Chapter 7.

Antibiotic stewardship for population-based *Helicobacter pylori* screen-and-treat programmes, including testing of cure and monitoring of antibiotic resistance

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Summary

- A population-based *H. pylori* screen-and-treat programme for gastric cancer prevention should follow robust antibiotic stewardship principles to minimize the risk of antibiotic resistance arising from the increased antibiotic use.
- An antibiotic stewardship checklist should be developed and implemented to ensure the appropriate use of antibiotics, guide best practices, and monitor the impact.
- *H. pylori* eradication rates can be assessed through routine follow-up testing of treated participants or by testing a representative subgroup to confirm treatment success.
- *H. pylori* isolates from a randomly selected subset of participants should be tested for antibiotic resistance. Establishing an antibiogram, which provides a summary of the susceptibility patterns of local bacterial isolates to various antibiotics, can aid in selecting effective drugs. The dosage and duration of treatment should also be carefully optimized to ensure efficacy and minimize the development of resistance.
- The impact of increased exposure to antibiotics through short-course eradication treatments in population-based programmes on antibiotic resistance in *H. pylori* and other human bacteria is not yet fully understood, and thus continued awareness and research are warranted.
- A prophylactic vaccine against *H. pylori* would be the ideal solution to the problems associated with antibiotic use in *H. pylori* screen-and-treat

programmes, but candidate vaccines are still in the preclinical stage of development.

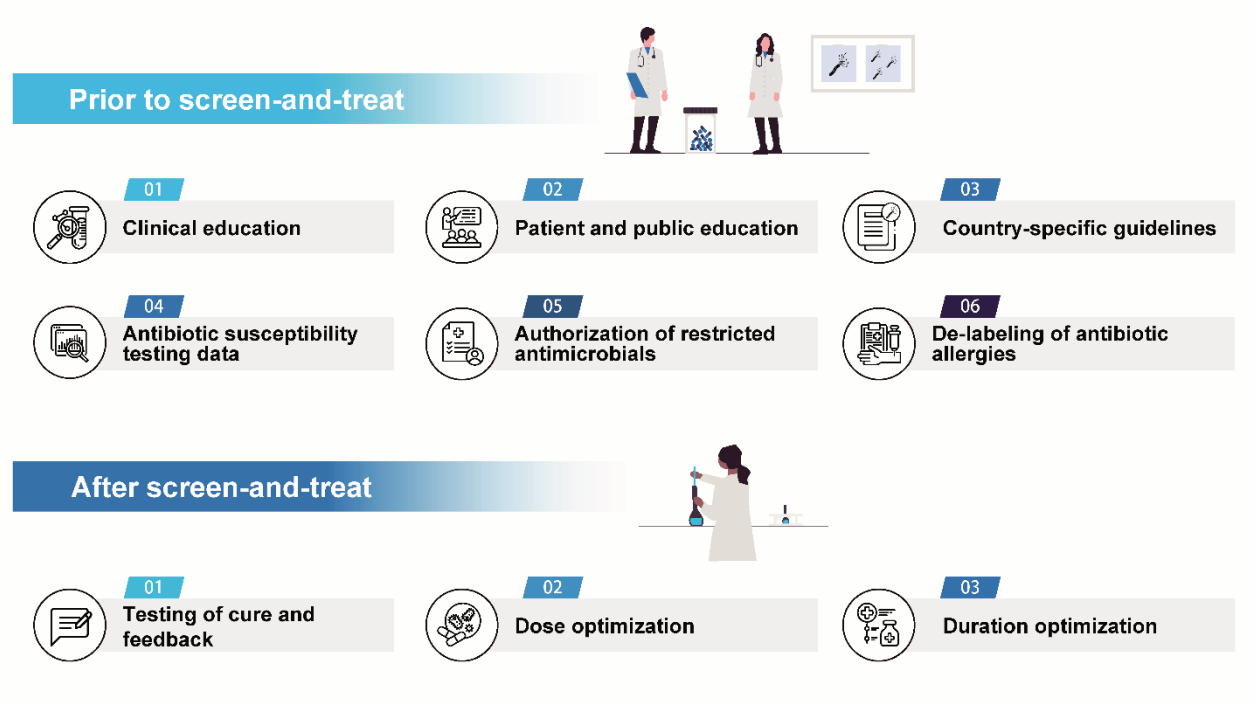

Fig. 7.1. Visual abstract.

7.1 Introduction

H. pylori infection is one of the most common chronic bacterial infections worldwide [1]. A systematic review of the global prevalence of *H. pylori* infection has shown a decrease in infection rates over time, from 53% (95% confidence interval [CI], 50–56%) before 1990 to 44% (95% CI, 42–46%) in 2015–2022 [2]. Multivariable regression analyses showed a decrease of 16% in the prevalence of *H. pylori* infection over the past three decades; a statistically significant decrease was observed in the Western Pacific, South-East Asia, and Africa. In the same study, the incidence of gastric cancer decreased in the countries in which the prevalence of *H. pylori* infection decreased. Another systematic review found that the decrease in the prevalence of *H. pylori* infection was mirrored by a decrease in the incidence of gastric atrophy, intestinal metaplasia, and dysplasia over time [3]. Although the global gastric cancer incidence rate is decreasing because of improved sanitation, which reduces the transmission of *H. pylori*, and opportunistic screen-and-treat practices for *H. pylori*, the absolute number of new cases of gastric cancer remains high in some

regions, and the risk of gastric cancer is increasing in younger generations. Together with the predicted increase in the number of new cases of gastric cancer driven by population ageing, this indicates that gastric cancer remains a substantial public health challenge [4].

The decreasing prevalence of *H. pylori* infection has been accompanied by an increased rate of antibiotic resistance. A systematic review of antibiotic resistance in World Health Organization (WHO) regions, published in 2018 [5], which included data from 2006–2016, highlighted considerable heterogeneity among regions (Fig. 7.2) and a trend towards increasing resistance during the study period. Another study, which reviewed data from 2018–2021, found a global *H. pylori* clarithromycin resistance rate of 32% (95% CI, 29–36%) in the 54 countries studied when both primary resistance (which develops before treatment) and secondary resistance (which occurs after initial treatment failure) were included [6]. In the Asia–Pacific region, data from 2016–2022 indicated resistance rates of 30% (95% CI, 28–33%) for clarithromycin, 35% (95% CI, 31–39%) for levofloxacin, and 61% (95% CI, 55–66%) for metronidazole; the resistance rates for tetracycline and amoxicillin remained low (4–6%) [7]. The prevalence of clarithromycin resistance was highest in Central Asia, and the prevalence of levofloxacin and metronidazole resistance was highest in South Asia [7]. A systematic review of 26 studies in Africa, of which only four were published in 2016 or later, found resistance rates of 29% (95% CI, 27–32%) for clarithromycin, 17% (95% CI, 13–22%) for levofloxacin, and 76% (95% CI, 74–77%) for metronidazole [8]. A high level of heterogeneity was observed in the studies in Africa, and the results did not differentiate between primary and secondary resistance. Differences in the methods used to determine antibiotic resistance, which included disc diffusion, the E-test, and molecular testing for resistance genes, may also contribute to the observed heterogeneity.

