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Eradicating *Helicobacter pylori* via ^{13}C-urea breath screening to prevent gastric cancer in indigenous communities: a population-based study and development of a family index-case method

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ABSTRACT

Objective Screening and eradication of *Helicobacter pylori* help reduce disparities in the incidence of gastric cancer. We aimed to evaluate its acceptability and feasibility in the indigenous communities and develop a family index-case method to roll out this programme.

Design We enrolled residents aged 20–60 years from Taiwanese indigenous communities to receive a course of test, treat, retest and re-treat initial treatment failures with the ^{13}C-urea breath tests and four-drug antibiotic treatments. We also invited the family members of a participant (constituting an index case) to join the programme and evaluated whether the infection rate would be higher in the positive index cases.

Results Between 24 September 2018 and 31 December 2021, 15 057 participants (8852 indigenous and 6205 non-indigenous) were enrolled, with a participation rate of 80.0% (15 057 of 18 821 invitees). The positivity rate was 44.1% (95% CI 43.3% to 44.9%). In the proof-of-concept study with 72 indigenous families (258 participants), family members of a positive index case had 1.98 times (95% CI 1.03 to 3.80) higher prevalence of *H. pylori* than those of a negative index case. The results were replicated in the mass screening setting (1.95 times, 95% CI 1.61 to 2.36) when 1115 indigenous and 555 non-indigenous families were included (4157 participants). Of the 6643 testing positive, 5493 (82.6%) received treatment. According to intention-to-treat and per-protocol analyses, the eradication rates were 91.7% (89.1% to 94.3%) and 92.1% (89.2% to 95.0%), respectively, after one to two courses of treatment. The rate of adverse effects leading to treatment discontinuation was low at 1.2% (0.9% to 1.5%).

Conclusion A high participation rate, a high eradication rate of *H. pylori* and an efficient rollout method indicate that a primary prevention strategy is acceptable and feasible in indigenous communities.

Trial registration number NCT03900910.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Eradication of *Helicobacter pylori* infection can reduce the gastric cancer risk by about 50%.
⇒ Gastric cancer risks are twofold to threefold higher in indigenous individuals. The disparity is exacerbated by their poor uptake of and limited access to the disease prevention strategies.

WHAT THIS STUDY ADDS

⇒ Screening and eradication of *H. pylori* are possible and practical in indigenous communities with the structured design, organised execution and stepwise evaluation.
⇒ Unhealthy lifestyles are associated with a higher rate of *H. pylori* infection and a lower adherence rate to the programme.
⇒ The detection rate of *H. pylori* carriers is increased by twofold using a family index-case method to conduct outreach to the family members of individuals who test positive.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Mass screening using the family index-case method and actions to improve hygiene and lifestyles can accelerate the elimination of *H. pylori*-associated gastric cancer disparities in indigenous communities.

INTRODUCTION

Gastric cancer poses a significant threat to global health, with 1 089 103 new cases and 768 793 related deaths in 2020.[1] A unique feature of gastric cancer is the great variation in incidence rate by race/ethnicity and geography, with the disease tending to be more prevalent in populations with lower socioeconomic status and limited medical resources.[2] When the resilience of the healthcare systems is being stressed by eventful crisis such as the COVID-19 pandemic,[3] pre-existing disparities

are likely to be widened in any healthcare system, especially in one in which the infrastructure is not well prepared to bridge this gap.[4]

Gastric cancers are generated through chronic inflammation, which is mostly initiated by *Helicobacter pylori* infection, and then progresses from chronic gastritis to atrophic gastritis, intestinal metaplasia and eventually to gastric cancer.[5] The proportions of non-cardiac gastric cancer, cardiac gastric cancer and gastric non-Hodgkin's lymphoma attributable to *H. pylori* have been estimated as about 89%, 29% and 74%, respectively.[6]

In another study based on 512 715 Chinese adults, *H. pylori* infection was associated with about six times higher risk of non-cardiac gastric cancer and three times higher risk of cardiac gastric cancer.[7] Elucidating the natural course of gastric cancer and the causal role of *H. pylori* infection has prompted a paradigm shift, in which the emphasis traditionally placed on endoscopic early detection has shifted to mass screening and eradication of *H. pylori*. This transition overcomes the previous need to develop an intensive scheme for endoscopic screening and rely on a trained endoscopist workforce, while expanding the ability to arrest the progression of carcinogenesis.[8–10]

However, despite the unequivocal benefit from *H. pylori* eradication supported by randomised trials, cohort studies and cost-effectiveness analyses,[9] the population-wide application of this approach, beyond the scope of individual treatment, is rarely realised.[11] This gap partly results from the fact that the number of *H. pylori*-infected individuals tends to be large, without a sustainable goal with a staggered increase in the coverage rate; the result may be an unaffordable burden in the subsequent management of those who test positive. It is partly because the incidence of gastric cancer, correlating with the prevalence rate of *H. pylori* infection, differs so geographically and racially that such a programme needs to take into consideration the barriers resulting from cultural, administrative, geographical and economic distances.[4 12] Moreover, without the collaboration of healthcare policymakers, frontline general practitioners and the residents themselves, it is difficult to ensure that the quality of screening services can meet the population's expectations and that the programme can be made sustainable.[13]

Gastric cancer disparities are common in indigenous populations, such as Indigenous Australians, Maori in New Zealand, indigenous peoples from the circumpolar region, Native Americans and Alaska natives in the USA, and the Mapuche peoples in Chile; all show a disproportionally higher incidence rate than that of their non-indigenous counterparts.[14] A similar situation exists for the Taiwanese indigenous peoples, accounting for about 2.4% of the whole Taiwanese population. Their prevalence rate of *H. pylori* infection is as high as 60%, which is accompanied by an age-standardised gastric cancer incidence rate twofold to threefold higher than that of the overall population.[15] To tackle this cancer health disparity, a mass screening and eradication programme has been ongoing in Taiwanese indigenous communities. Using this unique opportunity, we tested the hypothesis that mass screening and eradication of *H. pylori* could be made acceptable and feasible for them. In addition, we developed a family index-case method as a means to roll out this programme.

