between dengue incidences and climate variables; therefore, we applied a time-series autoregressive integrated moving average (ARIMA) model for dengue prediction in the MDR of Viet Nam. To minimize the limitations of climate data from meteorological stations in spatial and time scales, we used the most accessible remote sensing data for climate variables: the Global Satellite Mapping of Precipitation (GSMaP) for rain data and the Moderate Resolution Imaging Spectroradiometer (MODIS) land surface temperature $_{n/d}$ (MOD11A2, US Geological Survey, Reston, VA, USA) for night (LST_n) and day (LST_d). Our aim was to investigate the capability of ARIMA to provide sufficient lead-time prediction of dengue[15] for a region of high incidence in a tropical climate. This was an effort to combine advanced geospatial data in a predictive model to assist public health control and response operations in the region.

METHODS

Study site

The study was conducted in the lower MDR in southwestern Viet Nam, using the average monthly number of dengue cases (**Fig. 1**). The MDR reported up to 65% of the total cases of dengue in Viet Nam during the period 2000 to 2016. This is a flat and low-lying area of 40 576 km^2 covering 13 provinces within a complex network of rivers, channels and floodplains. We divided this region into two subregions: subregion I has the higher dengue incidence provinces (An Giang, Dong Thap, Long An, Tien Giang and Ben Tre) and subregion II has the lower incidence provinces (Vinh Long, Tra Vinh Can Tho, Hau giang, Soc Trang, Bac Lieu, Kien Giang and Ca Mau), separated by a white line in **Fig. 1**. Dengue fever has been recorded as the second most frequent reason for hospitalization among communicable diseases in this region.[16]

Remote sensing data

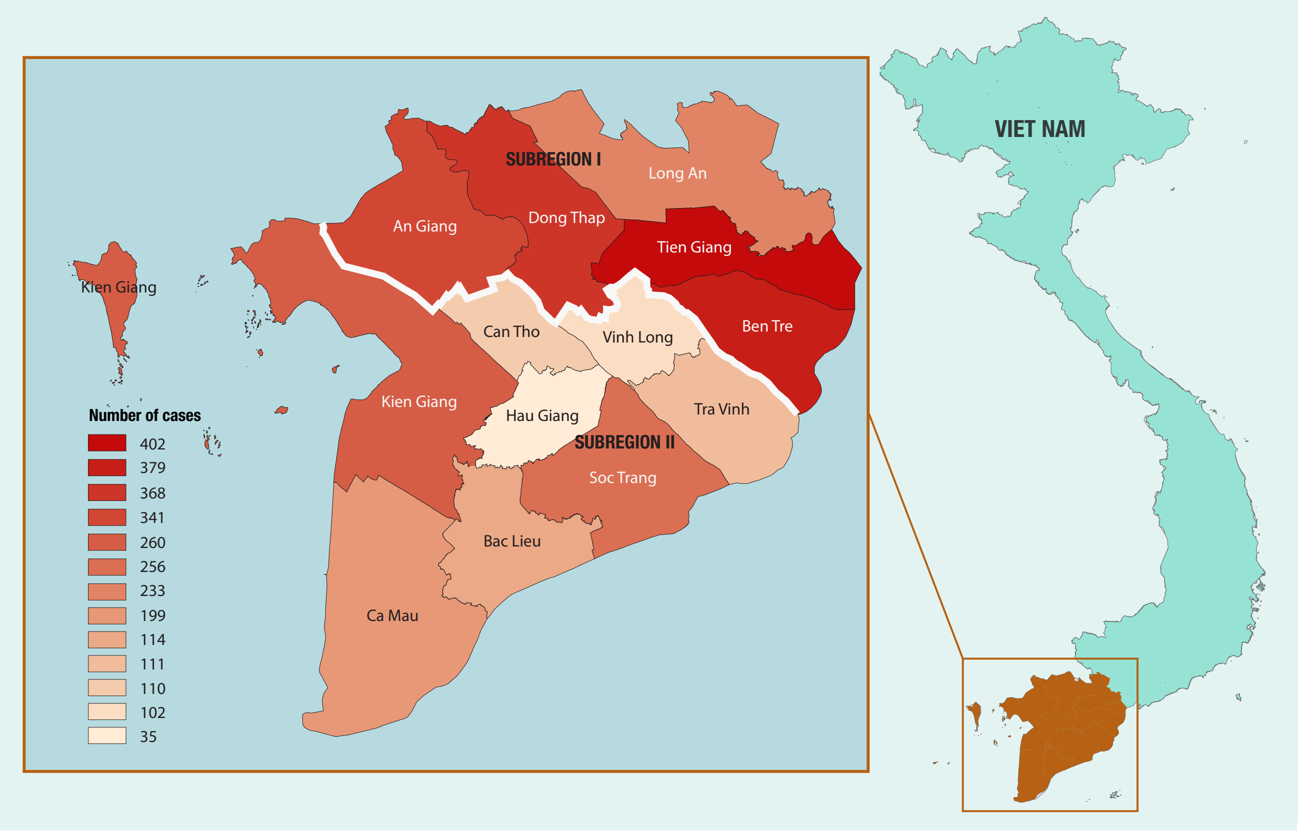
We used GSMaP data as an alternative for surface rainfall measurement in an attempt to expand the use of remote sensing data with the advantages of spatial coverage with high resolution and temporal availability. The daily GSMaP-version 6 data[17] with a spatial resolution of 0.1 × 0.1 degrees were extracted and accumulated to calculate monthly rain. We used monthly land surface temperature data from MODIS LST_d and LST_n (MOD11A2)[18] with a 1 km spatial resolution as a proxy for air temperature. In addition to climate variables, one of the most commonly used remote sensing–derived environmental variables, the normalized difference vegetation index (NDVI) from MODIS (MOD13Q1) with a 250 m spatial resolution, was also used in the model for its influence on dengue.[19] These remote sensing–based parameters were aggregated to compute mean monthly variables for each province as examples presented in **Fig. 2**, showing clear spatial variations among provinces and between variables.

Statistical analysis

We used the Box-Jenkins methodology[20] to fit ARIMA models to monthly dengue incidence in 12 provinces, using the statistical forecast package in RStudio software (version 1.1) (RStudio, Boston, MA, USA).[21] Dengue case definitions were based on WHO criteria[22] and collected through the disease surveillance systems according to Viet Nam's Ministry of Health regulations.[23] The dengue cases reported from 2001 to 2015 were used for developing the time series model, and the cases during 2016 were used for validating the model. To avoid effects from the non-constant variance, we stabilized dengue counts by natural log transformation.

