

Research Article

The Suitability of Stool Antigen Testing in the Detection of *Helicobacter pylori* in a Regional and Rural Area of Australia

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Background. *Helicobacter pylori* is considered the most widespread bacterial pathogen worldwide. Successful eradication protocols are well established, highlighting the importance of appropriate infection detection. Noninvasive testing (NIT) methods are commonly used to detect infection, with test selection dependent on access and previous infection. This study examined trends in NIT by age group and test selection for eradication screening as well as examining *H. pylori* area prevalence by socioeconomic status (SES) in the Illawarra Shoalhaven and surrounding region. **Materials and Methods.** This retrospective cohort quantitative study is based on 20,998 NIT including stool antigen test (SAT), urea breath test (UBT), or *H. pylori* serology via Southern.IML Pathology between 2018 and 2020. Test percentage positives per and total test percentages within age groups were calculated for each NIT. Positive sample postcode data was assigned to socioeconomic percentiles. Total test utilisation and prevalence were calculated and depicted as geospatial representations. **Results.** Overall: 58.5% UBT, 31% serology, and 10.5% SAT were performed, with 14.7% positive for any NIT. Highest percent positive age group: SAT 80-89yo (18.6%), UBT 0-9yo (20.8%), and serology 90-99yo (32.6%). Test majority per age group: SAT 0-9yo (67.4%), UBT 10-89yo (59.4%), and serology 90-99yo (48.3%). A trend was seen between increasing infection prevalence and increasing socioeconomic disadvantage ($p = 0.161$, $R^2 = 0.0361$). Prevalence rates visually correlated with total test utilisation. **Conclusions.** SAT was underutilised compared to UBT or serology. Serology was inappropriately used in older age groups, and the result validity was questioned following confirmed infection. SAT is a viable alternative for use in these settings. No significant correlation was seen between lower SES areas and higher *H. pylori* infection prevalence, but low-test utilisation suggests likely prevalence underestimation within the studied area and may indicate reduced accessibility to healthcare.

1. Introduction

Helicobacter pylori is an alarmingly widespread bacterial pathogen with a worldwide prevalence of >50% globally, or as high as 90% in developing and 35% in developed countries [1–3]. *H. pylori* has been confirmed as a causative agent of gastritis and peptic ulcer disease (PUD) and implicated in additional malignant and nonmalignant gastrointestinal pathologies including gastric carcinoma and mucosa-associated lymphoid tissue lymphoma [4–7]. Successful *H. pylori* eradication protocols are well established and typically involve the use of antibiotics in combination with an agent

to suppress gastric acid release, known as “triple therapy.” [3, 8] Due to the spectrum of pathogenicity and the availability of successful treatment protocols, *H. pylori* detection is vital in identifying affected individuals and limiting disease progression [2, 9].

H. pylori detection methods are classified as either invasive or noninvasive [10]. The invasive method of endoscopically collecting gastric antral biopsy samples is considered the gold standard to confirm *H. pylori* infection [11]. Biopsy samples can then be used in detection methods such as culture, histology, rapid urease tests, and polymerase chain reaction (PCR) [12]. The availability of culture and

histological data has seen it used as the reference standard in multiple studies [6, 9]. However, due to the invasive nature of biopsy collection, noninvasive tests (NIT) such as the urea breath test (UBT), serological testing, and faecal/stool antigen testing (SAT) are commonly used and preferred in the clinical setting [13].

SAT is performed by testing for the presence of *H. pylori* antigens in a stool sample using either monoclonal or polyclonal antibodies [14, 15]. Immunochromatography (ICT) and enzyme-linked immunosorbent assay (ELISA) are the two main methods that utilise these antibodies to detect specific stool *H. pylori* antigens [16]. ELISA testing is considered more accurate than immunochromatography, allowing for a quantification of potential *H. pylori* infection [17]. ELISA requires laboratory facilities, whereas immunochromatography provides a binary result and may have greater utility in resource-poor environments [18, 19].