METHODS

Study population and design of the programme

Our target population was the residents living in the 55 indigenous townships (736 tribes) in Taiwan.[16] Screening was designed as once in a lifetime for adults aged 20–60 years, at least 5 years before the mean age of gastric cancer diagnosis in indigenous peoples.[15] The workflow of the screening programme was developed by a multidisciplinary team that consisted of medical specialists, public health experts and indigenous culturists. To overcome the cultural distance, the team design, team launch and team process management were audited by a committee with representative members familiar with indigenous healthcare and culture, which was organised by policymakers from Health Promotion Administration (HPA), Taipei City, Taiwan.[17]

Prior to the screening, staff of the public health bureaus in charge of the indigenous townships were invited by HPA to join the programme. To overcome the geographical distance, a series of team-designed education activities were disseminated to the frontline physicians and public health workers. The target number of participants for each community was based on the local healthcare workforce and the annual budget. The HPA provided the population list and eligible residents were invited by the public health centres with self-designed approaches to receive screening for *H. pylori* infection. Pregnant or lactating women and patients with major comorbid diseases were excluded.

Upon screening, each participant's demographic data, social habits, family history and medical history were recorded and stored in an on-premises hosted software system (International Integrated Systems, Taipei City, Taiwan), in which the individual screening process could be traced, including the initial test results, referral to treatment, antibiotic regimens, compliance with treatment, occurrence of side effects and the retest results.[18] A phone call contact method was used to assess the compliance with antibiotic treatment and evaluate the occurrence of side effects.[19] Aggregating the above information generated the standardised quality indicators, so as to identify the bottlenecks in the workflow processes and overcome the administrative distance.

The reinfection of *H. pylori* had the potential to reduce the efficacies of the mass eradication programme.[20] Two years after successful eradication therapy, about 10% of participants were randomly selected from each community to receive retests to determine the reinfection rate.[21]

Development of the family index-case method

Most of our eligible subjects lived in either remote or high-mountain areas, so an efficient method was needed to increase the detection rate of *H. pylori,* given the limited resources. An index-case method was therefore proposed based on the clustering of *H. pylori* infection in families, related to the person-to-person transmission.[22–24] After the initial screening, the family members of those testing positive for *H. pylori* (constituting the positive index cases) would be subsequently contacted to receive screening. We only included family members who lived together in the same house. We hypothesised that, following this approach, the detection rate of *H. pylori* infection based on the positive index cases would be higher than that based on the negative index cases.[25] We selected a representative indigenous township to initiate a proof-of-concept study. Then, we verified the results in the mass screening setting when participants from different townships were enrolled.

Screening and treatment for *H. pylori*

The screening and treatment were provided free of charge, overcoming the economic distance. In subjects who had fasted for at least 4 hours, *H. pylori* infection was documented via the ^{13}C-urea breath test (Hwang's Pharmaceutical Company, Yunlin County, Taiwan). The test was chosen because of its non-invasiveness, relative ease of use and the high stability of isotope 13 carbon in storage and transport, in addition to a high

sensitivity and specificity of 95% or more.[26] Baseline and 30 min breath samples were assayed with an infrared spectrometer that produced computer-generated results in the certified laboratory (Taipei Institute of Pathology, Taipei City, Taiwan). Patients with inconclusive results received another ^{13}C-urea breath test. For the initial screenees, the family index-case method would be suggested to invite his/her family members to join the programme.

There was one public health centre in each indigenous township. With a standard print report, those who tested positive for *H. pylori* were contacted by the staff of public health centres and referred to the nearest or the most convenient public health centre to receive the anti-*H. pylori* treatment: a four-drug treatment course for 14 days (lansoprazole 30 mg plus amoxicillin 1 g for the first 7 days, followed by lansoprazole 30 mg, clarithromycin 500 mg and metronidazole 500 mg for another 7 days; all drugs given orally two times per day). This regimen was chosen as the first-line treatment because most participants either did not report any associated symptoms or were treatment-naïve for the eradication treatments. The sequential schedule was advantageous in identifying the drug, among a multidrug combination, responsible for any side effects or allergic reactions that occurred, in addition to showing an eradication rate as high as >90%.[27] Post-treatment, *H. pylori* status was assessed by another ^{13}C-urea breath test at 6–8 weeks after completion of treatment. For subjects with an allergic history to certain antibiotics, an alternative three-drug or four-drug treatment, replacing the allergic one, was prescribed. To facilitate the above process, a teleconsultation service was developed for the healthcare workers with the LINE group that enabled instant communication with the experts. The current health insurance in Taiwan did not reimburse the eradication treatment without an endoscopic diagnosis of peptic ulcers. Therefore, the medications, with the standardised regimen, dose and duration, were distributed from National Taiwan University Hospital after a centralised bidding process, ensuring the quality of treatment. We did not differentiate the treatment regimen depending on whether an eradication has been received previously because the information could not be ascertained. During treatment, we advised participants to reduce smoking as much as possible to increase the chances of successful treatment.[28]

Those who did not respond to the initial course were re-treated with a bismuth-based four-drug treatment for 10 days (lansoprazole 30 mg two times per day, bismuth (III) oxide 120 mg four times a day, amoxicillin 500 mg four times a day and tetracycline 500 mg four times a day; all drugs given orally).[29] For subjects who could not tolerate the bismuth-based treatment, a 10-day levofloxacin-based three-drug treatment (lansoprazole 30 mg two times per day, amoxicillin 1 g two times per day and levofloxacin 500 mg once daily; all drugs given orally) was prescribed. Cases with alarming symptoms or who failed two courses of antibiotic treatments were referred to the nearest hospital with facilities for endoscopic examination. In addition to any suspicious lesions, biopsy specimens (one from the gastric antrum and the other one from gastric body)[30] were collected and cultured on plates containing *Brucella* chocolate agar with 7% sheep blood and incubated for 14 days under microaerobic conditions. The minimum inhibitory concentrations were determined by the agar dilution test in the laboratory of the National Taiwan University Hospital or Kaohsiung Medical University Hospital. The resistance cut-off values for amoxicillin, clarithromycin, metronidazole, tetracycline and levofloxacin were defined as greater than 0.5, 1.0, 8.0, 0.5 and 1.0 mg/L, respectively.[31] The test was done to monitor the prevalence of antibiotic resistant strains or, in patients with repeated treatment failure, to design a tailored regimen.

Outcome

Our outcome was the acceptability and feasibility of this screening programme to achieve eradication, which was evaluated by answering whether the screening quality indicators could reach the minimal requirements set up by the team (online supplemental figure 1), beginning from completing a participation rate of ≥60%, attaining a positivity rate of ≥40%, receiving a referral-to-treatment rate of ≥60%, to achieving an eradication rate of ≥80%.

