1

APPENDIX

This appendix has been provided by the authors to give readers additional information about the work.

Supplement to: Lei WY, Lee JY, Chuang SL, *et al*. Eradicating *Helicobacter pylori* via ¹³C-urea breath screening to prevent gastric cancer in indigenous communities: A population-based study and development of a family index-case method

Item	Description
Supplementary Table 1	Baseline characteristics of participants for the family history, medical history, and ethnic groups, with relationship to *Helicobacter pylori* infection
Supplementary Table 2	The infection-pedigree relationships in a representative Taiwanese indigenous township in the proof-of-concept study. (A) *H. pylori* infection status of the index case and his/her family members, and (B) *H. pylori* infection status in the consanguinity relationship
Supplementary Table 3	The risk of *H. pylori* infection according to the status of the index case and his/her family members. (A) Results in the proof-of-concept study and (B) results in the mass screening setting
Supplementary Table 4	Referral-to-treatment rate in the participants who tested positive for *H. pylori* infection and results of the first-line eradication treatment
Supplementary Table 5	Reinfection rates of *H. pylori* in the Taiwanese indigenous communities
Supplementary Fig. 1	The workflow of the screening and eradication program
Supplementary Fig. 2	Risk factors associated with the 797 treatment failure among 4601 subjects who received the first-line treatment for *H. pylori* infection according to the per-protocol analyses
Supplementary Fig. 3	Risk factors associated with the 25 reinfection of *H. pylori* after successful eradication in 498 subjects

Supplementary Table 1. Baseline characteristics of participants for the family history, medical history, and ethnic groups, with relationship to *Helicobacter pylori* infection

Baseline characteristics	Indigenous peoples (N=8852)		Non-indigenous peoples (N=6205)	
	No. of subjects	No. of *H. pylori* carriers (%)	No. of subjects	No. of *H. pylori* carriers (%)
	8852	5055 (57.1)	6205	1588 (25.6)
Family history				
Family history of *H. pylori* infection	681	360 (52.9)	437	117 (26.8)
Family history of peptic ulcer	1135	630 (55.5)	695	177 (25.5)
Family history of gastric cancer	489	274 (56.0)	139	47 (33.8)
Medical history				
Personal history of peptic ulcer	1075	538 (50.0)	446	101 (22.6)
Previous *H. pylori* infection	710	172 (24.2)	374	56 (15.0)
Non-steroidal anti-inflammatory drug user	1958	1132 (57.8)	1343	316 (23.5)
Anti-platelet agent user	130	69 (53.1)	58	18 (31.0)
Anti-coagulant user	97	51 (52.6)	43	13 (30.2)
Diabetic drug user	754	463 (61.4)	223	82 (36.8)
Iron supplement user	113	64 (56.6)	53	9 (17.0)
Ethnic groups[*]				
Amis	2683	1331 (49.6)	-	-
Bunun	1394	940 (67.4)	-	-
Cou	12	9 (75)	-	-
Hla'alua	22	13 (59.1)	-	-

Kanakanavu	28	21 (75)	-	-
Kebalan	37	20 (54.1)	-	-
Paiwan	1168	656 (56.2)	-	-
Puyuma	300	169 (56.3)	-	-
Rukai	302	189 (62.6)	-	-
Sakizaya	23	10 (43.5)	-	-
Say-Siyat	5	1 (20)	-	-
Seediq	96	61 (63.5)	-	-
Tao/Yami	193	100 (51.8)	-	-
Taroko	1669	1000 (59.9)	-	-
Tayal	822	492 (59.9)	-	-
Missing values	98	43 (43.9)	-	-

[*] There were 16 officially recognized ethnic groups in Taiwanese indigenous peoples. Every ethnic group has its own distinct culture, language, customs and social structure.