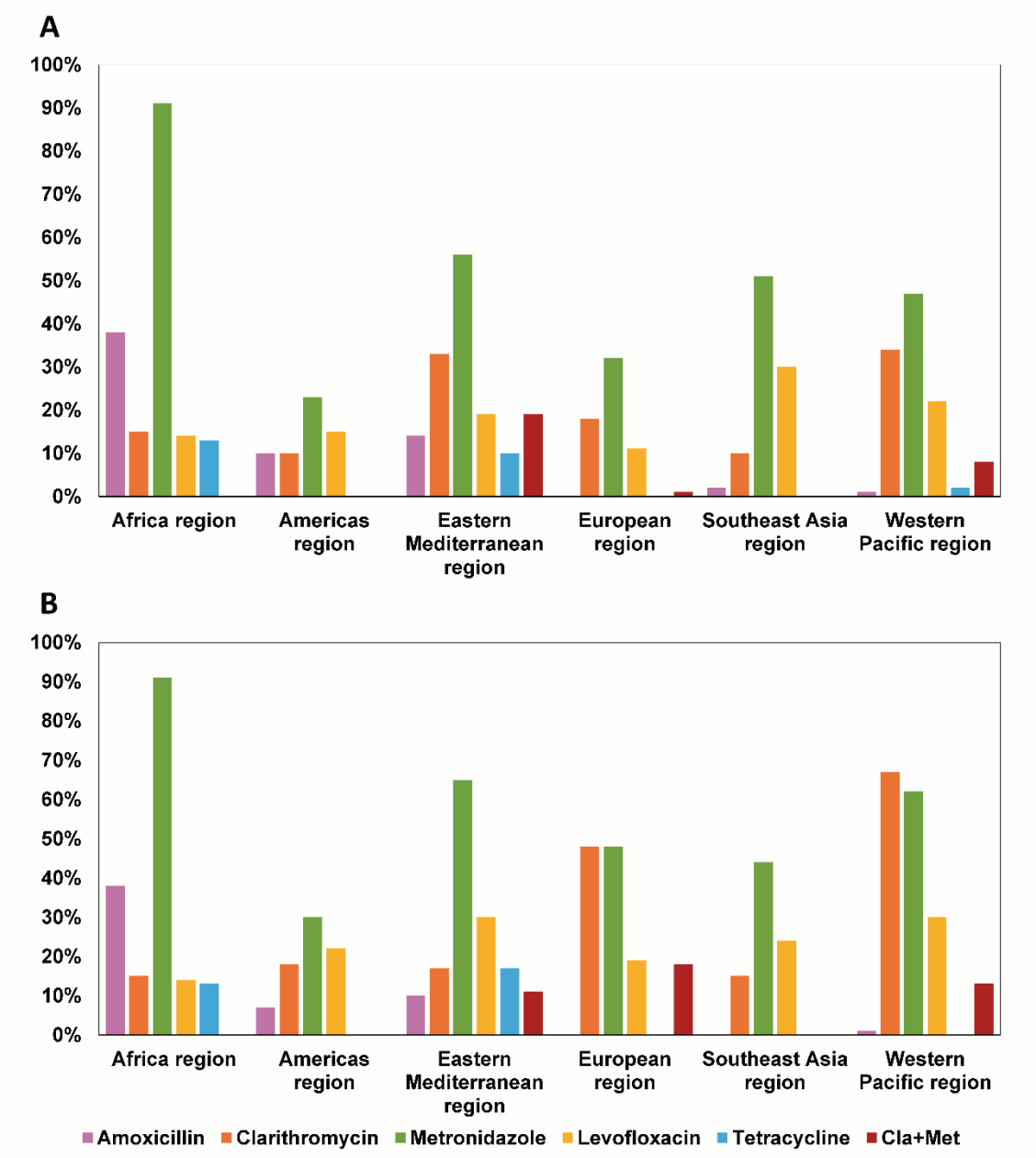

Fig. 7.2. Cumulative antibiograms of primary and secondary resistance of *H. pylori* in World Health Organization (WHO) regions in 2006–2016: (A) primary resistance rates of *H. pylori*; (B) secondary resistance rates of *H. pylori.* Primary resistance rates included individuals who had not yet received antibiotic treatment. Secondary resistance rates included individuals in whom one course of treatment had failed. In Africa, the antibiograms did not differentiate between primary and secondary resistance; therefore, the same data are presented in (A) and (B). These prevalence data were based on only three publications, from Cameroon, the Congo, and Senegal, and their representativeness should be interpreted with caution. Cla+Met, dual resistance to clarithromycin and metronidazole. Source: Compiled from Savoldi et al. (2018) [5].

Information on resistance rates in Latin America is also scant and out of date; the most recent publication was in 2014 [9]. The review reported primary resistance rates of 4% for amoxicillin, 12% for clarithromycin, 53% for metronidazole, 6% for tetracycline, 3% for furazolidone, 15% for fluoroquinolones, and 8% for dual resistance to clarithromycin and metronidazole.

In Europe, studies have been performed every 10 years; the most recent survey was in 2018. The primary resistance rates of *H. pylori* were 21.4% for clarithromycin, 15.8% for levofloxacin, and 38.9% for metronidazole [10]. The European Registry on *Helicobacter pylori* Management (Hp-EuReg) also provides data on antibiotic resistance [11]. In 2017–2020, the resistance rates observed in Europe were close to those reported in the 2018 survey [10], except for metronidazole (24.5% vs 38.9%).

The increasing rates of *H. pylori* antibiotic resistance are most probably caused by the global increase in antibiotic prescribing [12], which increased by 60% in 2000–2015 and has increased a further 16% since then, despite a decrease in antibiotic use during the COVID-19 pandemic [13]. A population-based *H. pylori* screen-and-treat programme will further increase antibiotic use. Therefore, any programme that is adopted must have robust antibiotic stewardship policies. This chapter evaluates the impact that *H. pylori* screen-and-treat programmes could have on population antibiotic use and suggests the antibiotic stewardship approaches that should be taken when choosing *H. pylori* eradication therapies and monitoring resistance.

Section 7.2 estimates the impact of population-based *H. pylori* screen-and-treat programmes on population antibiotic use. The importance of antibiotic stewardship is discussed in Section 7.3, with a checklist for assessing the antibiotic stewardship in a programme. Strategies for assessing *H. pylori* eradication rates and monitoring antibiotic resistance are discussed in Section 7.4, and real-world examples are provided in Section 7.5. Section 7.6 provides a perspective on the development of a vaccine against *H. pylori*.

7.2 Estimated impact of *H. pylori* screen-and-treat programmes on population antibiotic use

All screening programmes must balance harms against benefits, and one of the key disbenefits of a population-based *H. pylori* screen-and-treat programme is that it will inevitably increase antibiotic use. It is estimated that in 2021 antimicrobial resistance contributed to more than 4.7 million deaths, of which more than 1.1 million deaths

were directly attributable to antimicrobial resistance, and that these figures will increase to more than 8.2 million deaths and more than 1.9 million deaths per year by 2050 [14]. Population-based *H. pylori* screening and treatment could further add to this problem in any country that institutes such a policy. Therefore, it is important to try to estimate the potential impact of such programmes when introduced in various countries. The Working Group conducted a modelling exercise using a best-case scenario in which a programme would use two antibiotics and standard daily doses for 1 week in an eradication regimen, and would screen people aged 40–69 years (approximately modelling the randomized trials in this topic area [15–16]). It was assumed that 20% of the eligible population would be invited to be screened annually, to reduce the impact of antibiotic use each year, and that of those invited, 70% would attend, which is the best uptake rate that has been achieved by a new screening programme [17]. A recent systematic review was used to provide the estimates for the prevalence of *H. pylori* infection in each country, and data for the total population and the proportion of the population aged 40–69 years were taken from nationally available data [2]. The current total defined daily dose (DDD) [18] prescribed in each country in 2023 was estimated using published sources [13], and projections were made for how this would increase if a population-based *H. pylori* screen-and-treat programme was introduced in that country.