Two other NIT methods for the detection of *H. pylori* are UBT and serology. UBT involves the ingestion of urea labelled with carbon isotopes, C-13 or C-14. There has been concern regarding radioactivity of C-14, though the dose has been approximated to background radiation [20]. If *H. pylori* is present, the bacteria that produced urease will catalyse the labelled urea into labelled carbon dioxide, which will be expired, collected, and quantified [21]. Serological testing is preferred by general practitioners in Australia as it is widely accessible [22]. However, the use of serological screening following eradication does not differentiate between an active or past *H. pylori* infection [9, 23]. SAT and UBT both detect active *H. pylori* infection within the gastrointestinal tract and are thus appropriate tests in the posteradication setting.

One unique advantage of SAT is that it does not require the ingestion of a substance or sample collection, which can be of benefit for different patient demographics including pregnancy. The use of SAT is preferred in children < 6 years old as UBT accuracy decreases in this age group due to limited patient compliance [17]. A systematic review and meta-analysis conducted by Leal et al. [24] demonstrated that C-13 UBT *H. pylori* detection in children younger than 6 years of age had a lower sensitivity and specificity as compared to those who were older than 6 years.

There are currently limited studies that provide a direct comparison between NIT methods. Indirect comparison of 99 studies by the Cochrane Review [6] found that UBT and serology were more sensitive than SAT. However, the studies in the Cochrane Review varied in terms of SAT methodologies, and inconsistent or unknown sensitivity thresholds were utilised between studies, with 83% of SAT studies not specifying the use of either monoclonal or polyclonal antibodies. In contrast to the lower sensitivity reported for SAT (83%) by the Cochrane Review [6], Skrebinska et al. [13] reviewed 4 studies that found immunochromatography SAT sensitivity ranging between 87.7% and 97.9% and specificity ranging between 92.5% and 100%. This contradiction between studies may be explained by the varying methodologies included in the Cochrane Review [6] as well as the threshold variations between studied *H. pylori* NIT methods, creating potential comparative inconsistencies. Nevertheless, primary SAT may be the

most appropriate choice in certain clinical situations such as in paediatric and pregnant populations for detection of active infection or eradication screening.

H. pylori infection is likely to occur during childhood and can be influenced by multiple demographic factors including socioeconomic status (SES), gender, ethnicity, and educational status [25]. Variations in SES have been demonstrated to impact access to appropriate healthcare and health outcomes. Low SES is associated with both reduced access to healthcare and poor health literacy, which contribute to reductions in health status and quality of life [26]. Increasing *H. pylori* prevalence rates have been identified in developing countries and areas of lower SES [27]. In Australia, SES has been found to be lower in rural and remote areas suggesting a likely increased prevalence of *H. pylori* in these areas and increased disease burden [28].

This study describes the use of noninvasive *H. pylori* detection methods in the Illawarra Shoalhaven and surrounding region, the region served by Southern.IML Pathology. This study will investigate the preferences for different NIT methods across different age groups and the likelihood of a positive result for *H. pylori* infection according to demographic factors such as age and SES.

2. Material and Methods

This study is a retrospective cohort quantitative study utilising raw data from Southern.IML Pathology (3 Bridge Street, Coniston New South Wales (NSW) 2500) for patients who underwent NIT for the presence of *H. pylori* infection between 2018 and 2020. Ethics approval for this analysis was received from the University of Wollongong Illawarra Shoalhaven Local Health District Human Research Ethics Committee (HREC approval number: 2021/377).

2.1. Sample and Setting. Southern.IML Pathology performs 90% of the pathology in the community for the Illawarra Shoalhaven region [29]. Study participants were patients who were referred for investigation by general practitioners or specialists in routine clinical practice. Clinical symptoms at the time of the test were not available; however, it can be assumed that testing was conducted on patients due to clinical suspicion of *H. pylori* infection or screening for the status of infection posttreatment. There were no specific criteria for inclusion or exclusion of participants from this study other than the testing types and time period.

Due to the invasive nature and limited accessibility of gold standard testing via gastric antral biopsy sampling as well as the availability of highly accurate NIT, NIT is preferred for primary investigation and screening [13]. In this study, NIT selection of either SAT, UBT, or *H. pylori* serology was determined by the referring clinician. This was likely due to test accessibility, cost, previous clinical experience, and patient/clinician preference; however, specific clinician reasoning for test selection was not available.