Statistical analysis

For baseline characteristics, categorical data were expressed as a percentage (%) and continuous data were expressed as mean (IQR). We compared categorical data using the χ^2 test and compared continuous data with the Student's t-test. The performance of the family index-case approach was verified by making a comparison of the *H. pylori* infection rates between the family members of the positive and negative index cases. Results were expressed as crude and adjusted ORs and the corresponding 95% CIs in a generalised estimating equation, taking into account the correlation within the family.[32]

For the screening quality indicators, the participation rate was defined as the number of participants divided by the number of invitees. The positivity rate was calculated as the number of positive test results divided by the number of participants. The referral-to-treatment rate was calculated as the number of individuals who received anti-*H. pylori* treatment divided by the number of positive test results. The intention-to-treat (ITT) and per-protocol (PP) analyses were carried out to assess the eradication rates. All patients who received anti-*H. pylori* treatment were included in the ITT analysis; the PP analysis included those who took more than 80% of treatment drugs or whose post-treatment *H. pylori* status was known. Univariate and multivariate logistic regression analyses were performed for each quality indicator to identify the risk factors significantly associated with the quality of screening. Results were expressed as crude and adjusted ORs and the corresponding 95% CIs. We applied the complete case analyses by removing missing data from the regression analyses as only about 5% of records were missing in the questionnaire data.

The reinfection rate was defined as the number of positive test results divided by the person-years of follow-up. Poisson regression analyses were used to evaluate the risk factors for reinfection. Statistical analyses were performed using SAS V.9.4 (SAS Institute). P values of <0.05 were considered statistically significant.

Role of the funding source

Staff from HPA were not only involved in this study as the funding source but also served as collaborators who made contributions to the design of the programme, the audit of quality indicators, the interpretation of results and the decision to submit this paper for publication.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

The participation rate and baseline data

Between 24 September 2018 and 31 December 2021, a total of 18 812 eligible subjects were invited in 40 of 55 indigenous

Table 1 Baseline characteristics of participants to the gastric cancer prevention programmes, with relationship to *Helicobacter pylori* infection

	Indigenous peoples (N=8852)		Non-indigenous peoples (N=6205)	
Baseline characteristics*	No of subjects	No of *H. pylori* carriers (%)	No of subjects	No of *H. pylori* carriers (%)
	8852	5055 (57.1)	6205	1588 (25.6)
Age, in years				
20–29	1221	620 (50.8)	737	82 (11.1)
30–39	2047	1129 (55.2)	1412	283 (20.0)
40–49	2470	1471 (59.6)	1979	532 (26.9)
50–60	3114	1835 (58.9)	2077	691 (33.3)
Sex				
Male	3144	1846 (58.7)	2313	609 (26.3)
Female	5708	3209 (56.2)	3892	979 (25.2)
Social habits				
Smoking				
Current	2269	1413 (62.3)	623	209 (33.5)
Former	1046	593 (56.7)	474	160 (33.8)
Never	5537	3049 (55.1)	5108	1219 (23.9)
Alcohol use				
Current	4905	2934 (59.8)	1671	486 (29.1)
Former	853	481 (56.4)	266	95 (35.7)
Never	3094	1640 (53.0)	4268	1007 (23.6)
Betel nut chewing				
Current	2468	1590 (64.4)	266	96 (36.1)
Former	990	589 (59.5)	313	102 (32.6)
Never	5394	2876 (53.3)	5626	1390 (24.7)

*The family history, medical history and ethnic groups are shown in the online supplemental table 1.

townships (representing 454 of 736 tribes) in Taiwan. Of these, a total of 15 057 participated (a participation rate of 80.0%, 95% CI 79.4% to 80.6%). There were no significant differences between participants and non-participants in terms of age (p=0.97) and sex (p=0.99). The most successful invitation strategies included the clinical services at the public health centres (22.4%), health screening services (21.8%), social activities (20.6%), telephone (20.0%), social media (9.7%) and the mail/email (5.5%).

Baseline characteristics of participants are shown in table 1 and online supplemental table 1. Overall, 9600 (63.8%) were women, with a mean age of 44.5 years (IQR 35.7–53.0). When we stratified the data into indigenous (n=8852) and non-indigenous subjects (n=6205), there were non-significant differences in the distribution of age, sex, family history related to *H. pylori*-associated diseases and medical history, except that the indigenous subjects had a higher prevalence of the social habits of smoking, alcohol drinking and betel nut chewing.

Positivity rates for *H. pylori* infection

Overall, the *H. pylori* positivity rate was 44.1% (95% CI 43.3% to 44.9%). Indigenous peoples had a higher positivity rate (57.1%) than that of their non-indigenous counterparts (25.6%) (table 1). The positivity rates increased with age. Those who had the habits of smoking, alcohol drinking and betel nut chewing had higher positivity rates. Those with a history of *H. pylori* infection had a lower positivity rate, likely related to their previous eradication treatments (online supplemental table 1).

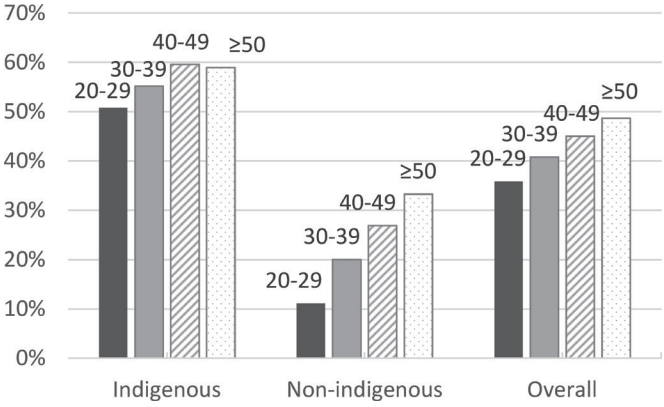

Figure 1 Prevalence rates of *Helicobacter pylori* infection by the age ranges (20–29, 30–39, 40–49 and ≥50 years), stratified by indigenous status.

When the data were stratified according to age range and indigenous status (figure 1), we found that the indigenous subjects aged 20–29 years already had a high infection rate (>50%), which then plateaued with age. By contrast, the infection rate in the non-indigenous subjects steadily increased with age from about 10% to 30%. These results may suggest that the intrafamilial transmission of *H. pylori* was more prevalent in indigenous families during childhood and adolescence.