This modelling exercise showed that in most settings the proportional increase in antibiotic prescribing is modest (Table 7.1); most countries were projected to have a 1–3% increase in DDD prescribed. The exception is China, in which the DDD would increase by 11%. This is mainly due to the current low level of antibiotic prescribing in China, possibly because of stricter regulations [19] compared with most other countries. Therefore, the proportional increase would be greater in China than in other countries. The projected 7% increase in antibiotic prescribing in Colombia is driven mainly by the high proportion of individuals aged 40–69 years with *H. pylori* infection in that country.

Table 7.1. Estimated effect of population-based *H. pylori* screen-and-treat programmes on antibiotic use in some representative countries

Country or territory	Current annual DDD	Annual DDD after screening	Percentage increase
China	2 217 311 459	2 460 275 422	11.0
Japan	550 550 145	567 613 839	3.1
Taiwan, China	133 800 475	136 988 969	2.4

Table 7.1. Estimated effect of population-based *H. pylori* screen-and-treat programmes on antibiotic use in some representative countries (continued)

Country or territory	Current annual DDD	Annual DDD after screening	Percentage increase
Republic of Korea	634 371 001	647 400 989	2.1
United Kingdom	470 375 747	477 633 709	1.5
France	615 807 647	622 585 863	1.1
Spain	513 346 264	523 279 432	1.9
Poland	304 587 086	313 734 497	3.0
Greece	137 247 694	139 107 945	1.4
Canada	209 056 368	211 829 698	1.0
USA	2 783 138 735	2 805 058 634	0.8
Colombia	182 865 559	196 330 098	7.3
Brazil	1 466 232 682	1 494 255 989	1.9

DDD, defined daily dose.

Note: DDD refers to the assumed average maintenance dose per day for an antibiotic used in adults. For example, the DDD for amoxicillin is 1000 mg per day.

These estimates of increased antibiotic use are reassuring, but the assumptions made were optimistic. A more judicious approach would aim to maximize the chances of eradicating *H. pylori* infection in individuals while minimizing antibiotic exposure. Rather than attempting to eradicate *H. pylori* infection in every possible case, the focus should be on achieving the greatest benefit per dose of antibiotics used. It was assumed that only 20% of the eligible population would be invited annually and that only a 1-week course of antibiotics would be prescribed, whereas the currently recommended eradication treatments typically last 10–14 days [20]. This will approximately double the percentage increase in antibiotic prescribing described in Table 7.1. The proportion will increase even more if all participants are screened for treatment failure and offered further eradication therapy. Therefore, there can be no room for complacency if an *H. pylori* screen-and-treat programme is implemented, and it is important that antibiotic stewardship principles are followed. The benefits of *H. pylori* eradication treatment for associated diseases should be weighed against the potential disbenefits of increased antibiotic use, although the consequences may largely be theoretical. In existing programmes that target high-risk populations, the impact of the concern about antibiotic resistance has not yet been observed or fully understood (see Section 7.5), and decision analyses have not yet incorporated this point into model assumptions (see Chapter 9).

7.3 Antibiotic stewardship in *H. pylori* screen-and-treat programmes

There are numerous guidelines [21] on appropriate antibiotic use and antibiotic stewardship. Although these have some different nuances, all have similar approaches to minimizing antibiotic use. The purpose of antibiotic stewardship is to optimize the use of antibiotics to preserve their effectiveness, minimize adverse effects, and reduce the development of antibiotic resistance (Box 7.1).

Box 7.1. The five Ds of antibiotic stewardship

In population-based *H. pylori* screening programmes, communication between primary care physicians, gastroenterologists, and infection specialists is increasing to optimize antimicrobial use. Antibiotic stewardship is commonly guided by the **five Ds** principles [22]. These principles emphasize accurate **diagnosis** to ensure that antibiotics are prescribed correctly to individuals with *H. pylori* infection. Appropriate **drug** selection is guided by antibiotic resistance patterns and therapeutic evidence from clinical trials. Adequate **dosing** should adhere to the best therapeutic interval and timing before and after eating, to ensure efficacy, while considering patient health conditions, including the adjustment of hepatic and renal functions, and potential drug–drug interactions. Optimal **duration** helps to limit the development of resistance, minimize side-effects, and improve patient compliance. Full adherence to an antibiotic regimen is essential, because incomplete adherence can result in lower eradication rates and the potential selection of resistant strains. Treatment may be **discontinued** when the potential harms of (repeated) courses of antibiotics outweigh the clinical benefits or when there are competing health considerations, thereby reducing unnecessary antibiotic use and the risk of resistance.

Systematic review data [23] suggest that stewardship programmes are effective in reducing antibiotic use. Therefore, it is important that any population-based *H. pylori* screen-and-treat programme has an antibiotic stewardship team in place to advise and to monitor any impacts on antimicrobial use [24]. Such a team should involve people with expertise in gastroenterology, infectious diseases, clinical microbiology, epidemiology, and clinical pharmacy [25]. The key considerations for evaluating antibiotic stewardship in a population-based *H. pylori* screen-and-treat programme are outlined in Table 7.2, which presents a checklist of coordinated actions designed

to support the responsible and effective use of antimicrobials. Treatment of *H. pylori* infection is primarily empirical rather than definitive. Therefore, the first-line regimen should prioritize the most effective options (e.g. bismuth-containing quadruple therapy) while minimizing the risk of selecting for or driving the development of antibiotic-resistant strains. Treatment strategies should align with regional guidelines and the recommended benchmarks for successful eradication. Antibiotics with a higher potential for resistance – for example levofloxacin and rifabutin, which are not exclusively related to treatment of *H. pylori* infection – should be restricted for empirical use and require approval from infection specialists or guidance from antibiotic susceptibility testing, to enable definitive treatment. For antibiotics with a high eradication rate and low resistance potential, such as amoxicillin and tetracycline, it is crucial to verify the accuracy of the patient's allergic history. Systematic collection of test-of-cure data is needed to optimize the antibiotic regimen, including its dosage and duration.

First, to reduce adverse events, the ideal regimen would include only one antibiotic, because using multiple antibiotics to treat a single infection is not encouraged if monotherapy is sufficient [26]. Vonoprazan–amoxicillin dual therapy meets this goal, with acceptable eradication rates in East Asia [27], but eradication rates for this therapy have been suboptimal in other countries [28–29]. It is likely that in most countries at least two antibiotics will be needed to achieve acceptable eradication rates (see Chapter 6).