SAT faecal samples were likely self-collected and presented to medical practice or directly to pathology providers, with UBT and serology samples requiring specialised collection

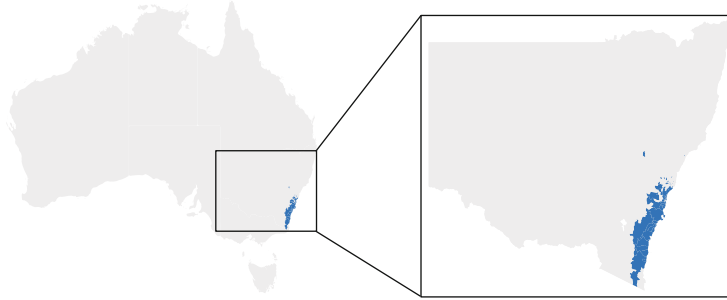


FIGURE 1: Geospatial representation of Australian/New South Wales postcode areas with ≥ 1 positive *H. pylori* noninvasive test during the 2018-2020 period.

(details of the testing protocols can be found in Supplementary data 1). Following sample collection, commercially available biochemical testing was performed. This study utilised the ELISA LIAISON® Meridian [30], PYtest® [31], and Immulite® 2000 system [32] for SAT, UBT, and *H. pylori* serology, respectively (Supplementary data 1). Each test had a quantification range used to designate a result as either negative, equivocal (indeterminate), or positive. A result determined to be equivocal was inconclusive, and repeat testing was recommended.

2.2. Data Management and Analysis. Data was collated and deidentified by Southern.IML Pathology. Patients were allocated a unique identification number allowing the matching of patients who have undergone multiple testing methodologies and/or repeat testing. Data fields for the study included a patient identification number, test episode number, patient age, patient postcode, test date, test type, test result, and test quantification result (where available). Data was securely stored in Cloudstor.

Data analysis was managed and performed using Microsoft Excel spreadsheet software. This included the processing of data and tabulation. Descriptive statistics were calculated for the *H. pylori* NIT, calculating total test number, total positive, total equivocal, and total negative as well as overall totals. Regression and analysis of variance statistics were used to determine significance ($p < 0.05$).

2.3. Demographic Factors. The first demographic factor examined in this study was age. Patients' ages were grouped by decade for comparison between percentage of tests positive for *H. pylori*. Test preference between patient age decades was determined by calculating the percentage of each NIT conducted within that age group.

The second demographic factor was SES. Utilising the 2016 Socioeconomic Indexes for Australia, as published by the Australian Bureau of Statistics [33], each postcode was designated a percentile from 1 to 100 (1 being the most and 100 the least disadvantaged) as per the postal area index of relative socioeconomic disadvantage. Positive NIT were collated into postcodes, and a total per postcode was calculated. There were 55 postcodes from NSW and 1 from Victoria with ≥ 1 positive NIT in the data set. These are depicted in geospatial representations (Figure 1), excluding the single Victorian postcode. This illustrates the Illawarra

Shoalhaven and surrounding region. Additionally, postcode totals were divided by the usual resident population for each postcode to calculate an estimated *H. pylori* infection prevalence for that postcode. Socioeconomic percentile was then compared to postcode prevalence.

The representations individually depicted total test utilisation, designated socioeconomic decile (1 being the most and 10 the least disadvantaged) determined as above, and previously calculated postcode area prevalence within each postcode area. Total test utilisation was calculated by determining the total NIT performed within each postcode area. This was divided by postcode area population and multiplied by 1000. Visual correlations were then made.

3. Results

3.1. Broad Analysis of NIT in the Illawarra Shoalhaven and Surrounding Areas. There were 20,998 noninvasive *H. pylori* tests conducted during the three-year period included in this study (2018-2020). Of these, over 50% of patients undertook UBT; one-third underwent serology, and only 10% participated in SAT (Table 1). Of all the NITs conducted, almost 15% were positive, and the percentage positive was similar for each of the NIT methods (Table 1). Additionally, 7% of noninvasive tests returned an equivocal result (Table 1). The number of NIT was seen to increase across the three years sampled, with 6,705, 7,050, and 7,243 NITs completed in 2018, 2019, and 2020, respectively.