4

Supplementary Table 2. The infection-pedigree relationships in a representative Taiwanese indigenous township in the proof-of-concept study

(A) *H. pylori* **infection status of the index case and his/her family members**

Family no.	Family name	Index case (age)	Family member (age)					
1	C1	●22	●40	■45	●21			
2	C10	■49	●22	■29	□28	●52	○24	●21
3	C11	●30	●63	■25	■67	■31	■43	
4	C12	■64	■41	●50	○63			
5	C14	●54	■57	●32	●54	○45	●24	
6	C16	○48	■65	□20	■55	□27		
7	C17	■46	□16	○38				
8	C18	○55	■60	●23	□30	○34		
9	C19	■64	○62					
10	C2	○56	■54	●54				
11	C20	■58	○55	●36	□37	■34		
12	C21	●56	□19	□55				
13	C22	●70	□36	○35				
14	C23	●37	○28					
15	C24	●49	□50	●29				
16	C25	●56	○27	■32	■31	■38		
17	C27	■62	■29	●60	□40			
18	C28	■26	■49	●26				
19	C29	■62	●66	■37				
20	C3	●54	□29	■60	□31	○28		
21	C30	■42	○28					
22	C31	■44	●55	■29				
23	C32	■61	●60					
24	C33	□30	○28	○60				
25	C4	○32	○59	■34				

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Gut

5

26	C5	○65	■66				
27	C6	□38	●38	○70			
28	C7	●43	■43	○76	●31		
29	C8	□58	■24				
30	F1	●53	□59	●29	■26		
31	F10	●52	■40	●34	●37		
32	F11	■27	■53				
33	F12	■69	●61	■45			
34	F13	●70	●41	●46	□44	■45	
35	F14	■86	□60	○49	●48	○85	■58
36	F15	●37	□68	■35	■46	●61	
37	F17	●53	●26	●21			
38	F2	○68	■67				
39	F3	●42	●33	●66			
40	F4	●40	□43				
41	F5	●43	○15	■76	□40		
42	F6	□52	○47				
43	F9	■72	●38	■50	●48	●66	□45
44	S1	○72	●52	○50			
45	S2	■34	□32	■31	●53	●27	
46	W1	●52	■55	■24	■28	●26	
47	W12	■67	●39				
48	W15	●56	■61	■38	■35	○35	
49	W16	○53	■31	●32	●29	●31	
50	W17	○58	■36	■61			
51	W18	○32	■39	■63			
52	W19	■48	●11	■18			
53	W20	○58	●33				
54	W21	●51	○24	■28			

55	W22	○31	○36	●23	○57	□53	
56	W23	□50	○50	□23			
57	W28	●42	■47	●44	○43		
58	W3	○62	□65	■30			
59	W30	○54	○81	○29	■61	○32	
60	W31	●58	■61				
61	W32	□43	■79	●69	□47	○35	□27
62	W33	○55	○22	□57			
63	W35	●61	■61	□27			
64	W36	○50	□22	○25	■54		
65	W37	●61	■40	●36			
66	W38	■56	●81	□88			
67	W40	□61	■30	●28			
68	W41	■71	●46				
69	W6	○33	○61	■69	○41		
70	W7	●57	●68	■63			
71	W8	●46	■53	□18	●20		
72	W9	●61	□58	●35			

A square indicates the male sex and a circle indicates the female sex. The black color indicates the positivity for the *H. pylori* infection while the white color indicates negativity.

* In the proof-of-concept study, there was no age restriction for enrollment.

(B) *H. pylori* infection status in the consanguinity relationship

	Spouse +	Spouse –
Index case +	19	11
Index case –	8	5
	Sibling +	Sibling –
Index case +	13	5
Index case –	5	4
	Parent-child +	Parent-child –
Index case +	48	19
Index case –	14	16

+ indicates *H. pylori* infection; – indicates *H. pylori* non-infection

Supplementary Table 3. The risk of *H. pylori* infection among the family members according to the status of the index case and his/her family members

(A) Results in the proof-of-concept study

	OR	95% CI	aOR*	95% CI
Status of the index case[†]				
[13]C UBT results				
Negative index case	1		1	
Positive index case	1.89	0.97–3.66	1.98	1.03–3.80
Age				
Increase of 10 years	0.99	0.77–1.28	0.96	0.74–1.25
Sex				
Female	1		1	
Male	0.81	0.43–1.55	0.55	0.27–1.10
Smoking				
Never	1		1	
Former	2.51	1.05–6.05	2.87	1.17–7.02
Current	2.98	1.43–6.23	2.87	1.31–6.33

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; UBT, urea breath test
* Adjusted for the age, sex, and the smoking habit in the generalized estimated equation models.
[†] All the participants in the proof-of-concept study were indigenous.