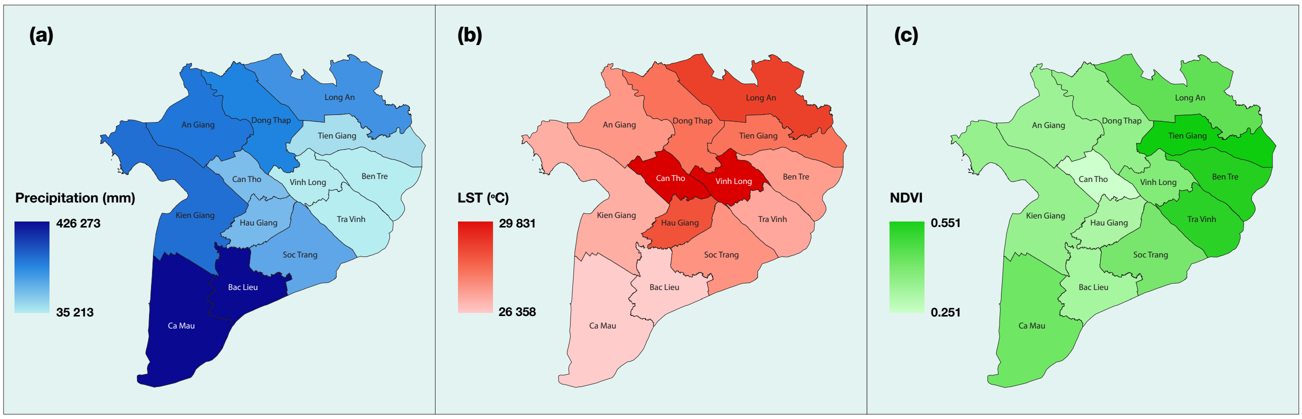
First, to confirm that ARIMA models were suitable for this analysis, we examined the data for seasonality and

Fig. 1. **Average monthly numbers of dengue cases for 13 provinces in the Mekong Delta region, divided into subregions I and II by a white line, 2000–2016**



interannual variations of dengue incidence and climate and environmental variables (rain, LST_d, LST_n and NDVI) during the period 2000–2016 for each province. Then, the adequacy of each model for each province was verified by histogram, by autocorrelation of the standardized residuals, and by the Ljung-Box test, similar to previous studies.[24–26] Next, the structure of the model followed the standard form for ARIMA, $(p,d,q)(P,D,Q)_s$, where p is the order of autoregression; d, the degree of differencing; q, the order of the moving average; P, the seasonal autoregression; D, the degree of seasonal differences; Q, the seasonal moving average; and s, the seasonal period.

Fig. 2. **Examples of monthly estimates for (a) GSMaP rain, (b) MODIS LST_d and (c) MODIS NDVI in the Mekong Delta region, November 2010**



GSMaP = Global Satellite Mapping of Precipitation; MODIS LST_d = Moderate Resolution Imaging Spectroradiometer land surface temperature, day; MODIS NDVI = Moderate Resolution Imaging Spectroradiometer normalized difference vegetation index

Different ARIMA model forms (combinations of *p, d, q, P, D* and *Q*) were tested to fit the log-transformed time series data without environmental covariates. The best ARIMA model was selected as that with the lowest Akaike information criterion,[24] a measure of the relative goodness of fit of a model across the 12 provinces (Hau Giang province was excluded as it had politically separated from Can Tho province in 2004). Then, multivariate ARIMA models were fitted with log-transformed dengue cases in relation to all the climate variables with time lags that were chosen by their best correlation with dengue.

RESULTS

Seasonal variation of dengue and climate parameters

Fig. 3 presents an example of the time series of dengue, rain, LST_n and NDVI during 2000- 2016 for An Giang province. The plots showed strong seasonal and interannual variations of all variables. We found this seasonal pattern apparent and consistent for all provinces in the region with higher dengue cases coinciding with rainy seasons. This enabled us to apply the ARIMA model to the entire MDR.

Model in association with variables

Fig. 4a presents an example of an ARIMA fitting model plot for An Giang province and the comparison of fitted with reported dengue cases; **Fig. 4b** shows the regression function with its root mean square error value for the fitted period of 2000–2015. The final model for each province was confirmed by the Ljung-box test[27] of the residual with no correlation for fitted data.

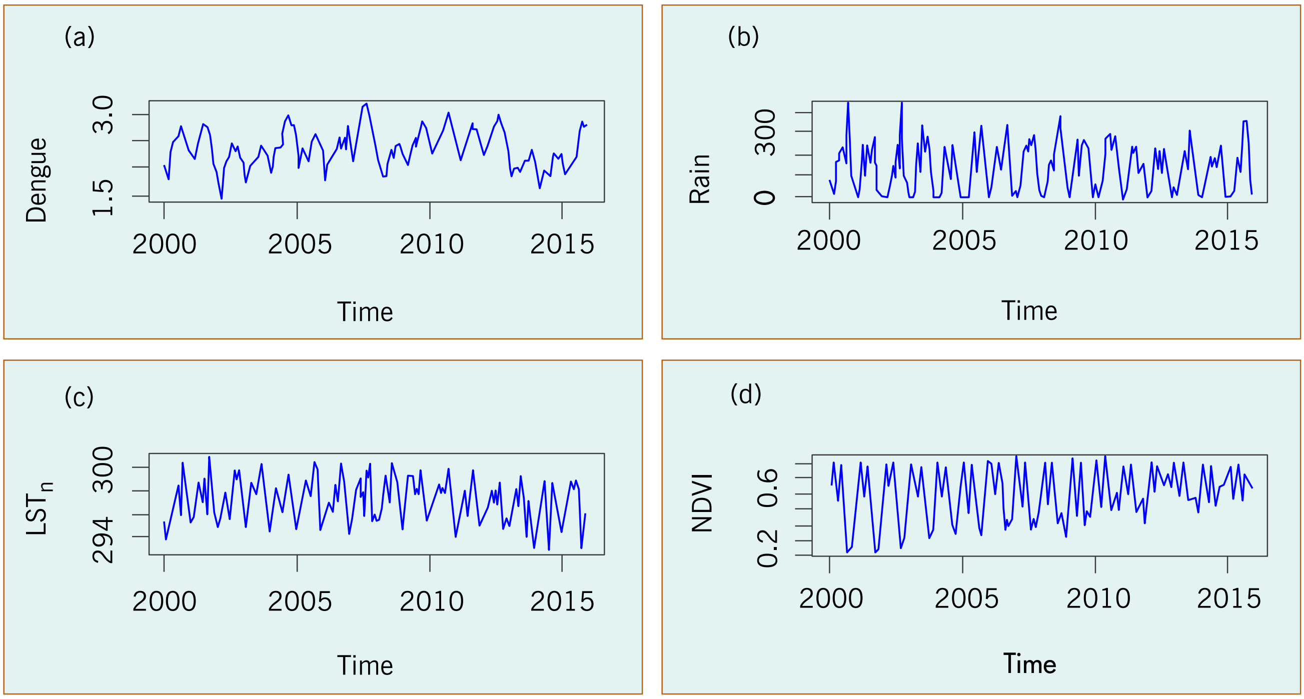
We generated 12 final models that closely fitted dengue incidence from every province in incorporating climate and environment variables as external predictors. After careful screening, those variables with the highest correlation with dengue incidence at specific time lags were kept in the final ARIMA models (**Table 1**) that show the correlation value, and the monthly time lag is shown in brackets. Correlations between these variables and dengue are spread over a range of time lags across provinces. Dengue had the strongest correlation with rain at a 1-month time lag across all provinces, reaching 0.60 at Long An province; dengue had a comparable correlation with LST_d and LST_n at 1-month to 4-month time lags. In addition, dengue had both positive and negative correlation with NDVI at 4-month to 5-month time lags. Notably, we found that the two subregions had different climate and environmental influences on dengue based on their correlations and time lags. In subregion I, dengue was found to have a higher correlation with rain with a 1-month time lag, and NDVI had a 5-month time lag; dengue was also associated with LST_d generally with a 4-month time lag and LST_n with a 1-month time lag. These findings are different than those for provinces in subregion II along the coast of the MDR where dengue was found to have a weaker correlation with rain and a negative correlation with NDVI with a 4-month time lag. For provinces in subregion II, dengue was correlated with a 1-month shorter time lag for LST_d but a 1-month longer time lag for LST_n compared to subregion I. For other provinces, including Vinh Long, Can Tho, and Kien Giang, dengue was found to have relatively low correlations with all variables and at mixed time lags. The variability in the association between dengue and climate and environmental factors across provinces in the study region emphasizes the need for a separate time-series model for each province.