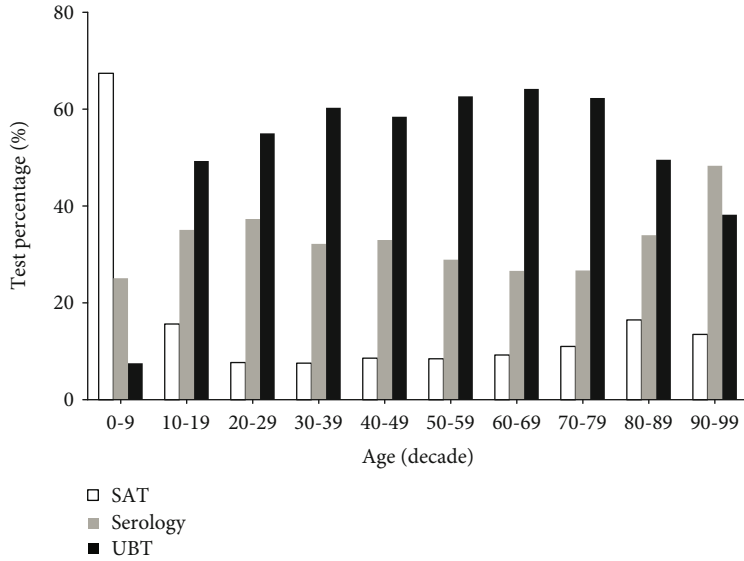
3.2. Impact of Demographic Factors on NIT. The preference for each individual NIT method was examined across each age group (Figure 2(a)). In the paediatric population (0-9 years age group), SAT was used in 67.4% of patients (215/319), as compared to serology (25%, 80/319) and UBT (7.5%, 24/319) (Figure 2(a)). In contrast, serology was the most common NIT used within the 90-99 years age group accounting for 48.3% (43/89) of tests. For the other age groups, between age groups 10 and 89 years, UBT was conducted more than other NIT with 59.4% (12,223/20,588) (Figure 2(a)).

The percentage positive of each NIT method during the 2018-2020 period was also calculated for each age group by decade (Figure 2(b)). The highest percent positive finding for SAT was 18.6% (24/129) in the 80-89 years age group, and the highest percent positive finding for

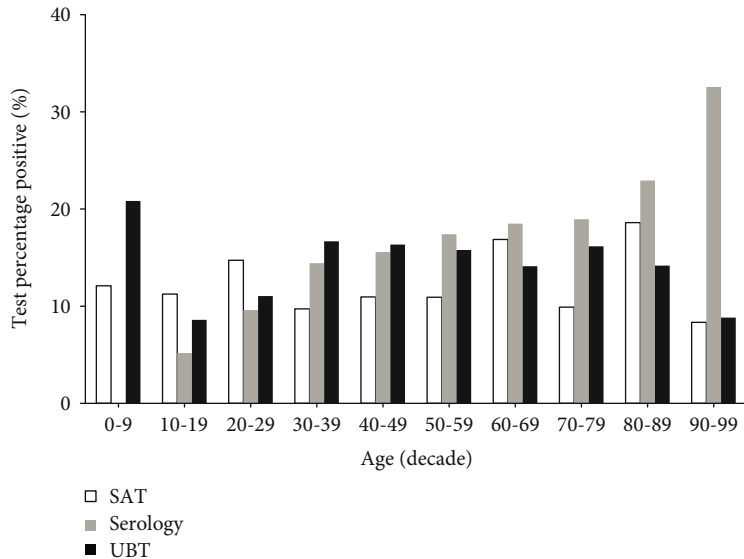
TABLE 1: Noninvasive *H. pylori* testing during the 2018-2020 period by Southern.IML Pathology.

	SAT	Serology	UBT	All noninvasive
Total test number	2201	6515	12282	20998
Positive	12.49% (275)	14.89% (970)	14.66% (1800)	14.72% (3090)
Negative	84.64% (1863)	80.08% (5217)	77.01% (9458)	78.76% (16538)
Equivocal tests	2.86% (63)	5.03% (328)	8.34% (1024)	6.74% (1415)

The total, equivocal, positive, and negative result numbers of each detection method have been included. Totals of each result have been calculated for the noninvasive tests and all tests inclusive. A percentage as compared to column total test number has been calculated and displayed with test number in brackets, e.g., % (*n*).