Multivariable regression analyses (figure 2) consistently showed that the indigenous peoples had a significantly higher risk of *H. pylori* infection, whether they lived in the mountain areas or in the plains areas (adjusted ORs 3.59, 95% CI 3.25 to 3.95 and 2.24, 95% CI 1.96 to 2.55, respectively), as compared with non-indigenous peoples. Older age, current and former smoking (adjusted ORs 1.19, 95% CI 1.05 to 1.35 and 1.17, 95% CI 1.00 to 1.37, respectively, compared with never smoking), current alcohol drinking (adjusted OR 1.21, 95% CI 1.09 to 1.34, compared with never use), and current and former betel nut chewing (adjusted ORs 1.54, 95% CI 1.35 to 1.75 and 1.24, 95% CI 1.05 to 1.47, respectively, compared with never use) were also significantly associated with a higher positivity rate.

Verification of the family index-case method

This approach was first evaluated in Wulai District (New Taipei City, Taiwan). In this proof-of-concept study, a total of 72 index cases participated in the initial screening, including 48 tested positive for ^{13}C-urea breath test (the positive index case) and 24 tested negative (negative index case). The mean number of relatives per family was 3.6 (IQR: 2). Two representative family structures are shown in figure 3. The infection–pedigree relationships of 258 participants (72 families) are shown in the online supplemental table 2A. The results indicated that family members from the positive index case were associated with a higher risk of *H. pylori* infection than those of the negative index cases (adjusted OR 1.98, 95% CI 1.03 to 3.80), adjusted for the age, sex and smoking habit (online supplemental table 3A). Current and former smokers were also associated with the higher risk than never smokers (adjusted OR 2.87, 95% CI 1.17 to 7.02 and 2.87, 95% CI 1.31 to 6.33, respectively).

There were 43 couples, 27 siblings and 97 parent–child relationships among the 72 families. Their consanguinity relationships are shown in online supplemental table 2B. The positive index case was significantly associated with a higher risk of infection in his/her parent or children (OR 2.89, 95% CI 1.18 to

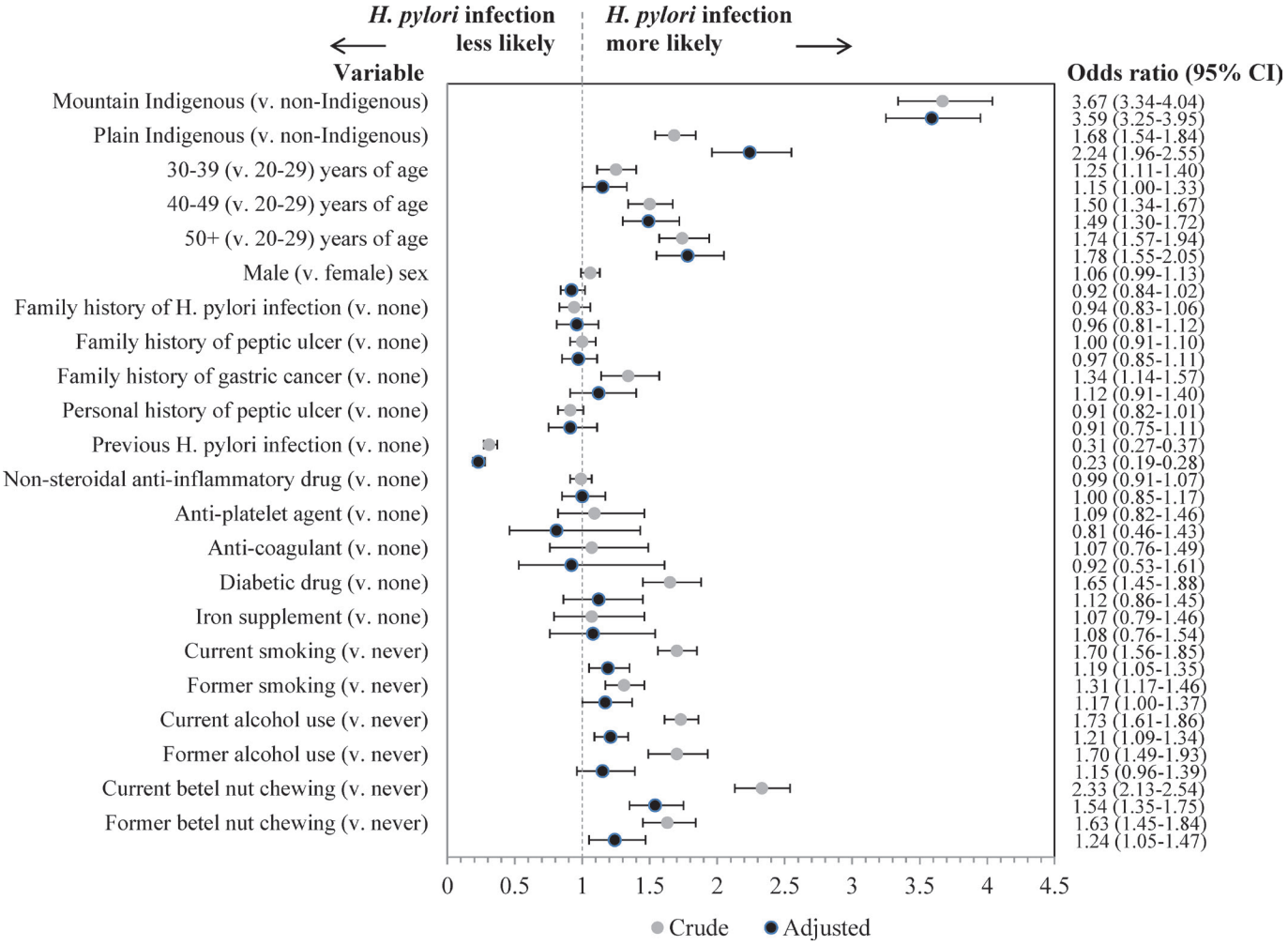

Figure 2 Risk factors associated with 6643 positive results of the ^{13}C-urea breath tests among 15 057 participants in the indigenous communities. The multivariable model, adjusted for all variables, is shown in the forest plot. An OR greater than 1.0 (dotted line) indicates an increased risk of *Helicobacter pylori (H. pylori*) infection.

7.05, p=0.02) than the negative index case. A higher infection risk was seen in the siblings (OR 2.08, 95% CI 0.39 to 11.06, p=0.39) but the result was not significant due to the small case number. There was no significant difference in the couples (OR 1.08, 95% CI 0.28 to 4.13, p=0.91).