(B) Results in the mass screening setting

	OR	95% CI	aOR*	95% CI
Status of the index case				
[13]C UBT results				
Negative index case	1		1	
Positive index case	2.28	1.90–2.74	1.95	1.61–2.36
Indigenous status[†]				
Non-indigenous	1		1	
Indigenous	2.68	2.20–3.27	2.31	1.88–2.84
Age				
Increase of 10 years	1.22	1.14–1.31	1.22	1.13–1.32
Sex				
Female	1		1	
Male	1.28	1.08–1.52	1.15	0.95–1.39
Smoking				
Never	1		1	
Former	1.38	1.07–1.77	1.13	0.85–1.50
Current	1.84	1.49–2.27	1.51	1.20–1.90

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; UBT, urea breath test
* Adjusted for the age, sex, smoking habit, and the indigenous status in the generalized estimated equation models.
[†] Participants in the mass screening setting included both indigenous and non-indigenous peoples.

Supplementary Table 4. The referral-to-treatment rate in the participants who tested positive for *H. pylori* infection and results of the first-line eradication treatment

	No. of participants	Test positive, no. (%)	First-line treatment		
			Treat, no. (%)	Re-test, no. (%)	Re-test positive, no. (%)
Indigenous peoples					
Male					
20–39	1197	648 (54.1)	499 (77.0)	417 (83.6)	110 (26.4)
40–60	1947	1198 (61.5)	974 (81.3)	843 (86.6)	166 (19.7)
Subtotal	3144	1846 (58.7)	1473 (79.8)	1260 (85.5)	276 (21.9)
Female					
20–39	2071	1101 (53.2)	876 (79.6)	733 (83.7)	206 (28.1)
40–60	3637	2108 (58.0)	1802 (85.5)	1573 (87.3)	350 (22.3)
Subtotal	5708	3209 (56.2)	2678 (83.5)	2306 (86.1)	556 (24.1)
Both sexes					
20–39	3268	1749 (53.5)	1375 (78.6)	1150 (83.6)	316 (27.5)
40–60	5584	3306 (59.2)	2776 (84.0)	2416 (87.0)	516 (21.4)
Total	8852	5055 (57.1)	4151 (82.1)	3566 (85.9)	832 (23.3)
Non-indigenous peoples					
Male					
20–39	856	148 (17.3)	123 (83.1)	110 (89.4)	19 (17.3)
40–60	1457	461 (31.6)	394 (85.5)	354 (89.8)	64 (18.1)
Subtotal	2313	609 (26.3)	517 (84.9)	464 (89.7)	83 (17.9)
Female					
20–39	1293	217 (16.8)	179 (82.5)	165 (92.2)	27 (16.4)
40–60	2599	762 (29.3)	646 (84.8)	577 (89.3)	82 (14.2)
Subtotal	3892	979 (25.2)	825 (84.3)	742 (89.9)	109 (14.7)
Both sexes					
20–39	2149	365 (17.0)	302 (82.7)	275 (91.1)	46 (16.7)
40–60	4056	1223 (30.2)	1040 (85.0)	931 (89.5)	146 (15.7)
Total	6205	1588 (25.6)	1342 (84.5)	1206 (89.9)	192 (15.9)
Overall	15057	6643 (44.1)	5493 (82.7)	4772 (86.9)	1024 (21.5)

Supplemental Table 5. Reinfection rates of *H. pylori* in the Taiwanese indigenous communities