(a)



(b)

FIGURE 2: Comparison of NIT method by age. (a) Preference for each NIT method was considered across each age group. The percentage of each NIT *H. pylori* method per total NIT conducted per age group (decade) during the 2018-2020 period. Stool antigen test (clear), serology (grey), and urea breath test (black) have been separated adding to 100% for each age group. (b) Percentage positive of each noninvasive *H. pylori* testing method conducted per age group (decade) during the 2018-2020 period. Stool antigen test (clear), serology (grey), and urea breath test (black) have been separated.

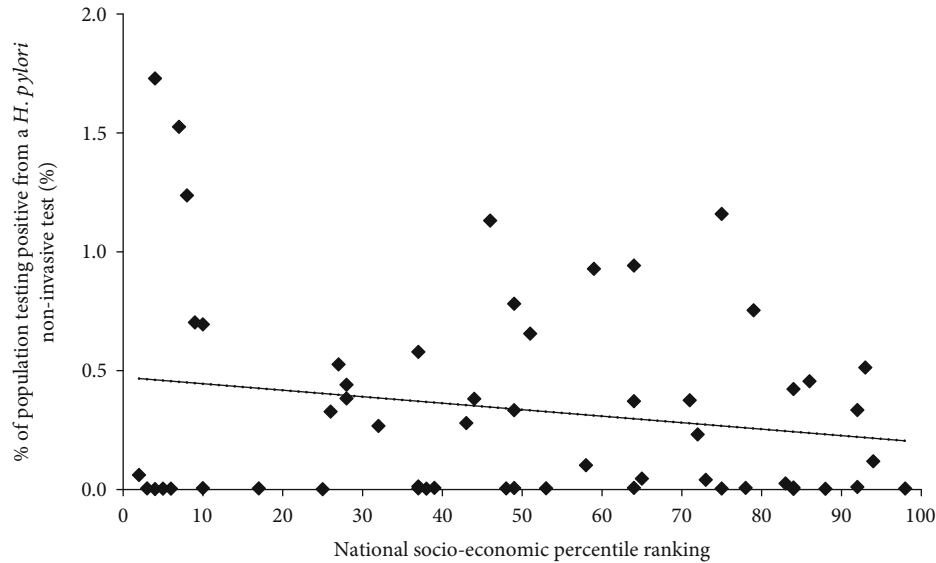


FIGURE 3: Socioeconomic distribution of *H. pylori* infection during the 2018–2020 period. National socioeconomic percentiles (1–100) were determined by postcodes and correlated with population (%) testing positive for *H. pylori* using noninvasive testing methods within each area. The level of socioeconomic disadvantage decreasing from 1 to 100. Population and national socioeconomic percentiles were obtained from the Australian Bureau of Statistics [33]. A linear trendline demonstrates the general data trend ($R^2 = 0.0361$, $p = 0.161$).

UBT was 20.8% (5/24) in the 0–9 years age group. Positive serology was highest with 32.6% (14/43) in the 90–99 years age group. Positive findings in serology were seen to significantly increase with increasing age ($p < 0.001$, $R^2 = 0.919$) (Figure 2(b)).

The prevalence of *H. pylori* in the Illawarra Shoalhaven and surrounding regions was estimated using the positive NIT results and the population estimates obtained from the Australian Bureau of Statistics [33]. There was a trend for an increase in the prevalence of *H. pylori* within socioeconomic percentiles (as determined by postcode), which indicated an increase in *H. pylori* infection prevalence with increasing socioeconomic disadvantage (Figure 3, $R^2 = 0.036$), although this did not reach significance ($p = 0.161$). The area with the highest prevalence of *H. pylori* was in the 4th percentile with 1.7% of the population testing positive.

Geospatial representations demonstrated visual correlation between prevalence rates and total test utilisation within postcode areas during the studied time period. *H. pylori* infection prevalence rates appear to increase with increasing total test utilisation (Figures 4(a) and 4(c)). Postcode areas with low decile, and therefore low SES, appeared to have low test utilisation and an associated low recorded prevalence (Figure 4(b)–4(c)). Due to low test utilisation in these low SES areas, prevalence may be underestimated due to the correlation as described above.