Table 7.2. Checklist for assessing antibiotic stewardship in a population-based *H. pylori* screen-and-treat programme

Before *H. pylori* screening and treatment
1. Clinical education
□ Is there an antibiotic stewardship team that includes experts from the gastroenterology, infectious disease, clinical microbiology, epidemiology, and clinical pharmacy departments?
□ Is there an initiative to enhance clinician education on screening tests and treatments?
□ Is there a system in place to maintain up-to-date knowledge on the practices and guidelines for antibiotic use?
2. Patient and public education
□ Is there an initiative to educate the patients and the public about the proper use of antibiotics for *H. pylori* infection?
□ Are there information technology or implementation resources available to communicate with the public?
□ Are the administrative and medical leadership committed to the programme?
3. Country-specific guidelines for the management of *H. pylori* infection
□ Are there guidelines available to standardize and reduce variation of the prescribing practices?
□ Are the guidelines evidence-based, and do they reflect the local epidemiology, treatment effectiveness, and drug availability?
□ Do the guidelines address diagnosis, drug selection, dosing, duration, and discontinuation of treatment?
□ Is there an available benchmark for appropriate antibiotic use that can be used for audit and feedback?
□ Is there an implementation strategy to encourage awareness and adherence to the guidelines?
□ Is there a mechanism to enable targeted education for physicians, in terms of audit and feedback?
4. Antibiotic susceptibility testing data (cumulative antibiogram)
□ Are the local antibiotic susceptibility testing data available?
□ Are human resources and microbiology laboratory services available, with appropriate quality controls for in vitro antibiotic susceptibility testing?
5. Prior authorization of restricted antimicrobials
□ Is there a mechanism that requires clinicians to obtain approval for specific antibiotics, such as levofloxacin and rifabutin, before they are released from the pharmacy for administration to individuals with *H. pylori* infection?
6. De-labelling of spurious antibiotic allergies
□ Is there a mechanism to clarify antibiotic allergies through dedicated allergy assessments, particularly for amoxicillin and tetracycline, which can distinguish individuals who are unlikely to react to an antibiotic challenge from those at substantial risk of an adverse allergic reaction?
After *H. pylori* screening and treatment
1. Testing of cure and feedback
□ Are the test-of-cure data available for participants who received antibiotic treatment?
□ Are the test-of-cure data available for clinicians who prescribed the antibiotic treatment?
□ Is an audit system in place, and is feedback provided when treatment does not adhere to the guidelines?
2. Antibiotic dose optimization
□ Is attention given to participant characteristics, such as age, weight, and renal and hepatic function, that can influence the appropriate dose and dosing interval?
□ Can the dose optimization be updated and incorporated into the clinical guidelines?
3. Antibiotic duration optimization
□ Is the treatment duration determined on the basis of local evaluation, with the participant's response to therapy being reassessed?
□ Can the duration optimization be updated and incorporated into the clinical guidelines?

Source: Modified from WHO (2021) [24].

Also, it is imperative not to choose antibiotics that would be ineffective because of high rates of antimicrobial resistance. This is the situation with clarithromycin, to which > 15% of *H. pylori* strains are resistant in many parts of the world [11]. The regimen that is most likely to be successful worldwide is bismuth-containing quadruple therapy, which involves a proton pump inhibitor, bismuth salts, tetracycline, and metronidazole, for 10–14 days [30]. *H. pylori* resistance to tetracycline is rare, and although the in vitro resistance rate is high for metronidazole, *H. pylori* appears to remain susceptible to this antibiotic in vivo [31–32]. In vitro metronidazole resistance has minimal effects on bismuth-containing quadruple therapy. Although the impact is greater with triple therapies, the impact remains limited with a 14-day treatment duration because of the accumulation of metronidazole in the mucus and its long half-life in the higher intragastric pH [33]. The regimen is complex, but single-capsule formulations that contain bismuth subcitrate potassium, metronidazole, and tetracycline are available [34], which may improve treatment compliance in population-based interventions in which simplicity is important. Although bismuth-containing quadruple therapy is more effective and carries a lower concern about antibiotic resistance, it may cause side-effects such as nausea, diarrhoea, a metallic taste, and temporarily black stools, which should be explained in advance and monitored throughout the treatment to improve compliance. Although amoxicillin and tetracycline show lower resistance rates, in some areas, such as Africa and the Eastern Mediterranean, primary resistance rates may be not trivial (Fig. 7.2). Continuous monitoring, particularly through updated time-trend analyses, is needed.

Second, an antibiotic stewardship committee would have to monitor eradication rates and resistance [35]. The challenge in implementing this approach is that it will require retesting at least a subset of participants, to assess successful eradication rates and monitor the development of antibiotic resistance. If this approach is implemented, individuals who remain *H. pylori*-positive should be offered second-line eradication regimens, and, if they are still positive, third-line treatments. This clinical approach would result in multiple courses of different antibiotics for a single infection, which has the potential to conflict with general antibiotic stewardship principles. However, the number of patients who require repeated treatments is likely to remain small provided that an effective initial treatment is selected. The approaches to deal with this conundrum are discussed in Section 7.4.

The recommendations outlined above are aligned with the WHO Access, Watch, Reserve (AWaRe) classification of antibiotics [36]. Antibiotics are classified into the Access, Watch, Reserve, and Not recommended groups based on the risk of selecting for bacterial resistance. Of the antibiotics used for treating *H. pylori* infection, amoxicillin, metronidazole, tetracycline, and doxycycline were classified into the Access category of antibiotics that showed lower resistance potential. Clarithromycin, levofloxacin, ciprofloxacin, cefuroxime, and rifabutin were classified into the Watch category of antibiotics that had a relatively high risk of selection of bacterial resistance. Minocycline was classified into the Reserve category of antibiotics that should be tailored for use in highly specific patients when alternatives have failed or were not suitable [37].

WHO periodically updates its priority pathogen list on the basis of evolving global health needs, scientific evidence, and public health challenges. In 2017, clarithromycin-resistant *H. pylori* was included in the WHO priority pathogens list for research and the development of new antibiotics [38], because *H. pylori* is a common infection worldwide, affecting both adults and children, and is associated with peptic ulcer and gastric cancer. The increasing prevalence of antibiotic resistance has led to suboptimal eradication rates. Guidelines advise against standard triple therapy if regional clarithromycin resistance is > 15% or if eradication rates are < 85% (see Chapter 6). However, in the 2024 update of the list [39], five antibiotic-resistant pathogens, including clarithromycin-resistant *H. pylori*, were removed. The removal of clarithromycin-resistant *H. pylori* from the priority list does not decrease the global concern about its burden, transmission, treatability, and prevention. Furthermore, this change may potentially lead to reduced emphasis on the monitoring of clarithromycin resistance. Treatment guidelines may still include clarithromycin as a first-line treatment without giving warnings about the high likelihood of treatment failure and the emergence of resistant strains, or without recommending suitable alternatives.

7.4 Strategies for assessing *H. pylori* eradication rates and monitoring antibiotic resistance

A population-based *H. pylori* screen-and-treat programme requires continuous monitoring to ensure that the desired outcome of the programme is being achieved. The primary aim of the programme is to reduce the incidence and mortality of gastric cancer with minimal adverse events, and it may take at least a decade before any

effects on gastric cancer outcomes become evident. Therefore, it is crucial to evaluate process measures that are immediately observable in a screening programme (see Chapter 8). These should include assessing the *H. pylori* eradication rate in the population targeted by the programme and monitoring the prevalence of antibiotic-resistant strains, both specific to *H. pylori* and in bacteria more broadly. To achieve the goals, the primary approach involves retesting either all or a subset of the participants who have received anti-*H. pylori* treatment, to confirm treatment success. This approach also includes selecting a subset of participants who tested positive for *H. pylori*, as well as those who were treated but retested positive, to assess antibiotic resistance. Concerns about bacterial resistance should be significantly lower if an effective treatment (such as bismuth-containing quadruple therapy and vonoprazan–amoxicillin dual therapy) has been administered and clarithromycin has not been prescribed (see Chapter 6).

*Testing of cure in participants who have received the anti-*H. pylori *treatment*

Two approaches can be taken to test participants who have received anti-*H. pylori* treatment. The most accurate approach to evaluating *H. pylori* eradication is to assess each individual population that undergoes screening and treatment. In this approach, all participants who meet the eligibility criteria for the programme would be tested and those with *H. pylori* infection would be offered antibiotic therapy with a follow-up test. Many methods are available for *H. pylori* testing [40], including non-invasive and invasive tests (see Chapter 5). For most countries, a non-invasive test, such as the urea breath test [41] or the stool antigen test [42] at least 1 month after the completion of therapy, can be used to assess eradication success.