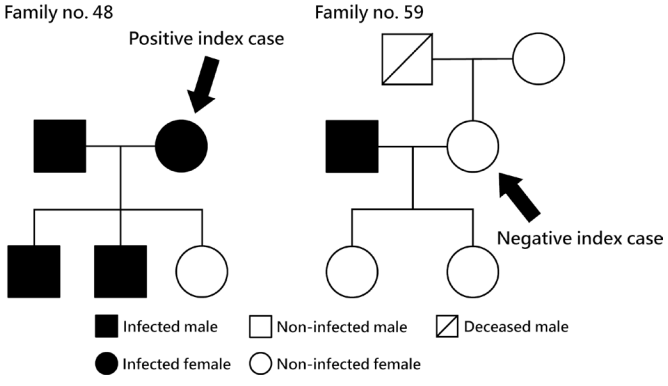

Figure 3 The infection–pedigree relationships of two indigenous families in the proof-of-concept study to demonstrate the rationale of the family index-case method. The prevalence rate of *Helicobacter pylori* infection in the family members of the positive index case will be about twofold higher than that in the family members of the negative index case due to intrafamilial transmission. The two families are the numbers 48 and 59 shown in the online supplemental table 2A.

In the mass screening setting, there were 1670 initial screenees (777 positive and 893 negative index cases) who had subsequent family outreach, totalling 4157 individuals (4157 of 15 057, 27.6%) within 1115 indigenous and 555 non-indigenous families. Consistently, family members of the positive index case were associated with a higher risk of *H. pylori* infection than those of the negative index cases (adjusted OR 1.95, 95% CI 1.61 to 2.36, adjusted for the age, sex, indigenous status and smoking habit) (online supplemental table 3B). Older age, indigenous people and current smokers were also associated with the higher risk (adjusted ORs 1.22, 95% CI 1.13 to 1.32; 2.31, 95% CI 1.88 to 2.84; and 1.51, 95% CI 1.20 to 1.90, respectively).

Referral-to-treatment rates

Among the 6643 subjects testing positive, 5493 (82.7%) were successfully referred to receive anti-*H. pylori* treatment. The results, stratified by age, sex and indigenous status, are shown in the online supplemental table 4 and indicated that indigenous subjects (adjusted ORs 1.70, 95% CI 1.26 to 2.29 and 2.53, 95% CI 1.89 to 3.40, respectively, for the mountain and plains indigenous subjects) and those in younger age groups had lower referral-to-treatment rates (relative to the 20–29 years age

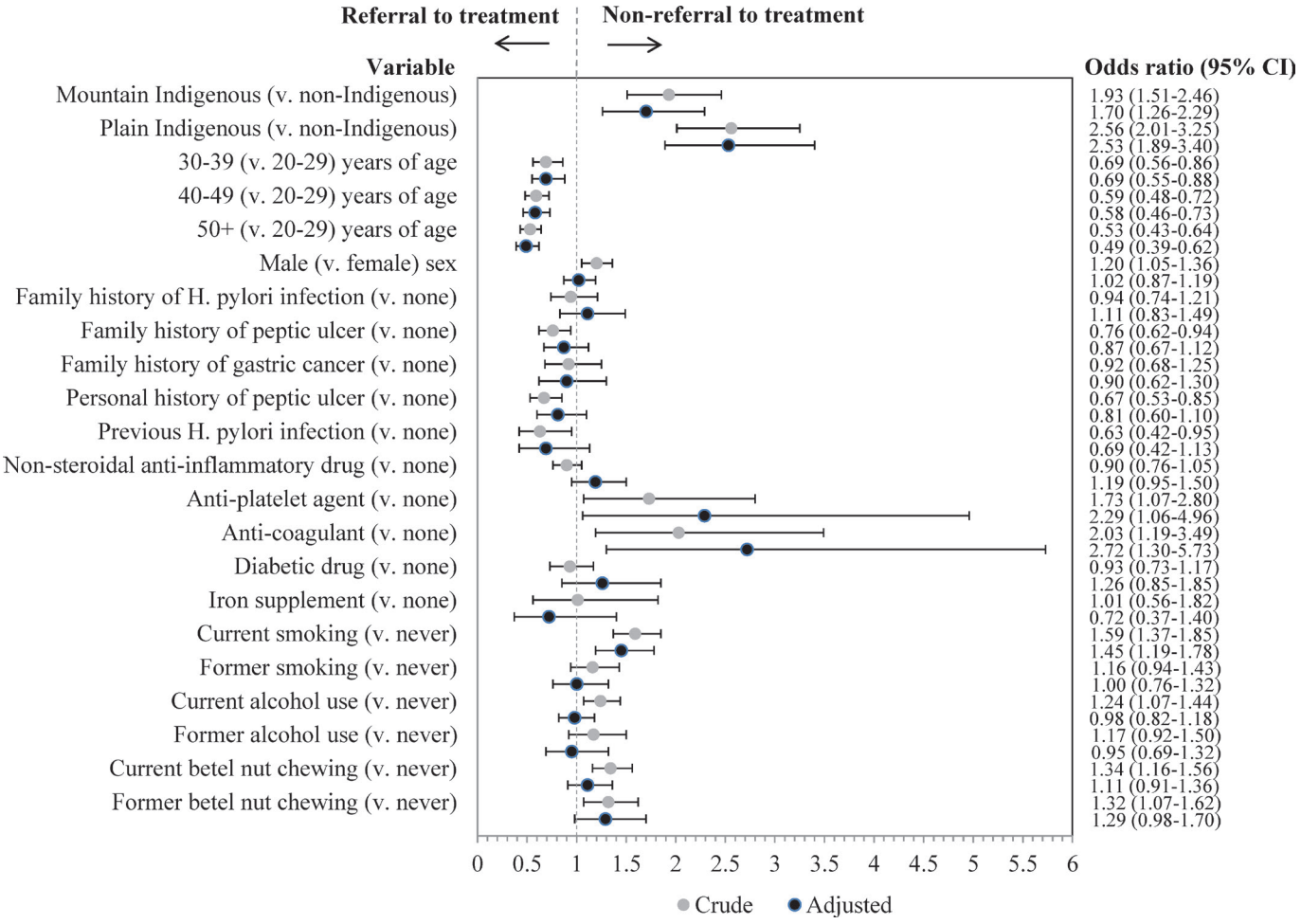

Figure 4 Risk factors associated with the 1150 non-referrals among 6643 participants who tested positive for *Helicobacter pylori (H. pylori)* infection. The multivariable model, adjusted for all variables, is shown in the forest plot. An OR greater than 1.0 (dotted line) indicates an increased risk of non-referral to treatment.

group: 30–39 years: adjusted OR 0.69, 95% CI 0.55 to 0.88; 40–49 years: adjusted OR 0.58, 95% CI 0.46 to 0.73; and 50–60 years: adjusted OR 0.49, 95% CI 0.39 to 0.62) (figure 4). Use of antiplatelet (adjusted OR 2.29, 95% CI 1.06 to 4.96) and anticoagulant drugs (adjusted OR 2.72, 95% CI 1.30 to 5.73) was also associated with a lower referral-to-treatment rate, likely related to the presence of comorbidities. Current smokers also had a lower referral-to-treatment rate (adjusted OR 1.45, 95% CI 1.19 to 1.78).