4. Discussion

This study found that approximately 15% of all NITs for *H. pylori* were positive. This matched the reported prevalence of *H. pylori* in Australia which has been estimated to range between 15.1% and 38.0% [34]. When looking at NIT methodologies, this study suggested that clinicians in the

Illawarra Shoalhaven regions prefer UBT as the primary noninvasive *H. pylori* detection method. UBT was utilised approximately twice as often as serology and six times more frequently than SAT. This was to be expected as UBT has been recognised to have the highest sensitivity and specificity of the *H. pylori* NIT [35, 36]. However, the value of SAT as a primary *H. pylori* detection method in older and younger populations cannot be overlooked, especially as SAT sample collection does not require the ingestion of radioactive substances or complying with instructions and some physical exertion [21].

It was determined that SAT was the preferred NIT for *H. pylori* detection in the paediatric populations (0–9 age group), contributing 67% of tests. This is also consistent with current practice as Stefano et al. [17] demonstrated decreased UBT accuracy for patients < 6 years due to poor compliance. Furthermore, Sabbagh et al. [1] indicated that no significant SAT performance variations are observed between age groups within paediatric populations. Sabbagh et al. [1] do allude to the recognised stigma of SAT sample collection as leading to potential SAT avoidance. A further advantage of obtaining a sample for SAT is that it can be used for *H. pylori* PCR and resistance markers, enabling initial therapy that is more likely to eradicate infection.

This study demonstrated serology was overused within the 90–99 age group with 48% of tests. This is surprising as serology is ineffective in distinguishing between active and previous *H. pylori* infection; it, therefore, appears counterintuitive as increasing age would be associated with increased lifelong exposure to *H. pylori* [9, 23]. Indeed, this study demonstrated 32% positive serology in the 90–99 age group, which was considerably higher than the alternate NIT (SAT or UBT). This inconsistency was supported by AL-Saad et al. [37] who found a significant correlation between increasing *H. pylori* IgG detection and increasing age, as was seen in