Model validation

The best time-series ARIMA model with final independent variables found for each province was applied to predict dengue for the period from January to December 2016. In most cases, rain and LST_n remained in the final model; LST_d and NDVI were occasionally removed when correlations were less than 0.25. We compared predicted dengue with reported cases for the whole MDR, as shown in **Fig. 5**. The results showed that predicted dengue in every province closely followed the trend of reported data (**Fig. 5a**) and that these data are in good linear regression with the square of correlation of 0.65 for the whole region (**Fig. 5b**).

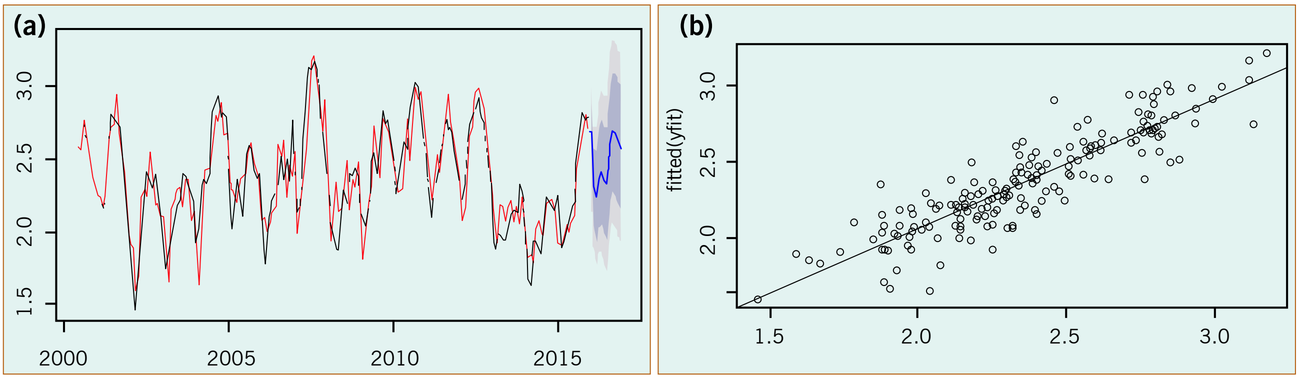
We also evaluated the association between monthly predicted and reported dengue incidence from January to December 2016 by calculating the Pearson correlation coefficient[28] for each province (the numbers presented correspond to the provinces in **Fig. 5a**). The correlation varies significantly, from approximately 0.22 to 0.85 (with $P < 0.05$) for different provinces; nine provinces had a correlation greater than 0.50, and only three provinces had a correlation below 0.50. We found that the predicted dengue during the period January to December

Fig. 3. **Time series of (a) dengue, (b) rain, (c) LST_n, and (d) NDVI for An Giang province, 2000–2015**



LST_n = land surface temperature, night
NDVI = normalized difference vegetation index

Fig. 4. **Example of ARIMA model for An Giang province: (a) model fitting and (b) scatter plot of fitted and reported dengue cases**



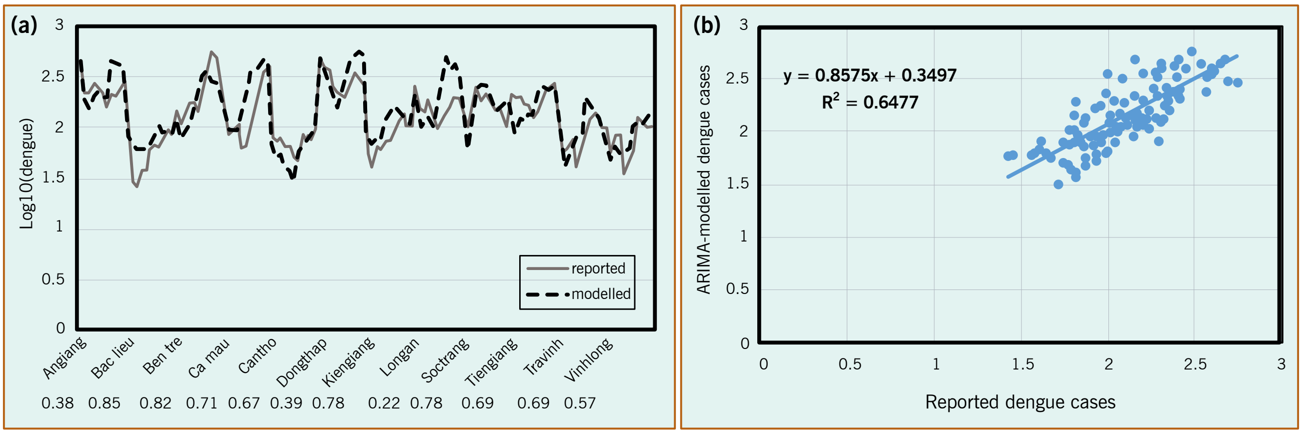
[a] Reported data in black, fitted model in red and predicted model in blue.
[b] In log scale.

Table 1. **Final ARIMA models with correlation of dengue with climate and environmental variables for each province in time lags**

	An Giang	Dong Thap	Long An	Tien Giang	Vinh Long	Bac Lieu	Ben Tre	Ca Mau	Can Tho	Tra Vinh	Kien Giang	Soc Trang
r with rain	0.515 (2)	0.509 (1)	0.604 (1)	0.471 (1)	0.342 (1)	0.291 (1)	0.536 (1)	0.437 (1)	0.482 (2)	0.370 (1)	0.403 (1)	0.314 (1)
r with LTSd	0.313 (4)	0.436 (4)	0.364 (4)	0.520 (4)	0.281 (4)	0.267 (3)	0.642 (3)	0.207 (3)	0.253 (4)	0.413 (3)	0.446 (2)	0.338 (2)
r with LSTn	0.444 (1)	0.522 (1)	0.394 (1)	0.339 (2)	0.296 (2)	0.354 (2)	0.501 (2)	0.304 (2)	0.388 (2)	0.449 (2)	0.410 (1)	0.461 (2)
r with NDVI	0.363 (5)	0.381 (5)	0.420 (5)	0.271 (5)	0.155 (5)	−0.402 (4)	−0.376 (4)	−0.392 (4)	0.190 (5)	−0.333 (4)	0.195 (4)	−0.297 (4)

r = correlation coefficient of dengue with difference variables
bracketed numbers = time lag

Fig. 5. **Forecast versus reported dengue cases in log scale for whole Mekong River Delta region: (a) series plot for January–December 2016 and (b) scatter plot with regression**



2016 was more similar to reported data for provinces in subregion II where dengue was found to have a negative correlation with NDVI and a positive correlation with LST_n at a 2-month time lag, as previously mentioned. For the provinces in subregion I, predicted dengue was found to have a weaker correlation with the reported data during the period January to December 2016, even though the stronger association of dengue with rain and NDVI was shown by the time-series data from the years 2000 to 2015.