The advantage of this approach is that it uses the largest sample size to assess the success of therapy and offers better generalizability. It also strengthens the patient–doctor interaction in the management of *H. pylori* infection. In addition, without the test-of-cure data, resistant strains are more likely to persist and spread within the community. The disadvantage of this approach is that it dramatically increases the cost and complexity of the programme, because it requires systems to be in place to inform participants of their results, check compliance, and offer alternative eradication therapies for individuals in whom eradication treatment fails. Providing the infrastructure needed to deliver such care, which becomes more

individualized with each round of treatment, would be expensive, and complex interventions at the population level are more likely to result in programme failure.

Other issues to consider with this approach are that a small but substantial proportion of the population would require treatment with multiple courses of differing antimicrobial regimens, and this will increase antibiotic exposure in this population [43]. There would also be a small proportion of the population who would still have *H. pylori* infection despite multiple attempts at treatment. This group may be left with anxiety that they have a carcinogenic infection that cannot be treated, and this may have an adverse psychological impact. Studies of breast cancer screening consistently find that women with breast abnormalities have increased anxiety and breast cancer-specific worry and distress [44]. There is some debate about whether these psychological impacts persist even after a negative diagnosis [45] or resolve [46]. These psychological effects may be influenced by the local disease burden and the community's perceived understanding of *H. pylori* infection.

Another approach that minimizes the potential harms of screening all individuals who receive therapy but still maintains the benefits is to screen a subgroup of those who have received therapy. A randomly selected subgroup would receive instructions, to check the success of therapy using the same methods as described in the first approach. The size of the subgroup selected would depend on the resources available and the size of the country offering screening, but it would usually be at the level of 10–20% of the population with *H. pylori* infection. The size of the subgroup also depends on the observed eradication rate in the population. If the eradication rate is high, a smaller sample size is required, but if the eradication rate is lower, a larger sample size is needed. The random selection would need to be stratified and weighted by region to ensure that vulnerable populations are not excluded or underrepresented. The advantage of this approach is that costs are lower, because fewer people would need follow-up. Also, fewer people would receive multiple antibiotic regimens and fewer people would have increased anxiety from knowing that they still have *H. pylori* infection despite having received therapy. The disadvantage of this approach is that if the proportion of the programme's population that is selected as the subgroup is not chosen appropriately, the estimate of the eradication rate may have wide confidence intervals. This problem can be overcome by continually monitoring the results and increasing the proportion tested as needed.

It could be argued that there are issues with not retesting the full population, given that no therapy is completely effective. For instance, after hypertension is detected, patients are prescribed antihypertensives and their blood pressure is rechecked until it falls within acceptable limits. However, *H. pylori* screening and treatment is not analogous to this, because blood pressure is a continuous measurement and can always be reduced, whereas some people will still have *H. pylori* infection despite any amount of antibiotic therapy. This group may experience heightened anxiety about what is a low absolute risk of developing malignancy. Screening for and treating *H. pylori* infection is more similar to screening for colorectal cancer using faecal immunochemical testing and offering colonoscopy to those who test positive. Good programmes introduce quality controls to minimize risks, but there is always a chance that polyps, or even colon cancer, may have been missed. Repeating the procedure more frequently is not practical, because it is prohibitively expensive and it increases the risks associated with colonoscopy. For an *H. pylori* screen-and-treat programme, testing the entire population would increase the cost of the programme and its complexity and would result in exposure to many antibiotics, and some participants would remain anxious despite the best efforts. This would prevent few gastric cancers and may not be justified. All participants entering any screening programme should be informed that there is never a 100% success rate in preventing the disease targeted by the screening.

The *H. pylori* screen-and-treat approach is also similar to screening for hepatitis B and C viruses for liver cancer prevention. Although the initial treatment may not always be effective, alternative treatments with a higher chance of success are available. The need to test for eradication may arise because of the observed eradication rate in the specific population, particularly after first-line treatment, when the eradication rate cannot be guaranteed to be high enough and effective second-line options are available. Depending on the health-care system, population screening can align with regular clinical practice, in which both the primary physician and the treated patient may need to know whether the treatment has been successful.

If a decision is made to test a subgroup of the population for therapy success and antibiotic resistance, the next question is how many years to wait before repeating the process. This refers to determining the frequency of testing of eradication rates and the emergence of resistance as part of a programme. The programme could be

either a continuous, rolling effort or an intermittent one. For countries that cannot afford a rolling programme, it is preferable to conduct intermittent testing of population samples. The interval should be determined based on the resources available for the programme. If resources are scarce, then an interval of 10 years, for example, may be all that is affordable. In higher-income countries, shorter intervals, such as every 2 years, would provide more timely information on whether eradication rates are decreasing and/or *H. pylori* antibiotic resistance rates are increasing.

Monitoring the antibiotic resistance

An important consideration in antibiotic stewardship is understanding which antibiotics are effective in curing infections; this is typically guided by the cumulative antibiogram (item 4 in Table 7.2) [47–48]. However, this raises the question of how to test for *H. pylori* antibiotic resistance. The reference standard would be gastric biopsy and culture, but this requires endoscopy and would be too expensive and invasive for many countries to implement. However, it may be feasible for countries that already offer population-based endoscopic screening, such as Japan [49] and the Republic of Korea [50]. Stool testing makes it possible to detect some of the *H. pylori* genetic mutations that confer antibiotic resistance by using real-time polymerase chain reaction (PCR) [51–53]. The stool PCR test has a low cost and is non-invasive, and testing could be done as a one-step process if stool antigen testing is also being used to assess eradication [54]. However, currently the sensitivity of the stool PCR test is not optimal, and only known mutations can be detected. For important antibiotics, such as metronidazole, both the mechanism of resistance and the significance of resistance mutations are unclear, and thus resistance cannot be determined by molecular methods. An alternative approach would be to use the string test method, which involves swallowing a capsule and, after retrieval of the capsule with a string, testing the gastric juice on the string, again with real-time PCR [55]. Public health programmes would need to determine whether this approach is feasible and applicable.

Treatment of *H. pylori* infection is generally based on empirical therapy rather than definitive treatment that is guided by susceptibility testing, as is done for other bacteria. However, it is still possible to conduct susceptibility testing before the antibiotic treatment. Invasive methods, including rapid urease testing, histology, culture, and antimicrobial susceptibility testing, cannot be adapted for population-

based screening for *H. pylori* infection in asymptomatic people, because they require upper digestive endoscopy. However, for countries that already conduct mass endoscopy screening to prevent gastric cancer, such as Japan [56] and the Republic of Korea [57], the antimicrobial susceptibility testing could be carried out at the same time as the gastric mucosa is evaluated. When endoscopic screening works together with *H. pylori* screening, this opportunity can be used to investigate the extent to which a population-based screen-and-treat approach has affected the levels of *H. pylori* antibiotic resistance.