Eradication rates

According to the ITT and PP analyses, the eradication rates were 91.7% (95% CI 89.1% to 94.3%) and 92.1% (89.2% to 95.0%), respectively, after one or two courses of treatment (table 2). Specifically for the first-line treatment, the eradication rates were 78.5% (76.3% to 80.8%) and 79.5% (77.2% to 81.7%) in the ITT and PP analyses, respectively; the results for the second-line treatment were 61.3% (59.6% to 63.1%) and 61.3% (59.4% to 63.3%), respectively. Multivariable regression analyses of the first-line treatment indicated that males were less likely associated with treatment failure (adjusted OR 0.82, 95% CI 0.68 to 0.98). Treatment failure was significantly associated with having a history of peptic ulcer (adjusted OR 1.35, 95% CI 1.02 to 1.79), having a history of *H. pylori* infection (adjusted OR 1.70, 95% CI 1.14 to 2.54) and current smoking (adjusted OR 1.38, 95% CI 1.10 to 1.73, compared with never smoking) (figure 5). However, the former smokers were not associated with the risk of treatment failure (adjusted OR 1.17, 95% CI 0.88 to 1.57, compared with never smoking).

The results for the PP analyses were mostly similar (online supplemental figure 2). Those who used iron supplements had a lower risk of eradication failure (adjusted OR 0.33, 95% CI 0.12 to 0.92) in the ITT analyses but not in the PP analyses (adjusted OR 0.38, 95% CI 0.14 to 1.07). Majority of subjects (155 of 166, 93.4%) who used the iron supplement were female, likely for the indication of iron-deficiency anaemia related to the gynaecological diseases. Being in an older age group was associated with a lower risk of treatment failure (compared with those aged 20–29: 40–49 years: adjusted OR 0.62, 95% CI 0.47 to 0.82; 50–60 years: adjusted OR 0.76, 95% CI 0.58 to 0.99). However, this significance was not observed in the PP analyses, which could be explained by the lower compliance-to-treatment rate in the younger age groups.

Side effects were generally uncommon but included allergic reaction (0.4%), nausea and vomiting (1.2%), headache (1.0%), diarrhoea (1.1%), and epigastric pain and poor appetite (0.4%). The rate of adverse effects leading to treatment discontinuation was low at 1.2% (95% CI 0.9% to 1.5%).

Antibiotic resistance rates

A total of 334 *H. pylori* carriers underwent antibiotic susceptibility tests to evaluate the primary resistance rates (table 3). The

Table 2 *Helicobacter pylori* eradication rates after one or two courses of antibiotic treatments, stratified by age and sex

Baseline characteristics	No of participants	Test positive, no (%)	Referral, no (%)	Eradication rate, intention-to-treat analysis, % (95% CI)*	Eradication rate, per-protocol analysis, % (95% CI)†
Indigenous peoples					
Male					
20–39	1197	648 (54.1)	499 (77.0)	89.6 (84.7 to 94.8)	92.1 (87.0 to 97.5)
40–60	1947	1198 (61.5)	974 (81.3)	92.5 (88.4 to 96.7)	92.4 (88.4 to 96.6)
Subtotal	3144	1846 (58.7)	1473 (79.8)	91.5 (88.4 to 94.8)	92.2 (89.1 to 95.5)
Female					
20–39	2071	1101 (53.2)	876 (79.6)	87.4 (83.8 to 91.3)	88.9 (85.2 to 92.8)
40–60	3637	2108 (58.0)	1802 (85.5)	91.5 (88.5 to 94.5)	91.1 (88.2 to 94.1)
Subtotal	5708	3209 (56.2)	2678 (83.5)	90.2 (87.9 to 92.6)	90.4 (88.1 to 92.8)
Both sexes					
20–39	3268	1749 (53.5)	1375 (78.6)	88.2 (85.2 to 91.2)	90.0 (87.0 to 93.1)
40–60	5584	3306 (59.2)	2776 (84.0)	91.8 (89.4 to 94.2)	91.6 (89.2 to 94.0)
Total	8852	5055 (57.1)	4151 (82.1)	90.7 (88.8 to 92.6)	91.0 (89.2 to 93.0)
Non-indigenous peoples					
Male					
20–39	856	148 (17.3)	123 (83.1)	93.5 (87.5 to 100)	93.8 (87.7 to 100)
40–60	1457	461 (31.6)	394 (85.5)	93.6 (88.9 to 98.6)	94.2 (89.5 to 99.2)
Subtotal	2313	609 (26.3)	517 (84.9)	93.6 (89.9 to 97.5)	94.2 (90.4 to 98.1)
Female					
20–39	1293	217 (16.8)	179 (82.5)	91.8 (86.9 to 97.0)	88.8 (84.0 to 93.7)
40–60	2599	762 (29.3)	646 (84.8)	96.1 (92.5 to 99.9)	96.3 (92.7 to 100)
Subtotal	3892	979 (25.2)	825 (84.3)	95.3 (92.4 to 98.3)	95.4 (92.4 to 98.4)
Both sexes					
20–39	2149	365 (17.0)	302 (82.7)	92.6 (88.7 to 96.6)	91.2 (87.4 to 95.2)
40–60	4056	1223 (30.2)	1040 (85.0)	95.1 (92.2 to 98.1)	95.5 (92.6 to 98.5)
Total	6205	1588 (25.6)	1342 (84.5)	94.6 (92.3 to 97.0)	94.9 (92.6 to 97.3)
Overall	15 057	6643 (44.1)	5493 (82.7)	91.7 (89.1 to 94.3)	92.1 (89.2 to 95.0)

*The intention-to-treat analysis includes those who received the *H. pylori* eradication.
†The per-protocol analysis includes those who received the *H. pylori* eradiation and took at least 80% of medication.

resistance rates to amoxicillin, clarithromycin, metronidazole, tetracycline and levofloxacin were 7.2%, 26.0%, 39.2%, 6.6% and 25.5%, respectively. The resistance rates did not significantly differ by age (20–39 vs 40–60 years). However, results stratified by sex indicated that females had a higher rate of resistance to metronidazole (47.8% vs 26.0%, p<0.001) and to tetracycline (8.9% vs 3.1%, p=0.048), which may explain the lower eradication failure rate in males in both the ITT and PP analyses (figure 5 and online supplemental figure 2).