DISCUSSION

In an effort to overcome the limitations of spatial and time scales in climate data collected from meteorological stations, we created a high-quality data set of satellite remote sensing data for climate and environmental factors, i.e. rain data from GSMaP and temperature and vegetation data from MODIS for the entire MDR for dengue modelling using a time-series approach. Different combinations of components were evaluated to construct the best predictive ARIMA models for 12 provinces across the study region. We decided to use the ARIMA model because it can cope with a stochastic dependence of consecutive data and to account for autocorrelations in time series as well as seasonality, long-term trends and time lags.[14] The selection of external variables was based on the best correlation of dengue with rain, LST_d, LST_n, and NDVI at different time lags for the 2000 to 2015 data. The results of the validation showed different performances of the ARIMA model over the region. The correlation of predicted and reported dengue during the period January to December 2016 was found higher in subregion II and lower in subregion I, controverting the distribution of dengue among these two subregions (as in **Fig. 1**). This is a limitation of ARIMA modelled with only climate factors relating to vector abundance; transmission of dengue is also affected by other factors such as population density and activities, relating human susceptibility to the disease. Therefore, an assessment of prevailing vulnerabilities to dengue could be independent of its spatial distribution,[29] but closely related to a combination of climate, environment and sociodemographic conditions.[30]

Possible reasons of inconsistent effects of NDVI on dengue incidence include subprovincial variations in precipitation and a variety of land covers. Climatologically, the onset of the rainy season in the MDR usually appears first along the coast (subregion II) and moves gradually inland (toward subregion I), resulting in a different temporal time lag in relationships between rain and dengue transmission over the region. Also, vegetation type and growth stage may play important roles in determining vector abundance, irrespective of their association with rain.[31] An analysis of NDVI distribution in relation to land cover data over the whole region indicated that lower values of NDVI in subregion II corresponded to more water bodies, shrubs and mixed horticulture land cover types. Higher NDVIs were found in subregion I, which corresponded to more rice paddy land cover.

Several investigators have examined the associations among climate variables, demography and dengue incidence in the southern provinces of Viet Nam using a wavelet time series analysis,[3,32] a standard multiple regression model, ARIMA and a Poisson distributed lag model.[33] We found that time-series analysis was useful in establishing the relationship between the change of weather parameters, environmental factors and the incidence of dengue diseases for the entire MDR. Input variables were selected based on the best correlation of dengue with precipitation, LST_d, LST_n, and NDVI data, for the period 2000 to 2015 at varying time lags as in previous studies.[19,33]

Limitations

One challenge to the existing statistical approaches in modelling dengue is the difficulty of quantifying the influences of myriad human activities on vector-borne transmission. An integrated approach might be to build an index framework for underlying socioeconomic and demographic factors.[29] Disease transmission is also closely linked with mosquito behaviour and population dynamics that are largely influenced by climate factors.[5] Therefore, direct modelling by using climate data could be useful in informing health and sanitation sectors of potential increases in mosquito activity and subsequent disease risk, especially if mosquito population data can be sampled and integrated.

Conclusions

This study focused on presenting climate and environmental factors from remote sensing data in modelling and predicting dengue fever in the MDR of Viet Nam. Our results indicate that this approach may be effective for predicting regional dengue incidence and trends. The results also revealed that the higher correlation of dengue using a single variable does not improve the model performance, and validation of the model is crucial for assessing its accuracy. Our findings support previously made conclusions that dengue prediction models vary due to their complexity and methodology and are dependent on the type of data collected and the nature of the variables.[14] No universal models exist for global analysis and prediction,[14] even if limited to a climatologically homogeneous area such as the MDR.

We describe the first effort to apply remote sensing data to perform time-series modelling of a vector-borne disease in Viet Nam to enhance the dengue early warning system. Similar approaches have been used throughout the world.[34–36] Integration of remote sensing and modelling to provide early warning of vector-borne disease outbreaks has been successfully demonstrated for malaria throughout Africa[35] and for dengue epidemics in Brazil.[14] To determine our model's usefulness as an early warning tool, the results of our study have been presented on the Internet not only for the MDR, but also for other regions of Viet Nam and the Philippines. However, the system should be evaluated by end users for its effectiveness for dengue predictions for two countries.

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Conflicts of interest

No potential conflicts of interest were reported by the authors.

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Quality microbiological diagnostics and antimicrobial susceptibility testing, an essential component of antimicrobial resistance surveillance and control efforts in Pacific island nations

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Problem: Emerging bacterial antimicrobial (antibiotic) resistance (AMR) is a global threat to human health. However, a majority of lower income countries do not have microbiological diagnostic testing for prompt, reliable confirmation of bloodstream infection and identification of AMR.

Context: Clinicians in Pacific island nations are increasingly challenged by patients who have infection due to antimicrobial-resistant bacteria. Treatment of infection remains empirical because of a lack of diagnostic testing capacity and may follow guidelines that were formulated without reference to local measures of AMR prevalence. There is limited understanding among clinicians of microbiology testing and test interpretation.

Action: Examine the lessons learnt from pilot laboratory development programmes in two Pacific island nations that focused on establishing standard procedures for micrological diagnostics and antimicrobial susceptibility testing (AST) and on improving the training of clinicians to increase their use of laboratory services.

Outcome: The pilot programmes addressed a range of logistical difficulties and evaluated two blood culture systems. They also examined and improved internal QC implementation and evaluated the prevalence of AMR.

Discussion: Continued development of microbiological diagnostic capability in the Pacific region is paramount. Pacific Island nations need to develop the capability of at least one central laboratory to culture AMR pathogens and subject them to quality-controlled AST or arrange for suitable referral to a nearby country.

PROBLEM

Antimicrobial resistance (AMR) is a major threat to human health.[1,2] Patients with sepsis who are treated with an antimicrobial for which the causative pathogen is non-susceptible have an increased risk of mortality.[2] The World Health Organization (WHO) Global Antimicrobial Surveillance System prioritizes the following bacterial pathogens, commonly associated with resistance, for surveillance: *Mycobacterium tuberculosis, Escherichia coli, Klebsiella pneumoniae, Shigella, Salmonella, Neisseria gonorrhoeae, Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus* and *Streptococcus pneumoniae*.[3] Resistance to these pathogens is associated with poor response to treatment, prolonged hospitalization and excess mortality.[4]

Knowledge of bacterial antimicrobial susceptibility testing (AST) patterns is the cornerstone of an effective

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clinical and public health response to AMR. Reliable AST results are decision-making support tools that enable clinicians to prescribe appropriate antibiotics for patients. As a public health tool, AST data that describe the prevalence, geographic distribution and temporal trends of resistant pathogens should inform standard treatment guidelines that are developed in the Pacific region.

A lack of laboratory infrastructure and microbiological expertise in many Pacific island nations has made AMR surveillance unreliable. Most published data are based on studies from major hospitals without details of quality control (QC),[5,6] or the testing standard used.[7] In addition, external to the laboratory, pre-analytical factors such as proper specimen selection and collection are often deficient. Reliably sensitive blood culture systems are generally unavailable, preventing effective diagnosis of severe bacterial infection and greatly impeding AMR surveillance.[8]

This manuscript aims to examine the importance of quality bacterial culture and antimicrobial susceptibility for clinician guidance and for effective AMR surveillance. It highlights important AST concepts that are perhaps poorly understood by laboratory and clinical staff in many Pacific island nations. It examines lessons learnt from pilot laboratory development programmes based in Solomon Islands and Papua New Guinea (PNG) and discusses recent AMR surveillance data from Port Moresby General Hospital in PNG.