The impact of population-based *H. pylori* screening on the general levels of antibiotic resistance, in bacteria other than *H. pylori*, can be measured using stool samples. Two hospital-based clinical trials used high-throughput DNA sequencing to evaluate the effects of antibiotic treatment on the dynamic changes in the gut microbiota and the resistome [58–59]. The number and abundance of microbial species (i.e. the diversity) and the antibiotic resistance genes of all bacteria (i.e. the resistome) were evaluated from stool samples taken before and after treatment for *H. pylori* infection, and the dynamic changes observed in the resistome are shown in Fig. 7.3. The results revealed a transient decrease in the diversity and an increase in the total resistome after antibiotic treatment, which may return to pre-treatment levels within about 2 months. Based on analyses of the minimum inhibitory concentration, the resistance rates of *Escherichia coli* and *Klebsiella pneumoniae* to levofloxacin, ciprofloxacin, ampicillin, and various cephalosporins temporarily increased 2 weeks after treatment. However, these rates returned to pre-treatment levels after 2 months and remained stable for up to 1 year. Collectively, the findings of these two studies provide some evidence against the concern about the long-term risks arising from antibiotic-resistant strains that might emerge in *H. pylori*-treated individuals, challenging the validity of this concern, which has yet to be demonstrated in practice. Nonetheless, there is a concern that the increased use of antibiotics may lead to more antibiotics entering the environment and negatively affecting ecosystems [60–61].

WHO promotes the One Health approach, which emphasizes an integrated strategy to achieve sustainable health outcomes for the entire ecosystem [62]. The One Health approach emphasizes addressing antibiotic resistance that can result from the overuse and misuse of antibiotics in various sectors, including human health

care, veterinary medicine, and agriculture, because these fields are closely interconnected. Improper practices may lead to an increase in antibiotic-resistant bacteria, which will make infections more difficult to treat. Consequently, a population-based *H. pylori* screen-and-treat programme should strictly adhere to robust antibiotic stewardship principles.

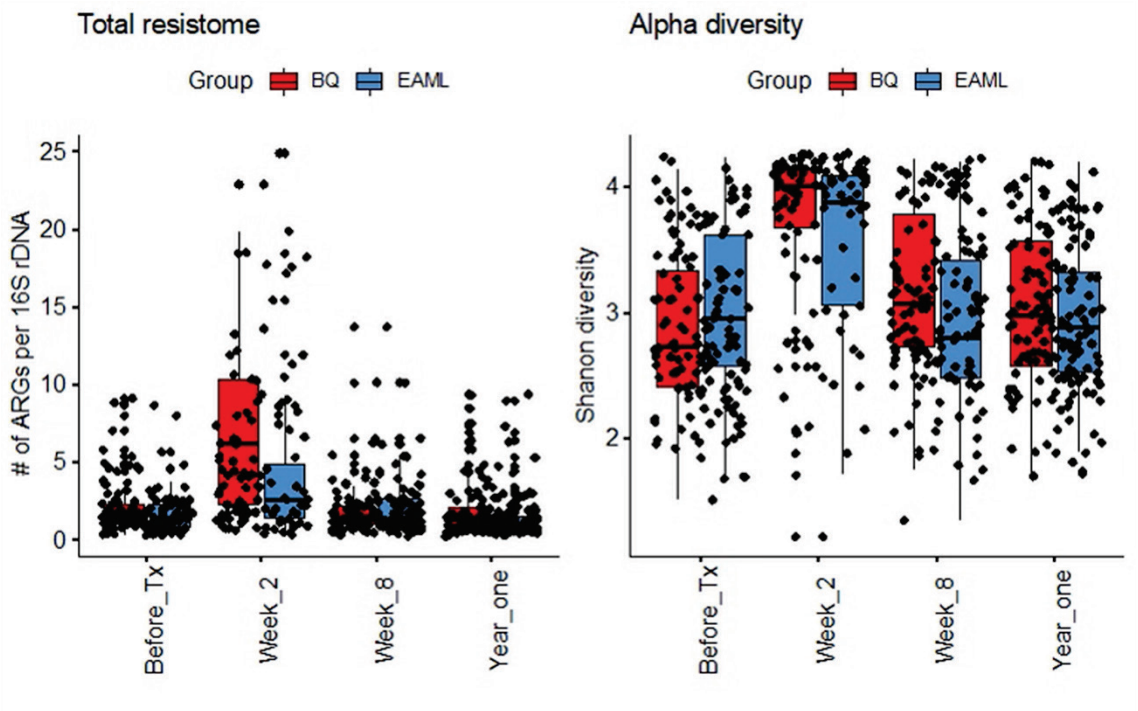

Fig. 7.3. The dynamic changes of the resistome before and after treatment (Tx) in a randomized clinical trial. Patients with *H. pylori* infection were randomized to receive second-line treatments of levofloxacin-based sequential quadruple therapy (esomeprazole, amoxicillin, metronidazole, and levofloxacin for 14 days; EAML) or bismuth-containing quadruple therapy (esomeprazole, bismuth, tetracycline, and metronidazole for 10 days; BQ). The abundance of antibiotic resistance genes (ARGs) at the type and subtype levels were normalized to the number of 16S ribosomal RNA (rRNA) genes for the quantification and downstream analysis of diversity indices. The treatments showed similar changes. The abundance of the total resistome was significantly increased 2 weeks after treatment, although the total resistome was similar to pre-treatment levels at 2 months (8 weeks) and 1 year. In the analyses, alpha diversity of the resistome showed consistent results. Source: Reprinted from Liou et al. (2023) [59]. Copyright 2023, with permission from Elsevier.

7.5 Examples of antibiotic stewardship in population-based *H. pylori* screen-and-treat programmes

There are existing *H. pylori* registries, such as the Hp-EuReg [63], which emphasize the value of structured, large-scale registries in tracking and understanding the epidemiology, management, and outcomes of *H. pylori* infection. The Hp-EuReg

collects data on empirical antibiotic prescriptions and cure rates for patients with *H. pylori* infection. Because the cure rate is highly dependent on *H. pylori* antibiotic resistance, this treatment-outcome registry may provide indirect estimates of the prevalence of *H. pylori* resistance to commonly used antibiotics [64–67].

In 2004, a community-based *H. pylori* screen-and-treat programme was implemented in the Matsu Islands, which are located in the East China Sea (see Chapter 3.10) [68]. A committee was established in collaboration with the Lienchiang County Bureau of Health and the Taiwan Community-based Integrated Screening Group [69]. This pilot programme lacked previous experience on the effectiveness of a 7-day triple therapy (esomeprazole, 40 mg once a day; amoxicillin, 1000 mg twice a day; and clarithromycin, 500 mg twice a day) in eradicating *H. pylori* infection in the general population. Therefore, routine retesting was included after the initial treatment to confirm treatment success, consistent with standard medical practices for *H. pylori* infection. If the retesting yielded positive results, retreatment was administered with a 10-day retreatment (esomeprazole, 40 mg once a day; amoxicillin, 1000 mg twice a day; and levofloxacin, 500 mg once a day). This approach sought to minimize the potential for selected antibiotic-resistant strains to remain in the community after the mass eradication, and to restrict them to a small, manageable subset of the population who would receive tailored therapies. Eradication rates with the initial therapy were 86.9% (95% CI, 84.7–89.1%) in all individuals who took medication and 88.7% (95% CI, 86.5–90.9%) in those who used at least 80% of the medication. The retreatment eradicated *H. pylori* infection in 91.4% (95% CI, 86.0–96.8%) of people who did not respond to the initial treatment. After one or two courses of antibiotic treatment, the *H. pylori* eradication rates were 97.7% (95% CI, 96.7–98.7%) in individuals who took medication and 98.8% (95% CI, 98.5–99.3%) in those who used at least 80% of the medication. This left a small subset of about 2% of participants who remained positive for *H. pylori* infection and required tailored management.