Characteristics	No. of subjects	No. of reinfection	Mean follow-up time (years)	Total follow-up time (person-years)	Reinfection rate (%)
Total	498	25	3.15	1569.02	1.59
Infection naïve	381	23	3.25	1238.36	1.86
Previous infected individuals	290	18	3.11	902.37	1.99
Age, in years					
20–29	39	3	3.03	118.22	2.54
30–39	123	6	3.10	381.61	1.57
40–49	166	8	3.20	531.27	1.51
50+	170	8	3.16	537.92	1.49
Sex					
Male	151	11	3.09	467.25	2.35
Female	347	14	3.18	1101.77	1.27
Medical history					
Family history of *H. pylori* infection	35	1	3.12	109.23	0.92
Family history of peptic ulcer	82	1	3.19	261.98	0.38
Family history of gastric cancer	30	3	3.36	100.72	2.98
Personal history of peptic ulcer	67	4	3.24	217.16	1.84
Previous *H. pylori* infection	36	1	3.28	117.96	0.85
Non-steroidal anti-inflammatory drug	100	8	3.15	315.40	2.54
Diabetic drug	28	2	3.26	91.37	2.19
Iron supplement	4	0	3.40	13.61	0.00
Social habit					
Smoking					
Current	63	6	3.20	201.80	2.97
Former	58	6	3.06	177.60	3.38
Never	377	13	3.16	1189.62	1.09
Alcohol use					
Current	280	20	3.20	896.49	2.23
Former	22	0	3.14	69.14	0.00

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Gut

Never	196	5	3.08	603.39	0.83
Betel nut chewing					
Current	105	11	3.20	336.43	3.27
Former	42	4	3.22	135.08	2.96
Never	351	10	3.13	1097.51	0.91

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Gut

Supplementary Fig. 1. The workflow of the screening and eradication program

Following the principles of an organized screening program, four quality indicators, including the invitation rate, positivity rate, referral-to-treatment rate, and the eradication rate were monitored periodically in an on-line system. The orange color indicates the *H. pylori* carriers and the blue indicates the non-carriers or those who received successful eradication treatments.
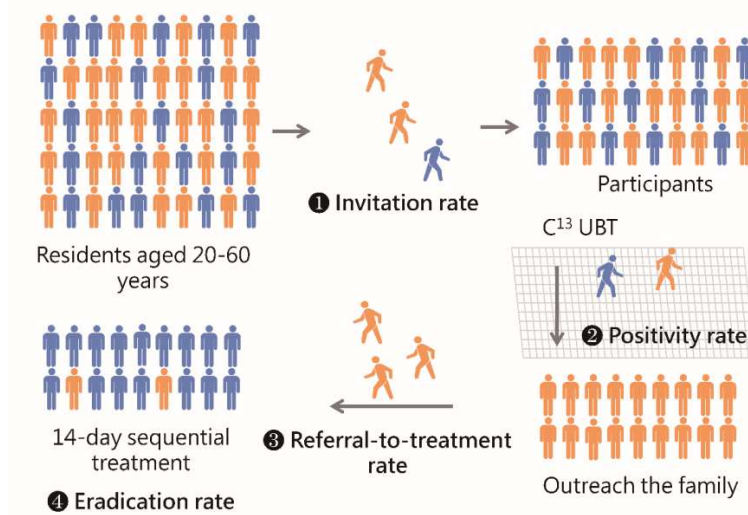
Supplementary Fig. 2. Risk factors associated with the 797 treatment failure among 4601 subjects who received the first-line treatment for *H. pylori* infection according to the per-protocol analyses