CONTEXT

Citizens of Pacific island nations are particularly vulnerable to the consequences of AMR. The burden of infection, in both the community and the hospital, is high, and appropriate treatment of antimicrobial-resistant infections often require prolonged treatment with expensive antibiotics that may not be available. Infection with resistant organisms results in longer hospital stays that increase the risk of further complications such as nosocomial infection (e.g. health care–associated pneumonia). Many hospitals in this region have limited infection prevention and control systems, and multiresistant organisms are frequently spread by health-care staff with unclean hands and fomites (e.g. contaminated, reused equipment, stethoscopes, clothing) and through contact with contaminated environments.

In many Pacific island nations, antibiotic use during health-care attendances is high, and common antibiotics may be purchased without prescription at markets. Unregulated antibiotic use in the agricultural sector occurs. Contamination of stream and tank water with enteric bacteria, including *Salmonella* Typhi, is documented within the region.[9] Increasing international travel provides another risk factor for AMR acquisition and spread. Taken together, these factors promote the emergence, acquisition and transmission of antimicrobial-resistant pathogens.

WHO has facilitated the development of national AMR plans that emphasize the importance of regional laboratories (serving human and animal health sectors) that are able to reliably perform bacterial culture and AST supported by an AMR reference laboratory that orchestrates QC measures and operates an external quality assurance (EQA) programme.[3]

How does quality microbiological culture and AST enable better patient care?

Where health literacy is low and infection rates are high, patients often present with severe infection due to delayed presentation and neglected co-morbidities. Effective diagnostic testing is an essential addition to the clinical assessment. Culture and AST of the infecting pathogen allow the clinician to modify treatment to adequately target a pathogen and ensure effective, definitive antimicrobial therapy. This improves patient outcomes and reduces mortality.[10] Therapeutic changes may involve moving to a narrow spectrum antimicrobial (e.g. benzylpenicillin or flucloxacillin) for susceptible isolates or using a broader spectrum agent when culture and AST demonstrate a resistant organism (e.g. extended-spectrum β-lactamase [ESBL; ceftriaxone resistant] producing *Klebsiella* or related species or methicillin [flucloxacillin-resistant *Staphylococcus aureus* [MRSA]).

What are the meanings of minimum inhibitory concentration and clinical breakpoint?

Due to the lack of medical microbiologists and limited scientific awareness of microbiology in most Pacific island nations, there is value in explaining these concepts. The minimum inhibitory concentration (MIC) indicates the particular antimicrobial concentration (mg/L) that is required to inhibit growth of the infecting organism in the laboratory. The MIC test is performed by exposing a bacterial isolate inoculated into broth to decreasing dilutions of the antimicrobial. After incubation, the broth well with the lowest antimicrobial concentration without bacterial growth (i.e. clear) becomes the MIC value. There are two standards organizations, the Clinical and Laboratory Standards Institute (CLSI)[11] and the European Committee of Antimicrobial Susceptibility Testing (EUCAST),[12] that specify use of the same international MIC testing reference standard (International Standards Organization 20776–1).[13] By considering a wide range of laboratory and clinical evidence for each bacterial species and antibiotic, each organization defines an MIC value that represents the clinical breakpoint that divides isolates into susceptible and non-susceptible (resistant) categories. If an isolate tests as non-susceptible to an antimicrobial, then treatment of a clinical infection with that drug is likely to fail. The clinical breakpoints determined by the two organizations may differ for the same antibiotic and organism combination because of differing processes of deliberation. It is important to specify the standard in use and reference the updates to clinical breakpoint tables that are published by EUCAST and CLSI every January. Clinical breakpoints are also set for other AST methods such as disc susceptibility testing derived by comparison with the ISO standard MIC test.

How is AST usually performed?

Disc susceptibility is the most commonly used method in the Pacific region (**Fig. 1**). A disc containing a quantity of antimicrobial is placed onto an agar plate that has been seeded with the organism in question. After 18 hours of incubation, the antibiotic will inhibit growth of the organism resulting in a zone of absent growth. If the measured zone of inhibition is larger than the prespecified clinical breakpoint zone size, this indicates that the organism can be reported as susceptible to that drug.

What challenges occur with AST?

There are many variables that affect the AST result, potentially causing error (e.g. a resistant isolate being reported as susceptible). The agar growth medium requires preparation with consistent quality of ingredients and thickness, and each batch requires QC for sterility and its ability to support growth of control organisms. Blood-containing media are required for some species (e.g. *Streptococcus pneumoniae* and *Haemophilus influenzae*), which remains problematic where required sheep or horse blood is unavailable. Expired human blood is therefore used widely in the Pacific region; however, this is not an appropriate substitute. The incubation temperature and duration must be correct. Antimicrobial discs must be in-date, of the right strength and stored correctly to avoid degradation. Discs from certain manufacturers have variable quality, highlighting the need to obtain them from reliable sources.[14] The technician reading the AST must ensure that the disc inhibition zone is measured and interpreted correctly.

ACTION

Laboratory capacity development in PNG (at Port Moresby General Hospital [PMGH]) and in Honiara, Solomon Islands by the Pacific Region Infectious Diseases Association has focused on improving the training of scientists and establishing standard procedures for the microbiology service. Commercial blood culture systems have been introduced to increase positive culture detection and reduce the turnaround time (reduced from 5 days to 2 days). Clinician education concerning the effective use of blood cultures, AMR and its detection has been conducted as a prelude to the introduction of hospital antimicrobial stewardship.

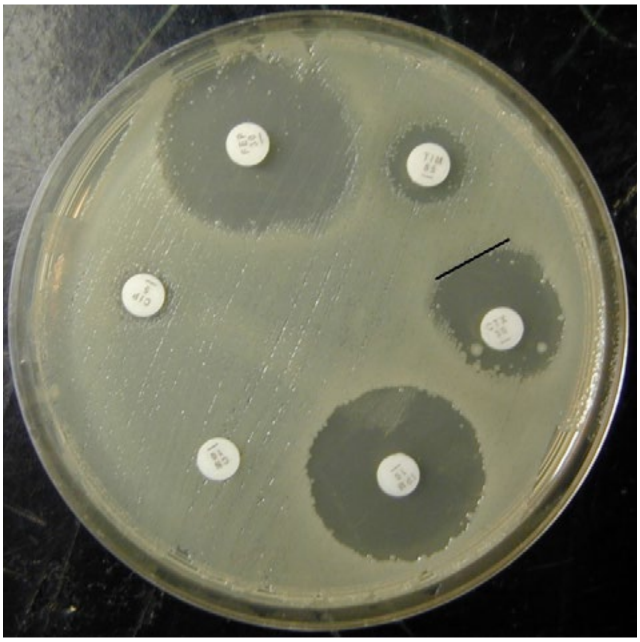
Internal QC systems have been introduced to provide assurance that AST results are correct. All antimicrobial discs are tested against QC bacterial strains weekly. If the tested zone size is within a specified range, then the process is controlled and the laboratory can issue a valid result. Both laboratories participate in EQA to regularly test unknown isolates from a reference organization.

OUTCOME

Logistics

- A range of issues have had to be addressed, including ordering and supply of consumables and availability of serviced incubators and fridges. The electricity supply has not been a limiting factor in these sites to date.