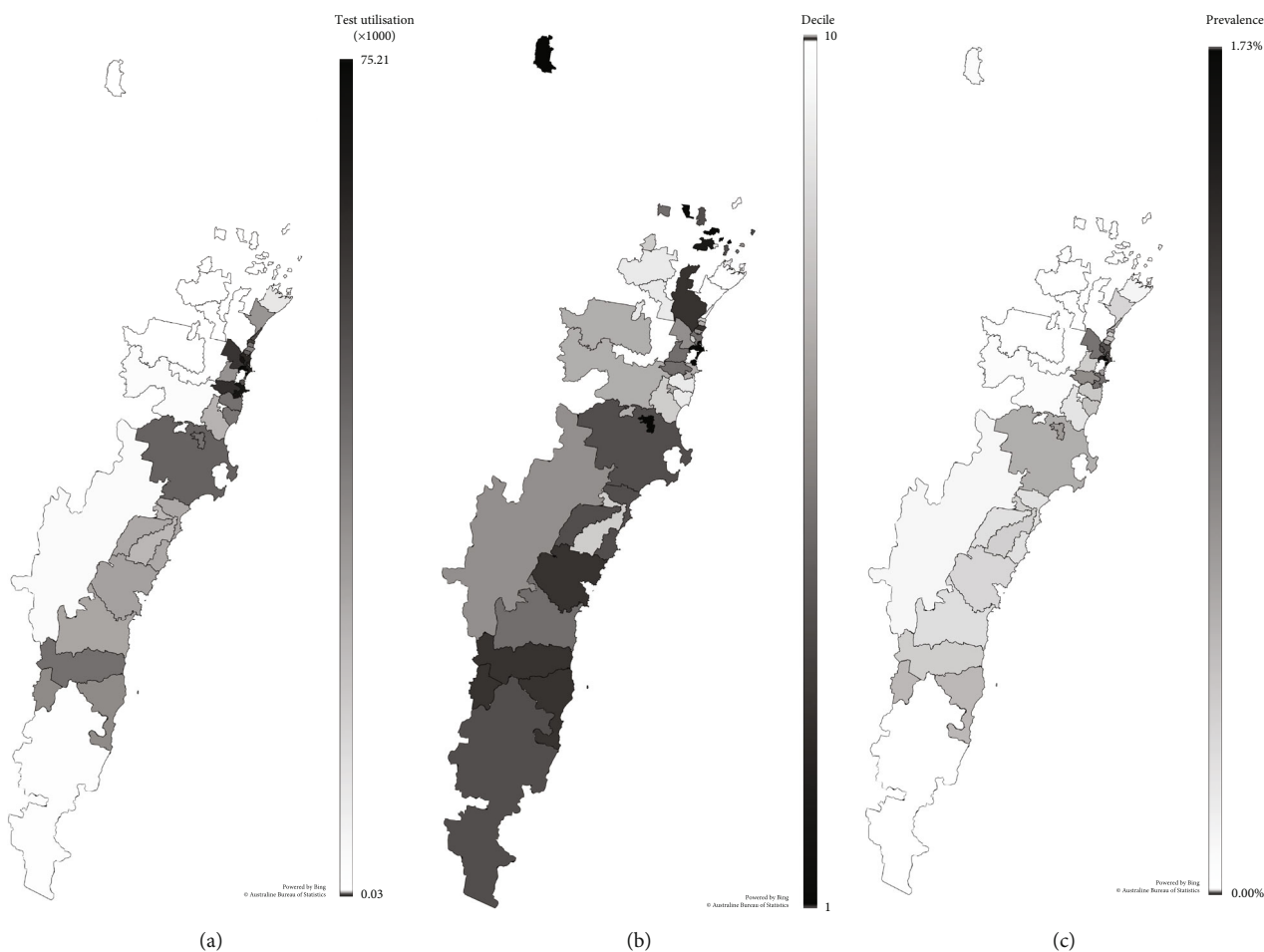


FIGURE 4: Geospatial representations of NSW postcode areas with ≥ 1 positive *H. pylori* noninvasive test during the 2018-2020 period. Representations demonstrate postcode area (a) noninvasive test utilisation rates by area population ($\times 1000$), (b) national socioeconomic deciles (1 decile is the most and 10 is the least disadvantaged socioeconomic areas), and (c) *H. pylori* infection prevalence. Population and national socioeconomic deciles were obtained from the Australian Bureau of Statistics [33].

this study. These findings suggest that in older age groups, SAT or UBT are more appropriate as primary *H. pylori* detection methods.

Additionally, this study observed a nonsignificant association between increased *H. pylori* infection estimated prevalence in lower SES areas within the Illawarra Shoalhaven area. This pattern has been previously recognised globally comparing both developed and developing areas with prevalence rates as high as 35% and 90%, respectively [1–3]. One potential reason that this finding did not achieve significance in the current data set is that patients in areas of socioeconomic disadvantage may not have been able to afford medical treatment including attendance at their GP in order to obtain a referral for NIT. Furthermore, this finding may be reflective of limited accessibility to healthcare and variabilities in health literacy in the studied area and other regional and remote areas.

In Australia, prevalence has been estimated to range between 15.1% and 38.0% with increasing prevalence recognised amongst subgroups such as indigenous or elderly populations [34]. For this study, the prevalence in each

population area was calculated under the assumption that the positive *H. pylori* result was representative of the total area population. This is appropriate as Southern.IML Pathology services 90% of the pathology tests in this region indicating that the data obtained was a good representation of the testing in the region. The highest estimated prevalence of *H. pylori* infection was 1.7% in socioeconomic percentile 4, which is considerably lower than the anticipated prevalence values [38]. This may be explained by demographic variations in Southern.IML Pathology's major areas of activity as well as unaccounted testing performed by competing pathology services in the same and peripheral areas.

Additionally, estimated prevalence was dependent on test utilisation. *H. pylori* infection is asymptomatic in many patients; therefore, no testing would have been undertaken. The prevalence rates quoted above included both symptomatic and asymptomatic people, but it is assumed that only symptomatic individuals are being screened for *H. pylori* infection in the current study. As only approximately 30% of infected individuals are symptomatic with upper gastrointestinal disease, this could reduce patient

presentation for testing [39]. Due to variable test utilisation rates, prevalence is likely to have been underestimated in the studied area.