The multivariable logistic regression model adjusts for all variables shown in the forest plot. An odds ratio greater than 1.0 indicates an increased risk of treatment failure. The use of anti-platelet agent is not included in the multivariate analyses due to the small case numbers. CI = confidence interval.
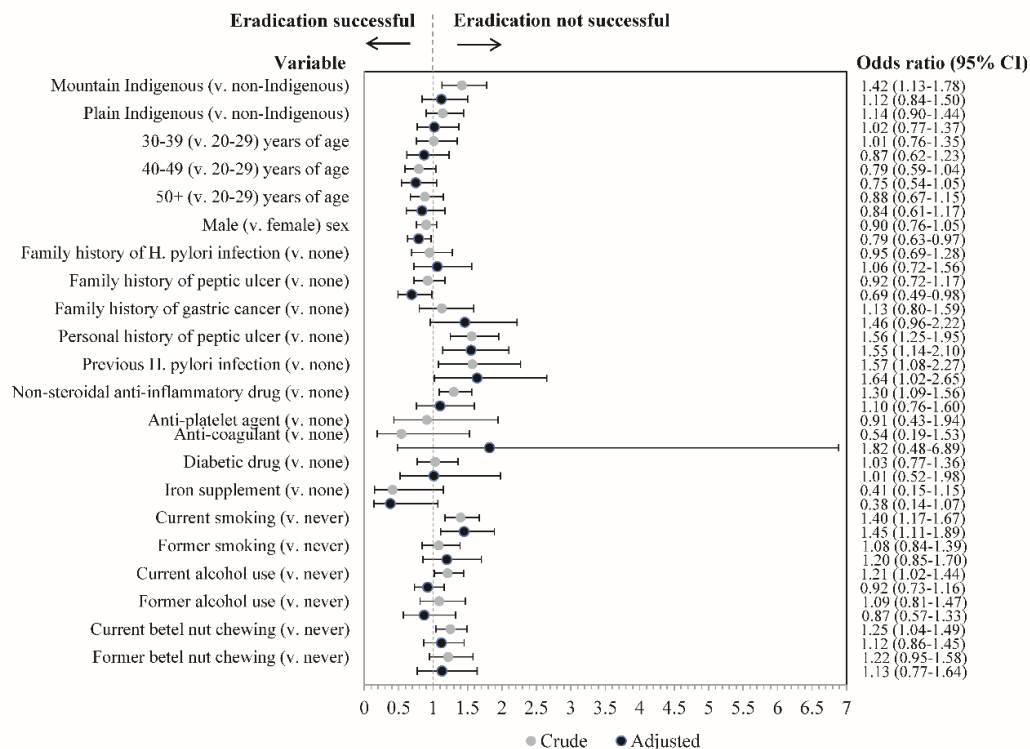
Supplementary Fig. 3. Risk factors associated with the 25 reinfection of *H. pylori* after successful eradication in 498 subjects

A rate ratio greater than 1.0 indicates an increased risk of the reinfection. Results of the Poisson regression models are shown in the forest plot. An odds ratio greater than 1.0 indicates an increased risk of reinfection. CI = confidence interval. Owing to the small reinfection case number, only univariate analyses are performed. There was no case of reinfection in the former alcohol users.

Variable	Odds ratio (95% CI)
Indigenous (v. non-Indigenous)	3.07 (0.72-13.02)
30-39 (v. 20-29) years of age	0.62 (0.15-2.48)
40-49 (v. 20-29) years of age	0.59 (0.16-2.24)
50+ (v. 20-29) years of age	0.59 (0.16-2.21)
Male (v. female) sex	1.85 (0.84-4.08)
Family history of peptic ulcer (v. none)	0.21 (0.03-1.54)
Family history of gastric cancer (v. none)	1.99 (0.60-6.64)
Personal history of peptic ulcer (v. none)	1.19 (0.41-3.45)
Previous H. pylori infection (v. none)	0.51 (0.07-3.79)
Non-steroidal anti-inflammatory drug (v. none)	0.52 (0.16-1.70)
Diabetic drug (v. none)	1.69 (0.39-7.35)
Current smoking (v. never)	2.72 (1.03-7.16)
Former smoking (v. never)	3.09 (1.18-8.13)
Current alcohol use (v. never)	2.69 (1.01-7.17)
Current betel nut chewing (v. never)	3.59 (1.52-8.45)
Former betel nut chewing (v. never)	3.25 (1.02-10.36)