Fig. 1. **Antimicrobial susceptibility test using the disc method**



This blood isolate of extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* came from a septic patient who died from the infection. There is resistance to ceftriaxone (CTX), ciprofloxacin (CIP), ticarcillin-clavulanate (TIM) and gentamicin (CN). A "keyhole" (partial zone enlargement) is present between CTX and TIM, indicating the presence of an ESBL enzyme. The size of the zone around cefepime (FEP 4th generation cephalosporin) and imipenem (a carbapenem) is sufficient to indicate susceptibility.

- Regular visits and teleconference support to train and mentor technical and scientific staff and assist with supervision by the in-charge pathologist have been useful.

- Development of standard operating procedures, in collaboration with scientific staff, and more general quality management systems have also been important. The WHO approach to stepwise implementation of laboratory quality management systems has been useful.

- Sheep or horse blood for production of blood-containing agar media is generally unavailable. Most laboratories are substituting expired, donated human blood. However, such media usually fail to grow important organisms such as *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*.

Commercial blood culture systems

- Evaluation of the automated blood culture system BACTEC (Becton Dickinson Company, Franklin Lakes, NJ, USA) at PMGH from 2016 to 2017 revealed blood culture detection rates for significant pathogens of 8.4% in adults and 6.0% in children. These rates were significantly higher than those obtained with in-house media and pathogens were isolated more rapidly. The 2018 data from Solomon Islands using the BacT/ALERT® (bioMerieux Company, Norwest NSW, Australia) system found a detection rate of 5.8%.

- Contamination rates were too high (adults, 7%; children, 15%) at PMGH and 8.8% in Honiara, Solomon Islands, highlighting the need for further effort and training to improve specimen collection practices.

Internal QC implementation

- Challenges included identification and maintenance of a −80 °C freezer for QC bacterial strain storage and implementation of correct handling procedures for master and working cultures of QC strains.

- Maintaining scientific supervision of QC testing to ensure it is properly performed regularly and that results are formally reviewed and acted on.

- QC troubleshooting: An important example was that of gentamicin susceptibility at PMGH, where the zone size was persistently below the expected range. A new batch of gentamicin discs showed a correct zone size, indicating that the existing discs, although in-date, had lost potency and needed replacement.

Prevalence of AMR

The 2018 PMGH cumulative antibiogram showed rates of methicillin-resistant *Staphylococcus aureus* (MRSA) of 39% to 60% across all groups (adult and paediatric, community and hospital locations). MRSA susceptibility for doxycycline and co-trimoxazole remained high. Samoa and East Timor have also recorded high rates of MRSA.[7,15] The 2017 data from Honiara, Solomon Islands indicated low rates of MRSA (2% of 53 isolates).

At PMGH, 63% and 25% of Gram-negative (*E. coli, Klebsiella* and related species) isolates showed non-susceptibility to ceftriaxone in inpatients and outpatients, respectively, indicating high levels of ESBL. Ceftriaxone non-susceptible isolates were usually also non-susceptible to ciprofloxacin and gentamicin, and a minority were susceptible to chloramphenicol. ESBL isolates are also prevalent in New Caledonia, Fiji and East Timor.[7,15,16] The 2017 data from Honiara found non-susceptibility to ceftriaxone to be 15% (200 tested isolates).

DISCUSSION

Continued development of microbiological diagnostic capability and reliability is paramount for clinicians and AMR surveillance. Owing to the unavailability of appropriate media, culture and AST of *N. gonorrhoeae* and *S. pneumoniae* are rarely performed. Each Pacific island nation needs to develop the capability for at least one central laboratory to culture these pathogens and subject them to quality-controlled AST or arrange for suitable referral to a nearby country.

MRSA is common in Pacific island nations, resulting in bone, joint, lung or blood-stream infections.[6,15] While inclusion of vancomycin on essential medication lists has cost and logistical implications, it needs to be considered for management of proven MRSA bacteraemia and empirical management of severe sepsis. Standard treatment guidelines will require revision, and clinicians will require education concerning the use and monitoring of vancomycin.

Rates of ESBL across South-East Asia and the Pacific region nations have been high for more than 10 years and have been associated with sustained hospital, neonatal and intensive care outbreaks with high mortality.[4] Community carriage is common and is exacerbated by overuse of antibiotics and a lack of infection control resulting in hospital patient-to-patient transmission and subsequent nosocomial infection. Where local data indicate high rates of ceftriaxone resistance, this agent cannot be relied upon for empirical use in situations where Gram-negative pathogens predominate (e.g. urinary, intra-abdominal, biliary sepsis, nosocomial infection). Meropenem, a carbapenem class of β-lactam antibiotic, that is not widely available in Pacific island nations, is the recommended first-line option for treatment of ESBL bloodstream infections.[17] In line with recent WHO recommendations, meropenem should be incorporated into national essential drug lists. When meropenem becomes available, clinician education and restrictive measures will be required to ensure appropriate prescribing. Overuse of meropenem leads to the emergence of meropenem-resistant, Gram-negative species (carbapenemase-producing *Enterobacterales* [CPE]). CPEs have very limited treatment options due to multiresistance and are now prevalent in many world locations, especially in Asia. Pacific island nations will need to prepare for CPE emergence, including the ability to reliably detect CPE in laboratories.

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Comparing age and sex trends of chlamydia, gonorrhoea, hepatitis and syphilis infections in Samoa in 2012 and 2017

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In Samoa, the seroprevalence rates of sexually transmitted infections other than HIV have been endemically high over the past decade, despite years of prevention programming. Odds ratio and χ^2 tests were conducted to compare the rates of positivity of chlamydia, gonorrhoea, hepatitis B and C, and syphilis across age groups from 2012 and 2017 surveillance data in Samoa. Young people aged 15–19 years were significantly more likely to have a chlamydia infection compared to all other age groups in both 2012 and 2017. Hepatitis B infections were more common in males and those aged 30 and above in both 2012 and 2017. Hepatitis C had no significant differences in age, but it was more common in males in 2012 and more common in females in 2017. Older age groups (aged 45 and above) were more likely to have a positive syphilis test in both 2014 and 2017 when compared to those aged 15–24 years. The results of this analysis confirm previously observed trends in Samoa for younger age groups' prevalence of chlamydia and gonorrhoea, and for older age groups' prevalence of hepatitis B and C. But the analysis also unexpectedly found that older age groups (aged 45 and above) are more likely to test positive for syphilis (for years 2014 and 2017). Further studies are needed to assess behavioural risk factors associated with older populations in order to explain the increase in risk and to design interventions suited to this demographic.

Sexually transmitted infections (STIs) are an ongoing health challenge in Samoa and across the Pacific. Samoa consists of four inhabited islands with a relatively small population of approximately 196 000 people.[1] The country's close-knit community dynamic poses unique social barriers to voluntary testing and treatment, and population coverage remains low.[2] Samoa has historically reported high rates of chlamydia and gonorrhoea and low rates of HIV and syphilis from cross-sectional antenatal prevalence studies. The first seroprevalence survey in the country, conducted in 2000, found that chlamydia and trichomoniasis infections were common among pregnant women (30.9% and 20.8%, respectively), with a low prevalence of gonorrhoea and syphilis (3.3% and 0.5%, respectively).[2] One analysis found that young women aged < 25 years were three times more likely to have an STI than older women.[3] Chlamydia is endemic among women, with those < 25 years having greater positivity than those ≥ 25 years (26.1% compared to 11.9%).[3] Women who are unmarried or are 18–24 years of age were more likely to test positive for chlamydia.[4] Chlamydia infections are also associated with subfertility in Samoan women.[5] Maternal and congenital syphilis in Samoa has increased since 2018.[6] Untreated maternal syphilis has been associated with fetal loss, neonatal death, premature birth and lower birthweight.[7] These results indicate significant health challenges for women of childbearing age.