In addition, endoscopic biopsy for bacterial culture was performed on a subset of 624 individuals with *H. pylori* infection who had not previously received antibiotic treatment; it revealed modest changes in the rates of resistance to clarithromycin, metronidazole, and levofloxacin over time. The antibiotic susceptibility data (cumulative antibiogram) are shown in Chapter 3.10. The reinfection rate was < 1 per 100 person-years.

Another example is a community-based randomized clinical trial for *H. pylori* screening that was conducted in Changhua County under the platform of the Taiwan Colorectal Cancer Screening Program [15]. The trial targeted 240 000 residents aged 50–69 years who were eligible for colorectal cancer screening, and the trial protocol adhered to the antibiotic stewardship principles (see Table 7.2). Before initiating screening, the Changhua County Public Health Bureau established a steering committee of experts in public health, general medicine, gastroenterology, infectious diseases, and pharmacy. Local guidelines for the clinical management and surveillance of *H. pylori* infection were developed through a consensus among these experts [70]. To enhance clinicians' management of *H. pylori* infections, a series of educational activities was conducted that focused on the latest knowledge about antibiotic treatments. This initiative was supported by strong commitments from the administrative and medical leadership. Benchmarks, including for eradication rates, were set based on the experiences of the pilot, to enable the programme to be audited and to provide feedback after the programme was implemented (see Chapter 8). Monitoring of the antibiotic susceptibility data was planned in advance.

The central laboratory developed the antibiogram profile for the community in which the trial was being conducted by using biopsy samples collected from the participating hospitals. These samples were used both to test for antibiotic resistance genes and to test for minimum inhibitory concentration. These data were used to guide individualized treatments for individuals in whom treatment had failed, and also were periodically summarized and presented as percentages of *H. pylori* isolates that were resistant to commonly used antibiotics. This information was shared with the participating hospitals to enable them to optimize the first-line treatment strategies.

After the trial was implemented, the drug selection, dosage, and treatment duration were audited. Retesting was conducted in accordance with standard medical practice to evaluate treatment outcomes, aligned with the trial's pragmatic design. The first-line treatment used in the trial was a 10-day sequential therapy (days 1–5, esomeprazole, 40 mg once a day and amoxicillin, 1000 mg twice a day; days 6–10, esomeprazole, 40 mg once a day and clarithromycin, 500 mg plus metronidazole, 500 mg twice a day). Post-treatment *H. pylori* status was assessed using the stool antigen test at 6–8 weeks after the completion of treatment. Patients who remained test-positive received 10-day triple therapy (esomeprazole, 40 mg once a day; amoxicillin, 1000 mg twice a day; and levofloxacin, 500 mg once a day).

Individuals in whom eradication was not achieved after two courses of treatment received personalized treatment based on data from antibiotic susceptibility tests. In addition to the testing of cure, the antibiotic susceptibility testing data for *H. pylori* infection were assessed in a subset of participants who had endoscopic evaluation; this was used to optimize treatment protocols and address the potential changes in antibiotic resistance over time [11, 15].

For the test-of-cure data, after one or two courses of antibiotic treatment, the *H. pylori* eradication rates were 91.9% (95% CI, 91.3–92.5%) in all individuals who took medication and 97.6% (95% CI, 97.2–97.9%) in those who used at least 80% of the medication; 5.7% of individuals received more than one course of treatment. Among individuals in whom *H. pylori* eradication was successful, the reinfection rate was estimated as 0.3 per 100 person-years. For the antibiogram data from a total of 1110 individuals with *H. pylori* infection (Fig. 7.4), a stepwise increase in antibiotic-resistant strains was noted in all three groups: (i) individuals who had not yet received treatment; (ii) individuals in whom one course of treatment had failed; and (iii) individuals in whom two courses of treatment had failed and who required tailored management. The primary resistance rates over time mirrored the trends observed in the Asia–Pacific Region [7], with increases in resistance rates for clarithromycin, metronidazole, and levofloxacin, while resistance rates for amoxicillin and tetracycline remained stable.

The findings from this pragmatic clinical trial offer important insights into antibiotic stewardship in the context of an *H. pylori* screen-and-treat programme. First, the findings emphasize the importance of having the infrastructure in place to monitor whether antibiotic use aligns with the principles of antibiotic stewardship, supported by the commitment of health-care officials and professional leaders. Second, the findings from the antibiogram underscore the need to adopt more effective first-line treatment regimens. In this trial, the antibiotic resistance patterns aligned with the recommendations of the WHO AWaRe classification of antibiotics [36]. Resistance rates for clarithromycin and levofloxacin, compared with those for amoxicillin and tetracycline, showed a greater tendency to increase with treatment failures (Fig. 7.4A), which suggests that the empirical use of clarithromycin and levofloxacin may no longer be justified, particularly for retreatment. This highlights the need to consider bismuth-containing quadruple therapy as the most feasible option for initial treatment. Third, the prevalence of primary clarithromycin-resistant *H. pylori* infection

and levofloxacin-resistant *H. pylori* infection in treatment-naive patients has increased more over time compared with the prevalence of resistance to other antibiotics, probably because of the increased use of these antibiotics for other diseases (Fig. 7.4B). To implement an *H. pylori* screen-and-treat programme on a population scale, a simplified regimen that has fewer antibiotics, has a shorter duration, and uses antibiotics with a lower potential for emerging resistance, while maintaining efficacy, is needed to reduce overall antibiotic use.