Reinfection rates

Among 498 cases who received successful eradication therapy, 25 cases had documented reinfection (online supplemental table 5). Over the 1569 person-years of follow-up, the reinfection rate was estimated as 1.59% (95% CI 1.08% to 2.34%). Indigenous subjects had a higher risk of reinfection than their non-indigenous counterparts (rate ratio 3.07, 95% CI 0.72 to 13.2). The social habits of current and former smoking (rate ratios 2.72, 95% CI 1.03 to 7.16 and 3.09, 95% CI 1.18 to 8.31, respectively, compared with never smoking), current alcohol drinking (rate ratio 2.69, 95% CI 1.01 to 7.17, compared with never use), and current and former betel nut chewing (rate ratios 3.59, 95% CI 1.52 to 8.45 and 3.25, 95% CI 1.02 to 10.36, compared with never use) were significantly associated with a higher risk of reinfection (online supplemental figure 3).

DISCUSSION

Taiwanese indigenous peoples are linguistically and culturally associated with Austronesia. Their communal lifestyles and pan-spiritual traditional beliefs form a unique social system and interpersonal network.[33] In addition to the economic and social inequalities, they have experienced limited access to the qualified and timely healthcare. In the present study, with a three-tier foundation of input from policymakers, frontline general practitioners and the target communities, we prove that mass screening and eradication of *H. pylori* are achievable in indigenous communities where the barriers to any preventive intervention are generally the greatest. In addition to the foreseeable benefit from *H. pylori* eradication in a highly prevalent area, our programme provides a pragmatic method that can be readily generalised to other populations with similar gastric cancer health disparities, by reaching out to the family members of *H. pylori* carriers, mapping out the processes of screening and relieving any bottlenecks in resource allocation, to maximise the throughput and create a sustainable system.

There are two kinds of gastric cancer preventive interventions: primary prevention with screening and eradication of *H. pylori* infection, and secondary prevention with periodical endoscopic screening.[34] In this study designed for disadvantaged minorities using the first approach, we noted a high prevalence rate of *H. pylori* infection, together with the presence of multiple unhealthy lifestyle factors that may simultaneously

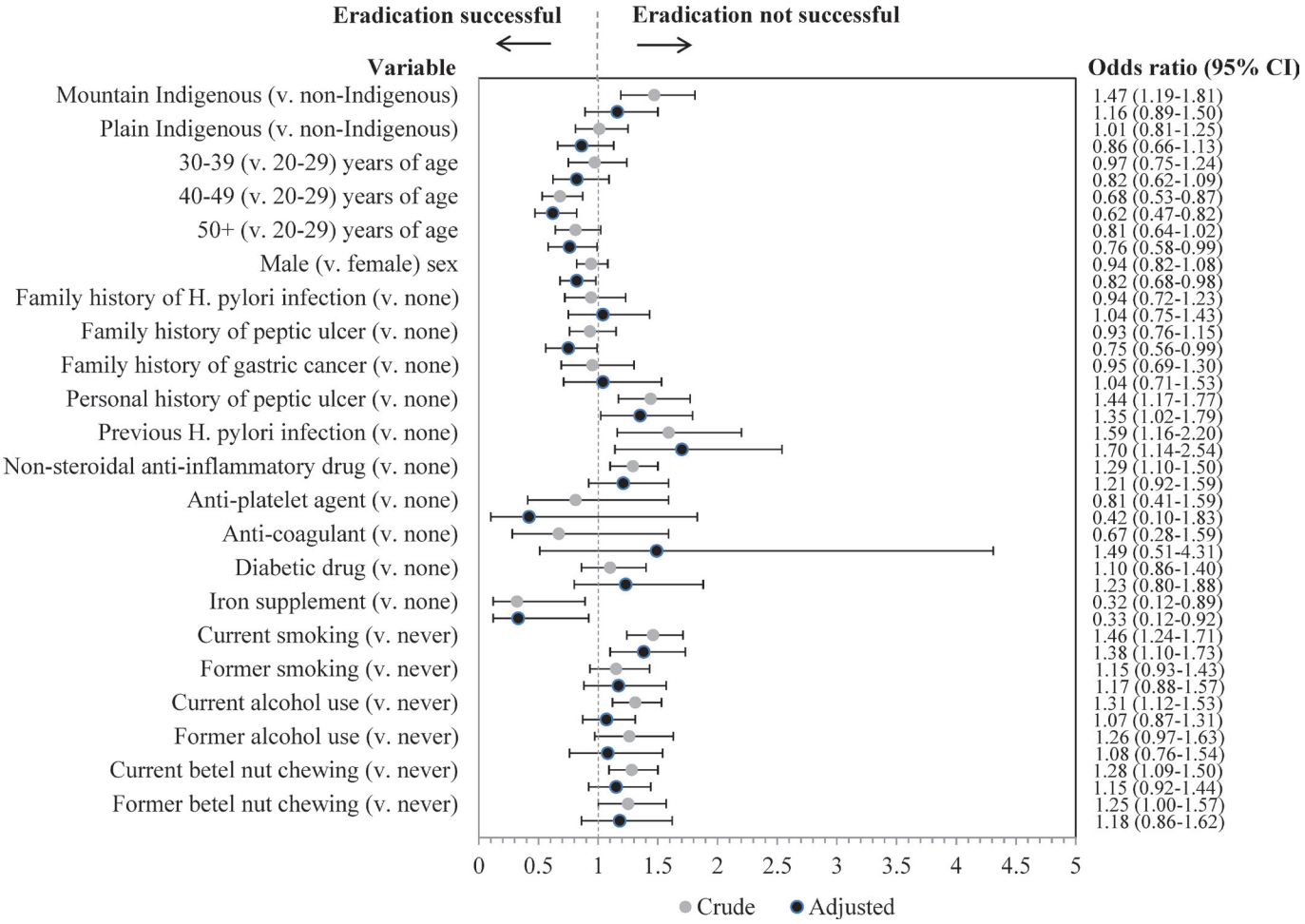

Figure 5 Risk factors associated with the 1024 treatment failures among 5493 subjects who received the first-line treatment for *Helicobacter pylori (H. pylori)* infection, according to the intention-to-treat analyses. The multivariable model, adjusted for all variables, is shown in the forest plot. An OR greater than 1.0 (dotted line) indicates an increased risk of treatment failure.

increase the risk of other cancers in the upper aero-digestive tract, such as oral cancer, hypopharyngeal cancer, oesophageal cancer and lung cancer. Similarly, these demonstrated cancer health disparities collectively contribute to the lower life expectancy of indigenous populations, about 8 years on average.[35] The higher infection rate in the indigenous peoples was likely related to the oral–oral, faecal–oral or gastro–oral transmission prevalent in the families,[36] which was supported by their higher infection rate in the young age group and the higher possibility of coinfection in the parent/children and sibling relationships than that in the couples. This should be prevented by improving hygiene behaviours.