The 2017 national positivity rates for chlamydia, gonorrhoea and syphilis (24.2%, 5.6% and 1.04%, respectively) are similar to previous prevalence rates.[8] This suggests a persistently high prevalence of STIs, particularly chlamydia, for the past decade. Conversely, Samoa has previously reported the lowest rate of syphilis worldwide (0%).[8] However, syphilis has increased globally among heterosexuals and men who have sex with men.[8] In Samoa, syphilis cases have steadily increased from 26 reported cases in 2015 to 78 cases in 2017.[6]

Although prevalence estimates were well established in previous studies, more recent data on sex and age are needed to inform intervention design. Using national

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surveillance data, this analysis seeks to update the status of the epidemic by comparing positivity rates among sex and age groups from years 2012 and 2017.

METHODS

For a cross-sectional study, the data of all patients in the country who had an STI investigation (routine or suspect) from any provider were analysed for years 2012 (n = 18 804) and 2017 (n = 48 898) to compare trends in the positive diagnosis of chlamydia, gonorrhoea, hepatitis B and C, and syphilis by age and sex. Due to the low sample size in 2012, syphilis data were compared for 2014 (n = 3865) and 2017 (n = 11 418). Patients with lost or insufficient specimens were excluded from the sample.

The HIV and STI Surveillance Database, which was used to construct the study sample, is managed by the Samoa Ministry of Health in the capital of Apia. The most complete full-year data sets (2012, 2014 and 2017) were used. Data are comprised of all diagnostic testing (both routine testing and suspect cases in the general population) that was recorded by the National Reference Laboratory (NRL) of Tupua Tamasese Meaole (TTM) Hospital, Apia. In 2017, all national diagnostic technologies were centrally housed in the NRL. All specimens collected in the country are processed by the NRL and recorded in the database. The assays used in the national testing algorithm include polymerase chain reaction (PCR) for chlamydia and gonorrhoea, rapid plasma reagin (RPR) and treponema pallidum haemagglutination (TPHA) tests for syphilis, hepatitis B surface antigen (HBsAg) tests for hepatitis B, the hepatitis C antibody (anti-HCV) test for hepatitis C. Clinicians collect and send specimens to NRL or refer the patient directly to the NRL for collection. Once specimens are processed, the requesting clinician and relevant authorities are notified, and the reporting is collated into the database.

We used Epi Info software (version 7.2.2.6) to estimate odds ratios and chi-square test (χ^{2}) to analyse trends (extended Mantel-Haenzsel). Odds ratios are suitable estimations of the prevalence of a disease when infections are less than 10%.[9,10] Samoa's syphilis positivity rates ranged from 0.13% in 2012 to 1.04% as of July 2018.[11] Cases were compared based on sex (comparing males to females), age (comparing all other age groups to those aged 15–19 years) and the type of STI. Since there were only 10 cases in 2012, data for syphilis were taken from 2014 when there were sufficient cases (n = 18) by age to run the analysis without violating the assumption of the extended Mantel-Haenzsel tests (80% of cells have more than five cases). Additionally, syphilis age groups were adjusted from five-year to 10-year age groups (< 45 and $\geq$ 45) for sample size, while other STI age groups are compared to those < 30 years and $\geq$ 30+ years.

Sample

The majority of tests come from routine testing (76.0% in 2012 and 78.7% in 2017, **Annex**). This includes testing of women attending antenatal care services, immigration screening for Samoan nationals and blood donation screening. Females represent more total tests than males (71.5% compared to 28.5% in 2012, and 56.7% versus 43.3% in 2017, respectively). There were 7861 tests in 2012 and 11 152 in 2017 in individuals < 30. Testing increased for individuals age $\geq$ 30 years (6428 tests in 2012 and 15 145 in 2017). Overall, STI positivity has decreased in the youth age group (15–24 years), from 11.9% in 2012 to 3% in 2017, and in antenatal care testing from 9.5% in 2012 to 1.1% in 2017. Chlamydia was the most common infection (27.9% in 2012 and 22.9% in 2017), with fewer tests in 2017 compared to 2012 (2207 to 4951, respectively). Gonorrhoea is the second most common infection (6.3% in 2012 and 10.0% in 2017), with more tests in recent years (2201 in 2017 compared to 208 in 2012). Hepatitis cases are low, with 2.6% positive rate in 2012 and 2.4% in 2017 for hepatitis B, and 1.1% in 2012 and 0.1% positive for hepatitis C. Testing for hepatitis B and C was higher in 2017 (9780 tests in 2012 and 22 312 in 2017). In 2014, there were 18 cases of syphilis from 3865 tests, and in 2017 there were 90 cases from 11 418 tests.

Results

Positivity for STIs varied based on age and sex (**Table 1**). Chlamydia and gonorrhoea positivity rates were higher in the age group 15–19 years. In 2012, relative to those aged 15–19 years, those aged 20–24, 25–29 and $\geq$ 30 years had significantly lower odds of testing positive for chlamydia (unadjusted odds ratio of 0.80, 0.58 and 0.32, respectively). In 2017, relative to those aged 15–19 years, those aged 25–29 years and $\geq$ 30 years had

Table 1. **Odds of chlamydia, gonorrhoea, and hepatitis B and C infections by age and sex, 2012 and 2017**

	Chlamydia		Gonorrhoea		Hepatitis B		Hepatitis C	
2012	**OR (95% CI)[c]**	***p*-value**	**OR (95% CI)[c]**	***p*-value**	**OR (95% CI)[c]**	***p*-value**	**OR (95% CI)[c]**	***p*-value**
Sex[a]								
Male	1.05 (0.742–1.48)	0.79	15.73 (3.37–73.42)	0.00*	2.37 (1.83–3.07)	0.00*	9.31 (1.27–68.44)	0.01*
Female	1		1		1		1	
Age group[b]								
15–19	1		1		1		1	
20–24	0.80 (0.67–0.96)	0.01*	1.84 (0.19–17.71)	0.58	1.75 (0.77–3.97)	0.18	0.44 (0.07–2.67)	0.36
25–29	0.58 (0.47–0.70)	0.00*	0.97 (0.08–11.48)	0.98	3.86 (1.74–8.56)	0.00*	0.57 (0.09–3.43)	0.53
≥ 30	0.32	0.00*	1.21 (0.10–14.43)	0.88	5.54 (2.57–11.92)	0.00*	1.28 (0.29–5.58)	0.74
2017	**OR (95% CI)[c]**	***p*-value**	**OR (95% CI)[c]**	***p*-value**	**OR (95% CI)[c]**	***p*-value**	**OR (95% CI)[c]**	***p*-value**
Sex								
Male	0.91 (0.65–1.26)	0.55	7.10 (5.13–9.82)	0.00*	2.48 (1.95–3.17)	0.00*	0.67 (0.21–2.12)	0.50
Female	1		1		1		1	
Age Group								
15–19	1		1		1		-	-
20–24	0.78 (0.52–1.15)	0.21	0.27 (0.13–0.56)	0.00*	2.56 (0.77–8.49)	0.11	-	-
25–29	0.55 (0.36–0.82)	0.00*	0.55 (0.29–1.04)	0.06	4.35 (1.34–14.12)	0.01*	-	-
≥ 30	0.27 (0.17–0.41)	0.00*	0.43 (0.23–0.82)	0.01*	11.82 (3.77–37.05)	0.00*	-	-

[a] reporting only cases where sex is known
[b] reporting only cases where age is known
[c] extended Mantel-Haenszel χ^2 for trend, two-tailed sig.
* significant at 0.05 level
- insufficient cases for analysis
CI = confidence interval
OR = odds ratio

significantly lower odds of testing positive (unadjusted odds ratio of 0.55 and 0.27, respectively). No significant results were observed for sex in 2012 and 2017.

