Original research

Helicobacter pylori antibiotic resistance: a global challenge in search of solutions

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ABSTRACT

Background *Helicobacter pylori* resistance to antibiotics commonly used in eradication regimens is increasing dramatically in many locations; new strategies are needed to manage this infectious disease.

Objective This study's aim was to collect and update information on antibiotic resistance (AR) rates in *H. pylori* as well as current strategies for *H. pylori* management, including public health issues, from a global perspective.

Design An international survey was conducted in 31 countries on 6 continents to address key issues concerning the management of *H. pylori*-related AR. Individual aspects included the prevalence of AR for specific antibiotics, antibiotic susceptibility testing (AST) in different healthcare systems, availability of drugs, reimbursement issues and strategies for *H. pylori* AR surveillance.

Results Resistance to the most effective antibiotics used in *H. pylori* eradication regimens is increasing globally, with clarithromycin and levofloxacin resistance exceeding 15% in 24/31 and 18/31 countries, respectively. Amoxicillin remains an exception, with resistance rates under 2% in 14/31 countries; though African countries have reported amoxicillin resistance rates of over 90%. Bismuth-based treatment regimens are the most effective and are recommended as first-line treatment in several countries. However, more than 1 billion inhabitants worldwide have no access to bismuth-based regimens. PCR-based tests for AR are used in 16/26 countries but are reimbursed in only 4, while next generation sequencing-based tests are available, but not reimbursed, in 3 countries. In 22/26 countries only culture-based methods are available (reimbursed in 9/26 countries). AR surveillance programmes have only been established in 4/26 countries. Therefore, in most countries, empirical therapy with the most effective local regimen available locally is practiced.

Conclusion The dramatic global rise in *H. pylori* antibiotic resistance requires an urgent revision of current management strategies. Possible solutions include AST-based selection of effective treatment regimens, identification of novel combinations of existing drugs and exploration of novel drugs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Many countries have reported an increase in *Helicobacter pylori* resistance, leading to significant failure rates of current eradication therapies. Most data on *H. pylori* antibiotic resistance in the community are based on phenotypic testing. Only recently has molecular genotypic testing become more widely available. For this analysis, we conducted a database search. Only English-language publications published between 2018 and 2024 were included. The search terms used were: 'Helicobacter pylori [Title/Abstract]) AND (resistance [Title/Abstract])) OR (resistant[Title/Abstract])) OR (antibiotic susceptibility testing [Title/Abstract])) OR (Metronidazole[Title/Abstract])) OR (Clarithromycin[Title/Abstract])) OR (Levofloxacin[Title/Abstract])) OR (country[Title/Abstract])) NOT (review[Title/Abstract])) NOT (meta-analysis[Title/Abstract]))'.

INTRODUCTION

The definition of *Helicobacter pylori* gastritis as an infectious disease has been a game changer in the management of *H. pylori* infection.[1]

Whereas previously, *H. pylori* eradication therapies were only recommended for specifically defined clinical indications, they are now recommended for all infected individuals, independent of the treatment of symptoms as well as for preventive purposes.[2] However, the widespread use of *H. pylori* eradication therapies has led to an increase in

WHAT THIS STUDY ADDS

⇒ Our survey updates and extends the global mapping of antibiotic resistance to include data from 6 continents and 31 countries. Results indicate a rapid growth in antibiotic resistance worldwide. Major challenges to *H. pylori* management were identified, including the limited availability of molecular antibiotic susceptibility testing to select individualised treatment regimens and a lack of reimbursement for these tests. In many countries, adequate empirical therapy is not accessible due to the unavailability of relevant medications (eg, bismuth).

⇒ Antimicrobial resistance rates reported in our survey exceeded the cut-off value of 15% recommended by national and international guidelines for the empirical use of clarithromycin and levofloxacin in first-line and second-line eradication regimens.

⇒ It is of concern that antibiotic resistance surveillance programmes have been implemented in only 5/26 countries.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We have identified limitations in current strategies to counteract the progressively increasing antibiotic resistance of *H. pylori*.