Furthermore, not only are unhealthy lifestyle habits associated with a higher positivity rate of *H. pylori* infection, they are also associated with a lower referral-to-treatment rate, a lower eradication rate and a higher reinfection rate, slowing down the system workflow. Therefore, our study indicated that improving stomach health can serve as an opportunity to raise population awareness about the importance of health-promotion lifestyles and provide synergic effects to improve upper digestive tract health as a whole.[37]

Two interesting findings were observed regarding the efficacies of antibiotic treatment. First, only the habit of active smoking but not the former smoking or the never smoking was significantly associated with treatment failure, which lent support to the fact that smoking can increase the acidity of the stomach, increasing the proportion of non-replicative bacteria and making it more difficult for antibiotics to work effectively.[28] Although we have advised the smokers to minimise smoking during treatment, the higher failure rate indicated the poor adherence to this advice. Second, *H. pylori* infection has been documented as a potential cause of iron-deficiency anaemia and treatment failure of iron supplementation.[38] In our study, we did not ask the participants to stop iron supplements during *H. pylori* eradication although gastric acid was required to increase the solubility and uptake of ferric iron. Surprisingly, we observed a better eradication rate in the users of iron supplements. As iron is essential for bacterial replication,[39] we suspected that the iron supplements may promote the growth of *H. pylori* into the replicative phase when it is more susceptible to the antibiotic treatment. This assumption requires further observations.

The strengths of our study include a healthcare system-level approach in delivering an organised screening service, an efficient approach in increasing the detection of *H. pylori* infection, quality assurance with the design of standardised performance indicators that are digitally assessable and the evaluation of outcomes in the context of a pragmatic study in indigenous communities. The similar magnitude of infection risk observed in both the indigenous or non-indigenous families supported the generalisability of the family index-case method. However, our study has limitations. First, it is known that the eradication rate of *H. pylori* is determined by patient compliance with treatment

Table 3 Primary antibiotic resistance rates of *Helicobacter pylori* in the Taiwanese indigenous communities

	Primary resistance rate of *H. pylori*		
MIC analyses*	Male (n=131)	Female (n=203)	Total (n=334)
Amoxicillin			
Age, in years			
20–39	4/24 (16.7%)	0/43 (0%)	4/67 (6.0%)
40–60	6/107 (5.6%)	14/160 (8.8%)	20/267 (7.5%)
Total	10/131 (7.6%)	14/203 (6.9%)	24/334 (7.2%)
Clarithromycin			
Age, in years			
20–39	8/24 (33.3%)	9/43 (20.9%)	17/67 (25.4%)
40–60	23/107 (21.5%)	47/160 (29.4%)	70/267 (26.2%)
Total	31/131 (23.7%)	56/203 (27.6%)	87/334 (26.0%)
Metronidazole			
Age, in years			
20–39	6/24 (25.0%)	21/43 (48.8%)	27/67 (40.3%)
40–60	28/107 (26.2%)	76/160 (47.5%)	104/267 (39.0%)
Total	34/131 (26.0%)	97/203 (47.8%)	131/334 (39.2%)
Tetracycline			
Age, in years			
20–39	2/24 (8.3%)	3/43 (7.0%)	5/67 (7.5%)
40–60	2/107 (1.9%)	15/160 (9.4%)	17/267 (6.4%)
Total	4/131 (3.1%)	18/203 (8.9%)	22/334 (6.6%)
Levofloxacin			
Age, in years			
20–39	6/24 (25.0%)	13/42 (31.0%)	19/66 (28.8%)
40–60	30/106 (28.3%)	35/157 (22.3%)	65/263 (24.7%)
Total	36/130 (27.7%)	48/199 (24.1%)	84/329 (25.5%)

*The resistance cut-off values for amoxicillin, clarithromycin, metronidazole, tetracycline and levofloxacin were defined as greater than 0.5, 1.0, 8.0, 0.5 and 1.0 mg/L, respectively.
MIC, minimum inhibitory concentration.

and by bacterial resistance to antibiotics.[40] Although our overall eradication rate could reach 90% after a test–treat–retest–re-treat course, there was room for improvement. As the efficacies of the ITT and PP analyses were similar to each other, our findings indicated that the major obstacle was the higher antibiotic resistance rates in the indigenous communities. Consistently, the observed resistance rates to amoxicillin, clarithromycin, metronidazole, tetracycline and levofloxacin were 7.2%, 26.0%, 39.2%, 6.6% and 25.5%, respectively, which were all higher than those observed in the general Taiwanese population (2.4%, 16.0%, 28.5%, 2.4% and 11.1%, respectively).[27 29] Solutions may include the selection of a regimen with a higher potency of acid suppression, a higher dose/duration of antibiotics or the use of less exposed antibiotics; choices must be weighed in the light of population compliance and follow the principle of antibiotic stewardship.[41] Second, similar to those designed for the screening of other prevalent cancers,[42] our quality indicators are readily generalisable for mass screening and eradication for *H. pylori* infection; however, the minimal requirement levels may need to be adjusted in a compliance-resistant population. Finally, the long-term goal of this programme is to reduce the rate of newly occurring gastric cancer,[43] which requires continuous observation of the trend in gastric cancer incidence and quantification of the magnitude of any declines, as adopted in our previous study with the number needed to treat of about 170 to prevent one gastric cancer.[9 11]

In conclusion, our study indicates that our plan for the mass screening and eradication of *H. pylori* is acceptable and feasible for the minority ethnic groups in Taiwan with a high prevalence of *H. pylori* infection and a high incidence of gastric cancer. The various barriers to success can be overcome by placing a strong foundation, developing an efficient method and auditing the quality indicators for screening. This plan of action provides the essential details to improve gastric cancer control by eliminating exposure to risk factors, efficiently reducing the existing health inequalities of this infection-associated cancer.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval This study involves human participants and the Research Ethics Committee of National Taiwan University Hospital (201804108RINB) and the Council

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