Typically, asymptomatic patients are not screened for *H. pylori* infection, which means a large proportion of the population is untested, further limiting the accuracy of population prevalence estimates [40]. Mitchell and Katelaris [41] suggest a *H. pylori* infection prevalence in asymptomatic non-Indigenous Australians to be between 15.4% and 30.6%. This is contrasted by various studies determining higher asymptomatic *H. pylori* infection prevalence such as 74.4%, 67.7%, and 69.5% in Pakistan, Zimbabwe, and Oman, respectively [42–44]. Further controlled studies would be required to make a direct evaluation of community prevalence within the studied area before any population screening recommendations can be made. Another complication of the current study was that the socioeconomic percentile and population data were obtained from the 2016 census data [33]. This may have changed for the study period of 2018–2020. Further analysis conducted on the study dataset comparing the percentage positive values of each area could be beneficial in demonstrating a relationship between SES and *H. pylori* infection prevalence.

5. Strengths and Limitations of Study

The major strengths of this study were the large dataset and ability to compare detection methods. A further strength is that whilst some testing within this region may have been performed at other laboratories, approximately 90% of the testing in the community of the Illawarra Shoalhaven region is undertaken at Southern.IML Pathology. This leads to consistency in terms of the testing methods across the study period and limited missing data in the dataset analysed. Specific limitations have been recognised in this study and were reflective of the retrospective cohort study design and data availability, which was limited by data fields extracted and availability for analysis. As such, further clinical correlations could not be made. Increased clinical and demographical information would allow for further deductions and correlations and could include ethnicity, gender, comorbidities, symptom presentation, and eradication treatment postinfection detection. This could also include a better representation of the studied population, such as the inclusion of both symptomatic and asymptomatic individuals. This would allow for the calculation of more accurate prevalence rates in studied areas and provide a true reflection of SES and *H. pylori* infection prevalence variations.

6. Implications for Practice

The main implication of this study is to highlight that SAT is underutilised as a NIT method for *H. pylori* detection. Faecal sample collection is both noninvasive and does not require technical collection. Novel techniques utilising faecal polymerase chain reaction to identify antibiotic resistance targets may improve treatment outcomes by providing information on the choice of antibiotic therapy as well as diagnosis [12, 45]. Additionally, SAT has been offered as a potential

alternative to serology and UBT, especially following treatment of *H. pylori* infection or reinfection and with increasing age. Serology is currently overused and has been recognised to be ineffective in these situations.

7. Conclusion

SAT was underutilised compared to UBT or serology, this study has suggested that SAT is a viable alternative for use in older age groups, active infection, or eradication screening, which could have clinical implications within the Illawarra Shoalhaven and surrounding region. Additionally, a significant correlation was not seen between lower SES areas and higher *H. pylori* infection prevalence; however, low overall test utilisation, suggesting prevalence, is likely to have been underestimated in the studied area and may indicate reduced accessibility to healthcare. Further studies are required to determine the significance of these findings and potential impact on the studied area and other regional and rural areas.

Data Availability

The raw data used to support the findings of this study was provided by Southern.IML Pathology (3 Bridge Street, Coniston New South Wales, 2500). Requests for data 6 months after publication of this article will be considered by the corresponding author in conjunction with Southern.IML Pathology.

Conflicts of Interest

All authors declare that they have no conflicts of interest. The study design, aims, and methods are the original ideas of and wholly contributed by the authors.

Authors' Contributions

The authors confirm their contribution to the paper as follows. T. Wearne, C. Keighley, K.J. Mansfield, S. Nadeem, and B. Wilson were responsible for the study conception and design; data collection is not applicable. T. Wearne, C. Keighley, K.J. Mansfield, S. Nadeem, and B. Wilson were responsible for the analysis and interpretation of results. T. Wearne, C. Keighley, and K.J. Mansfield were responsible for the draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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Supplementary Materials

The table contains information for each commercially available noninvasive *H. pylori* detection method used in this study. Information includes test type, sample type/collection, test preparation, and test detection range as well as negative, equivocal, and positive result thresholds for each noninvasive test. (*Supplementary Materials*)

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