⇒ This should raise awareness among healthcare officials and authorities of the need to develop appropriate logistics for *H. pylori* resistance testing, provide access to effective and safe drugs for use in *H. pylori* eradication regimens and seek affordable reimbursement regulations worldwide. It also encourages the establishment of global surveillance programmes to monitor antibiotic resistance rates and therapeutic efficacy in the management of *H. pylori*.

antibiotic resistance (AR) of *H. pylori,* as well as other bacteria, thereby increasing eradication failure rates.[3 4]

The high rates of *H. pylori* resistance to the antibiotics that were previously most effective in eradication regimens mandate the development of new strategies, including intensified regional antibiotic resistance surveillance, individual antibiotic susceptibility testing (AST) and the global implementation of antimicrobial stewardship measures.[5–10]

The antibiotics that have received much attention are clarithromycin, and to a lesser extent, levofloxacin.[11] Both drugs have strong bactericidal activity on susceptible *H. pylori* strains and are key components of current eradication regimens. Back in 2017, the WHO flagged *H. pylori* as a high-priority pathogen for antibiotic research due to the dramatic increase in clarithromycin resistance globally.[11 12] In 2024, 'based on evidence and expert consensus', clarithromycin was surprisingly removed from the priority list, despite the continued increase in clarithromycin resistance in most countries.[13] Recent data also suggest that *H. pylori* resistance to levofloxacin is increasing in many regions of the world, posing a further critical problem regarding the selection of effective alternative eradication regimens.[14] In case of high resistance to clarithromycin, the use of levofloxacin is prioritised in first-line and second-line eradication therapy, especially in the absence of bismuth.[6] As an exception, in Japan the use of sitafloxacin is recommended.[15 16]

The aim of this study is to update and extend information on global AR rates of *H. pylori* and on current strategies for *H. pylori* management. The survey includes public health aspects, recommendations from national and international guidelines/consensus reports, and suggests recommendations for an optimised management of *H. pylori* against the challenge of AR.

METHODS

An international group was assembled that included 24 gastroenterologists and 7 clinical microbiologists from 23 countries with substantial expertise and a relevant publication record in the field of *H. pylori*. General practitioners and family physicians are the essential healthcare providers in the clinical management of *H. pylori* infection. However, in most countries they are not directly involved in monitoring treatment effectiveness and surveillance of antibiotic resistance. They are responsible for patient care and reach out for guidance in optimised clinical management from guidelines and specialists. For this reason, we restricted the invitation to specialists, gastroenterologists and microbiologists, with special dedication to *H. pylori* and related diseases, to participate in the survey.

We first reviewed data on drug resistance from 2018 to 2023 using a search on PubMed to identify relevant publications via the following search terms: 'Helicobacter pylori [Title/Abstract]) AND (resistance [Title/Abstract])) OR (resistant[Title/Abstract])) OR (antibiotic susceptibility testing [Title/Abstract])) OR (Metronidazole[Title/Abstract])) OR (Clarithromycin[Title/Abstract])) OR (Levofloxacin[Title/Abstract])) OR (country[Title/Abstract])) NOT (review[Title/Abstract])) NOT (meta-analysis[Title/Abstract]))'. Secondary literature (eg, review articles and meta-analyses) was excluded from the data collected. Articles were checked for eligibility based on inclusion criteria: AR of *H. pylori* in therapy-naïve adults. Further updates on regional AR of *H. pylori* were provided by experts on the panel.

International and national guidelines were scrutinised for statements relevant to *H. pylori* therapy, with a focus on the management of *H. pylori* resistance (see online supplemental file 1).

All experts included in this study responded to questionnaires (see online supplemental file 1) on the real-world conditions of *H. pylori* management in their own countries, including logistics, access to and reimbursement of the AST and antibiotics as well as current or planned national resistance surveillance programmes.

RESULTS

The data obtained from the survey and literature research are summarised in tables 1–4. Table 1 shows the AR to clarithromycin, levofloxacin, metronidazole, amoxicillin, rifampicin, tetracycline and ciprofloxacin in each continent. Within each continent, there was considerable variation between each country, as shown in table 2 and figure 1.

The availability of drugs also varies considerably from country to country. While clarithromycin is universally available, other drugs are more restricted (eg, bismuth salts are not allowed in Nigeria, Democratic Republic of the Congo, Malaysia, Indonesia, Korea, Japan and Brazil; tetracycline is not allowed in Egypt, South Africa and Malaysia) (table 3). Bismuth in a single form or in a fixed formulation is unavailable in 7/26 countries included in the survey. This results in an estimated 1 billion people being denied access to bismuth-containing treatments.