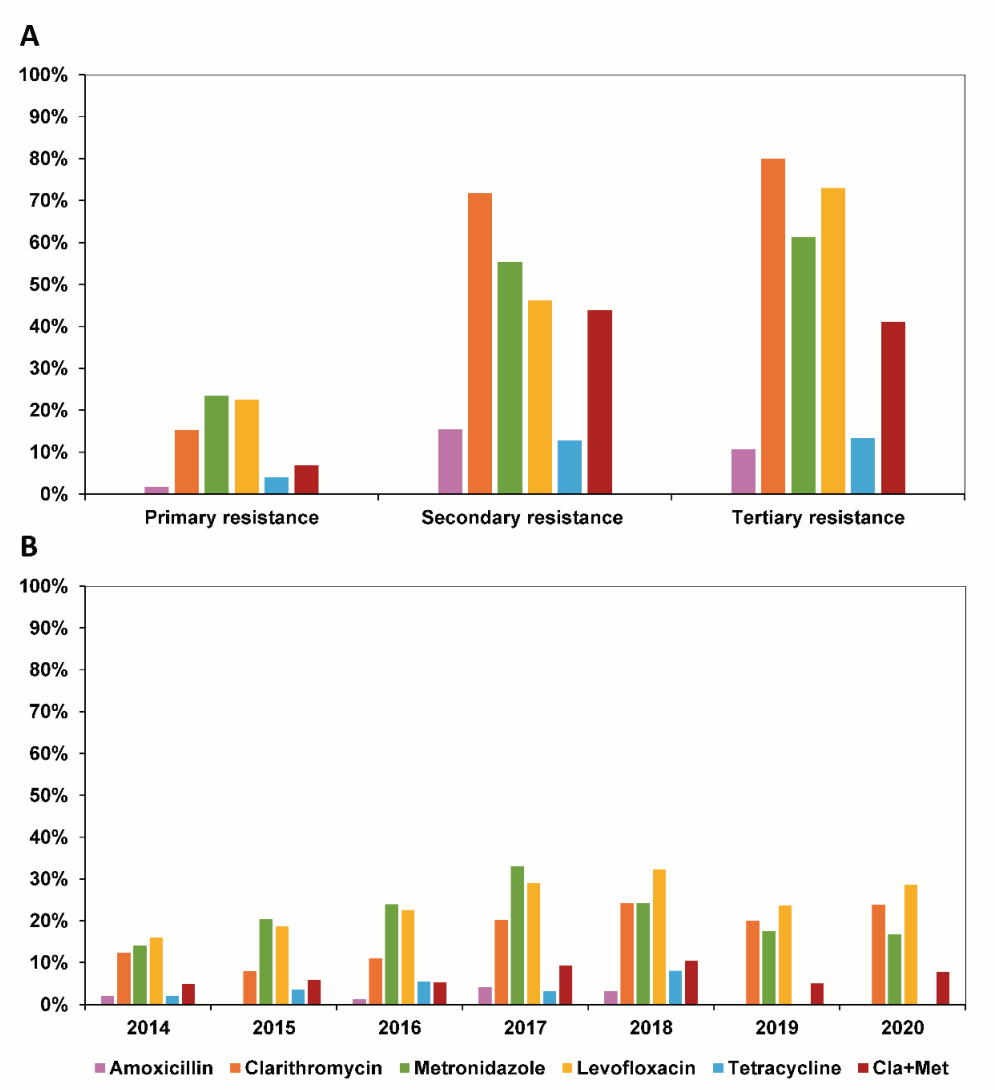

Fig. 7.4. Cumulative antibiograms of *H. pylori* for monitoring antibiotic resistance in a community-based randomized clinical trial to screen for *H. pylori* infection for gastric cancer prevention in 2014–2020: (A) primary, secondary, and tertiary resistance rates of *H. pylori*; (B) primary resistance rates of *H. pylori* over time. Primary resistance rates included individuals who had not yet received antibiotic treatment. Secondary resistance rates included individuals in whom one course of treatment had failed. Tertiary resistance rates included individuals in whom two courses of treatment had failed and who required tailored management. Cla+Met, dual resistance to clarithromycin and metronidazole. Source: Compiled from Lee et al. (2024) [15].

7.6 A prophylactic vaccine against *H. pylori*

Developing a prophylactic vaccine against *H. pylori* would be the ideal solution to the problems associated with antibiotic use in screen-and-treat programmes. In the USA, a cost–effectiveness analysis demonstrated that vaccinating children could prevent *H. pylori* infection and reduce the incidence of gastric cancer, which would save on long-term health-care expenses [71]. However, despite three decades of research on *H. pylori* vaccines, only a few candidates have reached the clinical trial stage and no single candidate induced long-lasting protection against *H. pylori* in terms of sterilizing immunity. Thus, no commercial vaccine is available on the market. This is because (i) *H. pylori* has developed several powerful strategies to evade both innate and adaptive immune responses upon infection [72–73], and (ii) the correlates of protection are still not known, which makes it challenging to guide clinical trials. The immune response to *H. pylori* infection is a complex interplay of innate and adaptive immune mechanisms that ultimately leads to chronic inflammation. *H. pylori* infection triggers the activation of various immune cells, including neutrophils, macrophages, and dendritic cells. This activation leads to the production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, IL-12, and IL-23, which are crucial for the differentiation of T helper (Th) cells into Th1 and Th17 cells. The adaptive immune response to *H. pylori* involves the activation of specific T and B lymphocytes, leading to the production of antibodies and the generation of memory cells. CD4-positive T cells, particularly those that differentiate into the Th1 and Th17 subsets, play a crucial role in orchestrating the immune response against *H. pylori*. Recently, CD8-positive cells have been shown to be involved in early responses to infection and long-term immunological memory [74]. Moreover, *H. pylori* virulence factors, especially CagA, play a pivotal role in enhancing the immune response. *H. pylori* has also developed numerous immune evasion strategies that not only enable chronic persistence but also complicate the development of a vaccine against this pathogen [72]. One of the primary mechanisms of immune evasion used by *H. pylori* is the modulation of host immune responses, particularly through the induction of regulatory T cells and the suppression of effector T cell functions. This skewing of the immune response towards a more tolerogenic state enables *H. pylori* to persist in the gastric mucosa despite the presence of a robust immune response [73]. Such immune

evasion mechanisms must be overcome to develop efficacious vaccines, but they have mostly been neglected in previous approaches to vaccine development.

Thus, the efficacy of *H. pylori* vaccines in the preclinical stage has been variable and remains a major challenge. In addition, regulatory hurdles, including the need for rigorous testing and approval processes, can substantially delay the introduction of a new vaccine [75]. Vaccine candidates must demonstrate safety and efficacy in extensive clinical trials, which are expensive and time-consuming. Regulatory agencies require comprehensive data on immunogenicity, long-term protection, and potential adverse effects. The complexity of the immune response to *H. pylori* and the design of an effective vaccine pose additional challenges [76]. Previous vaccine trials have encountered issues including inadequate immune responses and adverse events, which have complicated the path to regulatory approval [77]. However, a phase III trial in children published in 2015 has shown some protectivity for the first years after vaccination [78]. Although the effect was not long-lasting and protection was only 71.8% after 1 year, this was the first human trial ever that showed that prophylactic immunization can protect against *H. pylori* infection, and it fuels the hope that optimized vaccines can provide better protection. This prophylactic vaccine candidate (developed by Kangwei Biological Technology) did not enter the market, and beyond this there are no advanced vaccine candidates in clinical development (clinicaltrials.gov, as at 11 November 2024). Therefore, a vaccine is currently not a viable option for preventing gastric cancer, and the only approach is to offer antibiotic therapy to people with *H. pylori* infection.

However, there are a few vaccine candidates that are in preclinical development. One approach, by a European consortium of nine partners funded under the Horizon Europe programme [79], uses highly conserved surface antigens together with novel delivery technologies for mucosal immunization to achieve a protective mucosal immune response. The lead candidate is anticipated to enter the first clinical trial in 2026. A potential therapeutic vaccine being developed by scientists in Umeå, Sweden, uses an approach based on the natural immunity generated against *H. pylori*. This project identified antibody species directed against the BabA protein, which mediates the binding of *H. pylori* to stomach epithelial cells. By immunizing with a BabA epitope, the researchers were able to elicit a blocking immune response, which prevents binding of *H. pylori* as well as cancer development in mice [80], even

without clearing the infection. This approach is still at the preclinical stage and will require substantial capital investment if it is to advance to a clinical proof of concept.

7.7 Conclusions

In a population-based *H. pylori* screen-and-treat programme, increased antibiotic use is expected. To reduce the risk of increasing antibiotic resistance within the population, it is essential to establish an antibiotic stewardship programme in advance, guided by a multidisciplinary team. The programme should provide comprehensive guidance on the appropriate use of antibiotics for *H. pylori* infection that reaches both clinicians and the public and includes perspectives on both individual-level management and broader policy-making. Data from *H. pylori* antibiotic susceptibility testing, similar to the antibiogram methods used for other common bacteria, along with the use of test-of-cure data as an indirect approach, can help reduce population exposure to ineffective antibiotics, thereby lowering the risk of selecting for and driving the emergence of antibiotic-resistant strains. Currently, an effective *H. pylori* vaccine that is suitable for population-based gastric cancer prevention programmes is not available. Therefore, policy-makers implementing *H. pylori* screen-and-treat programmes must work to minimize the potential negative impacts of these programmes. Adopting robust antibiotic stewardship measures is of paramount importance; these include carefully selecting eradication regimens, using retesting strategies after therapy, and continuously monitoring eradication rates and antibiotic resistance.

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