For gonorrhoea, compared with females, males had greater odds of testing positive in both 2012 and 2017 (unadjusted odds ratio of 15.7 and 7.1, respectively). In 2012, positive tests did not differ significantly by age. In 2017, relative to those aged 15–19 years, those aged 20–24 years and those aged ≥ 30 years had significantly lower odds of testing positive for gonorrhoea (unadjusted odds ratio of 0.27 and 0.55, respectively).

For hepatitis B, compared with females, males had greater odds of testing positive in both 2012 and 2017 (unadjusted odds ratio of 2.4 and 2.5, respectively). In both 2012 and 2017, relative to those aged 15–19 years, those aged 25–29 and ≥ 30 years had significantly greater odds of testing positive (2012: unadjusted odds ratio of 3.9 and 5.5, respectively; 2017: unadjusted odds ratio of 4.3 and 11.8, respectively).

For hepatitis C, compared with females, males had significantly greater odds of testing positive in 2012, but not in 2017 (unadjusted odds ratio in 2012 of 9.3 and in 2017 of 0.67). In 2012, with respect to age, there was no difference in test positivity.

For syphilis, compared with females, males had lower odds of testing positive in both 2014 and 2017 (unadjusted odds ratio of 0.28 and 0.63, respectively) (**Table 2**). In 2014, relative to those aged under 45 years, those ≥ 45 years were 50-fold more likely to test positive. In 2017, compared with those under 45 years, those aged ≥ 45 years were 14-fold more likely to test positive. For 2017, there were sufficient data to compare smaller

Table 2. **Odds of syphilis infection by age and sex, 2014 and 2017**

	Positive	Negative	OR (95%CI)[c]	*p*-value
2014				
Sex[a]				
Male	6	476	0.28 (0.11–076)	0.01*
Female	12	3371	1	
Age (years)[b]				
15–24	0	1582	-	-
25–34	4	1492	-	-
35–44	1	486	-	-
≥ 45	9	128	-	-
< 45[d]	5	3560	1	-
≥ 45	9	128	50.06 (16.54–151.51)	0.00*
2017				
Sex[a]				
Male	30	4934	0.63 (0.40–0.97)	0.04*
Female	60	6190	1	
Age (years)[b]				
15–24	7	3437	1	-
25–34	16	4081	1.93 (0.79–4.68)	0.14
35–44	12	1892	3.11 (1.22–7.92)	0.01*
≥ 45	55	1055	25.60 (11.62–56.38)	0.00*
< 45[d]	35	9410	1	
≥ 45	55	1055	14.02 (9.13–21.52)	0.00*

[a] reporting only cases where sex is known
[b] reporting only cases where age is known
[c] extended Mantel-Haenszel χ^2 for trend, two-tailed sig.
[d] insufficient data for age groups 15–44, all < 45 were compared to 45+ in 2014
* significant at 0.05 level.
CI = confidence interval
OR = odds ratio

age groups. Compared to those aged 15–24 years, all older age groups had greater odds of a positive syphilis test (unadjusted odds ratio of 3.1 for those aged 35–44 years and 25.6 for those aged ≥ 45 years).

DISCUSSION

This analysis finds similar positivity rates to seroprevalence estimations, and it provides gender and age trends in positivity. As expected, young people generally had greater odds of testing positive for chlamydia (high prevalence in both 2012 and 2017) and gonorrhoea, while older age groups were significantly more likely to be positive for hepatitis B and C. This is a common trend as older age groups have longer windows of exposure to viral infections and have had more routine screening over their lifetime, while bacterial infections are more episodic and frequent with young people. Older individuals may also have lower vaccine coverage than younger ones for hepatitis B virus and hepatitis C virus. However, older age groups had greater odds of testing positive for syphilis.

The high positivity rates for chlamydia in 2012 and 2017, in particular, are of great concern. This is due to: 1) the lack of population interventions to reduce chlamydia prevalence; 2) diminishing prioritization of STIs; and 3) the social stigma surrounding sex and STIs that deters individuals from seeking health services and makes delivering comprehensive sexual health education to young people difficult. In a small and close-knit population, seeking services anonymously for taboo conditions is almost impossible and can result in social consequences.[12]

It is also unusual for syphilis to be more common in older age groups. We suggest this anomaly may be due to untreated syphilis cases being detected in late tertiary-stage years after an initial infection, when advanced symptoms resurface. Reports indicate a significant increase in infections between 2015 and 2016.[11] The odds ratio of syphilis infections was higher in those age ≥ 45 years both in 2014 and 2017. In addition to older generations being diagnosed in late stages, these results could illuminate a health system-level gap in case detection for syphilis.

From a cultural perspective, older individuals in Samoa are also afforded more social authority, allowing them more agency to freely pursue sexual activity and attend health services. Sexual activity in younger individuals, especially those not married, is considered a more serious taboo and is socially discouraged.[12] Additionally, older generations had comparatively less access to sexual health education and prevention. All of these factors would increase the odds of infection in older populations.

In Samoa, government-level STI prevention has focused on young people aged 15–24 years as a high-risk group with the largest burden of infection.[11] This study confirms such trends for chlamydia and gonorrhoea. However, syphilis interventions may require age-specific strategies for older populations. These results highlight the need to design age-specific interventions for case detection and prevention in older populations.

Limitations

The HIV and STI Surveillance Database at the Ministry of Health captures results of all diagnostic tests nationally, with the exception of rapid screening kits. Therefore, the data represent all patients (public, private, routine and suspect) in the country accessing clinical services who received a diagnostic test, excluding screened cases not referred for diagnostics and symptomatic cases treated presumptively. There is selection bias from suspect cases referred to testing by clinicians. Additional studies are needed to estimate the true population prevalence of populations that do not attend services. Information on the stage of infection, exposure and result per assay is not captured.

Each case in the database represents an episode of STI infection, with the possibility of a single patient having multiple episodes. However, anecdotal observations from the Ministry of Health indicate that patients often delay seeking testing and care until infections enter an advanced stage. For instance, only 52% of children under age 5 years with a fever were brought to a health facility for care or advice.[13] This late attendance suggests it may be unlikely for patients to report to services more than once a year for STIs.

To obtain a sufficient sample size for syphilis, data were taken from 2014, and age groups were recategorized into 10-year age groups before running the calculations by age and sex, which resulted in larger confidence intervals as the age group categories were less distinct from each other. Additionally, the positivity for TPHA/RPR may indicate chronic yaws infections in older adults, as opposed to syphilis; however, yaws was declared eliminated in the 1960s.[14]

CONCLUSION

The unexpectedly higher odds of syphilis positivity among adults aged $\geq$ 45 years compared to 15–24 years, as well as the persistently high rates of chlamydia infections between 2012 and 2017, highlight a need to re-strategize the promotion and delivery of STI testing and care services in Samoa. Prevention services and strategies should be age-specific, with further assessment of the different barriers for older and younger patients.

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