The availability and reimbursement of AST is shown in table 4. Access to phenotypic AST was limited to 13/26 countries, of which only 9 were reimbursed. Molecular testing (PCR) of AR is available and reimbursed in only 4/26 countries. PCR testing is not reimbursed in 12/26 countries and is not available in 10/26

Table 1 *Helicobacter pylori* antibiotic resistance (%) at continental level from 2018 to 2023 according to literature references and personal data from experts

	Clarithromycin	Levofloxacin	Metronidazole	Amoxicillin	Rifampicin	Tetracycline	Ciprofloxacin
Africa	13.6–66.7	20–65.7	62.7–100	97.1	90	2.9–100	17–100
North America	16.7–19	42.6	29.3–35	1.1	<1%	1.7	
South America	14.4–31.3	13.5–29	54	2.7		0.7	
Asia–Pacific	7.7–92.1	3.3–65.6	4.2–81.7	0–50	22.8	0–16.1	37
Europe	12–22.4	13–20.3	17–62.4	0–3.5	0–4.3	0–0.5	

countries. AST based on next generation sequencing (NGS) is only available in 3/26 countries. None of these three countries has a reimbursement policy for these tests in place.

Only 4/26 (15.3%) of the countries in this survey (Spain, Germany, Japan, Korea) have regular AR surveillance measures in place (data not shown).

DISCUSSION

This survey provides a representative picture of the development of *H. pylori* AR over the past 5 years. Globally, resistance rates to critical antibiotics used for eradication exceed the most recent data reported in the literature.[3 5 17 18] In this highly dynamic field,

Table 2 *Helicobacter pylori* antibiotic resistance (%) at country level from 2018 to 2023 according to literature references and personal data from experts

	Clarithromycin	Levofloxacin	Metronidazole	Amoxicillin	Rifampicin	Tetracycline	Ciprofloxacin
Africa							
Egypt[58–60]	40–52.8	20	100	81.9–95	90	25–37.5	17–41.7
South Africa	No current data	No current data	No current data	No current data	No current data	No current data	No current data
Nigeria[61 62]	25	nd	100	30–90.8	nd	13–100	100
Tanzania[63]	28.7	58.8	nd	nd	nd	nd	nd
Morocco[64]	14	nd	62.7	nd	nd	nd	nd
Cameroon[65 66]	13.6	nd	97.9	97.1	nd	2.9	nd
DRC[67 68]	23.5	65.7	90.2	34.3	nd	4	nd
Zambia[69]	28	nd	nd	nd	nd	nd	nd
Ethiopia[70]	66.7	nd	91.7	91.7	nd	37.5	66.7
North America							
Canada[71]	19	nd	35	nd	nd	nd	nd
USA[72]	16.7	42.6	29.3	1.1	nd	1.7	nd
Mexico[73 74]	12–32.2	18.5	58	1.8	nd	nd	nd
South America							
Brazil[75 76]	14.4–16.9	13.5	54	nd	nd	nd	nd
Chile[77 78]	26–31.3	29	2.7	2.7	nd	0.7	nd
Asia–Pacific							
Australia	no current data	no current data	no current data	no current data	no current data	no current data	no current data
Cambodia[79]	27.8	50	78.6	0	nd	0	nd
China[80]	34	35	78	3	nd	2	nd
Iran[22 80–82]	20.1	17.7	57.9	15.9	21.3	12.2	22.6
Japan[83–85]	35.5	nd	4.2	2.7	nd	nd	nd
Korea[86]	17.8	37	29.5	9.5	nd	0	37
Malaysia[87]	14.8	3.3	nd	0	nd	nd	nd
Myanmar[88]	7.7	33.8	80	4.6	nd	0	nd
Singapore[89]	13.7–16.6	16.6–16.9	nd	7–7.2	nd	0	nd
Thailand[90]	15.6	nd	34.1	0	nd	0	nd
Vietnam[91 92]	61.8–92.1	31.6–41.8	14.5–76.3	27.2–50	nd	0	nd
India[93–96]	8.7–45	11.5–65.6	27.2–81.7	0–24	nd	0–5.3	nd
Europe							
France[97]	20.9–23	17.6–18.1	58.6–47.5	0–0	0.9–0.7	0–0	nd
Germany[98]	17.4	20.3	17.4	0	4.3	0	nd
Italy[99–101]	37.8	19.2–25.6	16.4–33.6	1.6	nd	0	nd
Spain[51 66 82 94 102]	12–15 adults 45–53 children	13–17 adults 7.9 children	24–32 adults 6.3–16 children	0–3.5 adults 1–2 children	nd	0–0.5 adults nd children	nd
UK	No current data	No current data	No current data	No current data	No current data	No current data	No current data

DRC, Democratic Republic of Congo; nd, not done; UK, United Kingdom; USA, United States of America.

Table 3 Availability of antibiotics and acid suppressants used in *Helicobacter pylori* eradication regimens in various countries. (A) available and reimbursed, (B) available and not reimbursed and (C) not available

Countries in Africa	**Egypt**	**South Africa**	**Nigeria**	**Democratic Republic of Congo**			
Antibiotics and acid suppressants available/treatment regimens							
PPIs	A	A	A	B			
P-CABs	A	C	C	C			
Clarithromycin	A	C	A	B			
Amoxicillin	A	A	A	B			
Metronidazole	A	A	A	B			
Tetracycline	C	C	A	B			
Levofloxacin	A	A	A	B			
Tinidazole	A	C	B	B			
Bismuth	A	A	C	B			
Rifabutin	C	C	C	C			
Countries in Asia–Pacific	**Vietnam**	**Singapore**	**Thailand**	**Malaysia**	**Cambodia**	**Indonesia**	**Myanmar**
Antibiotics and acid suppressants available/treatment regimens							
PPIs	A	A	A	A	A	A	B
P-CABs	C	A	A/B depending on reimbursement scheme	A	B	B	C
Clarithromycin	A	A	A	A	A	B	B
Amoxicillin	A	A	A	A	A	A	B
Metronidazole	A	A	A	A	A	A	B
Tetracycline	B	A	A	C	A	A	B
Levofloxacin	A	A	A	B	A	A	B
Tinidazole	A	C	A	C	A	C	B
Bismuth	A	A	A/B depending on reimbursement scheme	C	B	C	B
Rifabutin	C	B	C	B	C	B	C
Countries Asia–Pacific (continued)	**China**	**Korea**	**Japan**	**Iran**	**Australia**		
Antibiotics and acid suppressants available/treatment regimens							
PPIs	A	A	A	A	A		
P-CABs	A	A	A	C	C		
Clarithromycin	A	A	A	B	A		
Amoxicillin	A	A	A	A	A		
Metronidazole	A	A	A	A	A		
Tetracycline	B	A	B	A	A		
Levofloxacin	A	A	B	B	A		
Tinidazole	B	C	B	C	C		
Bismuth	A	C	C	A	B		
Rifabutin	B	A	B	C	A		
Countries in Europe	**France**	**Germany**	**Italy**	**Spain**	**UK**		
Antibiotics and acid suppressants available/treatment regimens							
PPIs	A	A	A	A	A		
P-CABs	C	C	C	C	C		
Clarithromycin	A	A	A	A	A		
Amoxicillin	A	A	A	A	A		
Metronidazole	A	A	A	A	A		
Tetracycline	A	A	A	A	A		
Levofloxacin	A	A	A	A	A		
Tinidazole	A	C	A	A	A		
Bismuth	A	A	A	A	A		
Rifabutin	A	A	A	A	A		
Countries in North America	**Canada**	**USA**					
Antibiotics and acid suppressants available/treatment regimens							
PPIs	A	A					
P-CABs	C	A					

Continued

Table 3 Continued

Countries in Africa	Egypt	South Africa	Nigeria	Democratic Republic of Congo
Clarithromycin	A	A		
Amoxicillin	A	A		
Metronidazole	A	A		
Tetracycline	A	A		
Levofloxacin	A	A		
Tinidazole	A	A		
Bismuth	A	A		
Rifabutin	A	A		
Countries in South America	**Brazil**	**Chile**	**Mexico**	
Antibiotics and acid suppressants available/treatment regimens				
PPIs	A	A	A	
P-CABs	B	C	A	
Clarithromycin	A	A	A	
Amoxicillin	A	A	A	
Metronidazole	A	A	A	
Tetracycline	A	A	A	
Levofloxacin	A	A	A	
Tinidazole	A	C	A	
Bismuth	C	A	A	
Rifabutin	C	B	C	

P-CABs, potassium-competitive acid blockers; PPIs, proton pump inhibitors.

the time lag between data collection and publication release may account for this discrepancy.

The magnitude of the increase in AR varies between individual antibiotics used for eradication and also differs widely between continents and countries within each continent.

In Europe, clarithromycin resistance ranges from 12% to 22.4%. The most recent survey from Europe reported an increase of clarithromycin resistance by>10% compared with 10 years ago.[18] In Asia, clarithromycin resistance ranged from 7% to 92.1%. This is a dramatic increase when compared with

Table 4 Reimbursement and availability for different methods of antibiotic susceptibility testing according to health policies in various countries

Countries in Africa	Egypt	South Africa	Nigeria	Democratic Republic of Congo			
Antibiotic susceptibility testing availability and reimbursement							
Culture-based	B	B	B	B			
PCR-based	C***	C***	B	C***			
NGS-based	C***	C***	C***	C***			
Countries in Asia–Pacific	**Vietnam**	**Singapore**	**Thailand**	**Malaysia**	**Cambodia**	**Indonesia**	**Myanmar**
Culture-based	B	B	B	B	C	B	B
PCR-based	C***	B	B	B	C***	B	B
NGS-based	C***	C***	C***	C***	C***	C***	C***
Countries in Asia–Pacific (continued)	**China**	**Korea**	**Japan**	**Iran**	**Australia**		
Culture-based	B	C	B	C	A		
PCR-based	B	A	A*	C***	C***		
NGS-based	C***	C***	C***	C***	C***		
Countries in Europe	**France**	**Germany**	**Italy**	**Spain**	**UK**		
Culture-based	A	A	A	A	A		
PCR-based	A	B	B	A	C***		
NGS-based	B	C***	C***	C***	C***		
Countries in North America	**Canada**	**USA**	**Mexico**				
Culture-based	A	A	B				
PCR-based	B	B	B				
NGS-based	B	B	C***				
Countries in South America	**Brazil**	**Chile**					
Culture-based	C	A**					
PCR-based	C	C					
NGS-based	C***	C***					

(A) available and reimbursed, (B) available but not reimbursed and (C) not available. *restricted to clarithromycin, **restricted to metronidazole, *** not available, does not exclude the availability of technologies in countries (eg, reference centres or scientific laboratories) but not available for use in clinical practice.
NGS, next generation sequencing; PCR, Polymerase Chain Reaction.

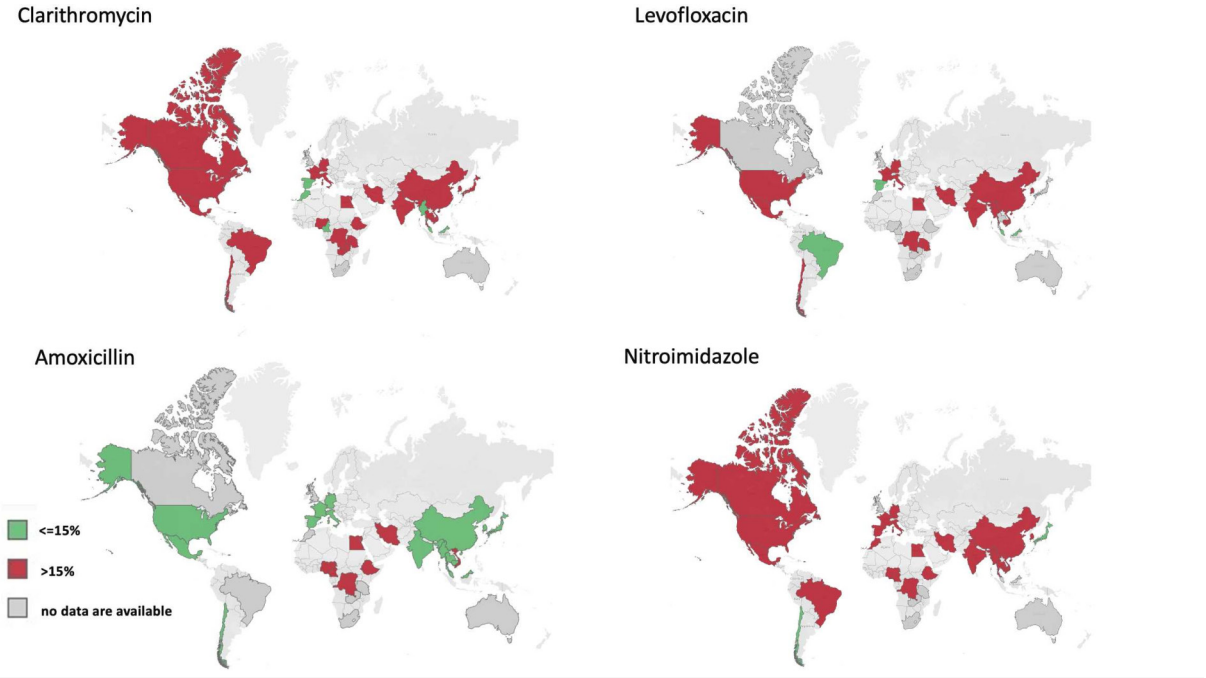

Figure 1 Antibiotic resistance of Helicbacter pylori against frequently used antibiotics. Data included were published between 2018 and 2023.

data released in 2024, which reported a primary clarithromycin resistance rate of 22%.[5] In Africa, clarithromycin resistance rates ranged from 13.6% to 66.7%, but no previous data were available. For comparison, according to our survey, levofloxacin resistance ranged from 13% to 20.3% in Europe, 42.6% in North America, 13.5% to 29% in South America, 20% to 65.7% in Africa and 3.3% to 65.6% in the Asia–Pacific region. A previous report showed an increase of levofloxacin resistance from 15.8% to 20.3% in treatment-naïve patients in Europe.[18] At the country level, increasing resistance rates are now reported in up to 50% of Asian countries (eg, Cambodia 50%, China 35%, Vietnam 31.6–41.8%, Korea 37% and Myanmar 33.8%).[17] Just as clarithromycin resistance cross-reacts with all macrolides, levofloxacin resistance affects all quinolones due to their cross-reactivity in inducing resistance (tables 1 and 2; figure 1). The increasing resistance to levofloxacin, which is recommended as the antibiotic of choice for second-line treatment by consensus reports in Europe,[6] Asia (except Japan, where sitafloxacin is the recommended second-line treatment[19]) and Africa,[20 21] hinders its empirical use and suggests selection should instead be based on AST.

Global resistance rates of amoxicillin vary from 0–97.1% and in most countries do not exceed 1%.[5] Confirmatory studies on amoxicillin resistance in Africa are important. In a recent analysis of time trends in the development of AR in children, amoxicillin resistance was consistently low at 4%.[22] Amoxicillin is an essential component of triple and dual therapy eradication regimens. High-dose proton pump inhibitor (PPI) therapy in combination with amoxicillin is an effective option for *H. pylori* eradication. Dual therapy can now be augmented by potassium-competitive acid blockers (P-CABs) to provide even stronger acid inhibition.[23 24] A potential limitation regarding the general recommendations for the use of dual therapies is that emerging amoxicillin resistance is>70% in some countries in Africa[25] and>15% in some countries in Asia (27.2–50% in Vietnam and 15.9% in Iran) (tables 1 and 2; figure 1). Reflecting antimicrobial stewardship measures the reported resistance rates from Africa and some Asian countries need to be confirmed by future studies. In most countries around the world amoxicillin resistance is currently not in focus, which is reflected by its excellent efficacy of dual therapies including amoxicillin and P-CABs.[26 27]

Rifabutin resistance is negligible, with a global resistance rate in the range of 0–0.2%, so AST is not currently required for this drug.[28] Rifabutin is generally used as a rescue medication, only used as a first-line drug in the USA. Reasons for limiting rifabutin-containing regimens as rescue therapy only are based on the use of this drug for other critical infections and the risk of severe although rare adverse events (eg, myelotoxicity).

Nitroimidazoles (eg, metronidazole) deserve special consideration because of the highest resistance rates worldwide. Chile is likely to be an exception, as furazolidone is predominantly used instead of metronidazole.[29–31] Nitroimidazoles have a subordinate role in PPI-based triple combinations and are usually preferred in combination with amoxicillin.

However, metronidazole has been used successfully in bismuth-based quadruple therapy (BQT).[32] Combination with bismuth may synergise with metronidazole and overcome resistance.[33] Real-world data from Europe confirm a therapeutic efficacy of>90% in BQT, independent of metronidazole resistance.[3 34] Tetracycline is also part of the BQT regimen and has an established resistance of less than 1%.[32]

The empirical use of BQT instead of PPI triple is an important strategy to limit further increases in AR and reduce treatment failures. International and several national guidelines recommend that BQT should be considered as first-line treatment due to the lack of need for considering AR.[6 9 20 35–46]

In many countries, BQT has only recently become available, but it is still not accessible to more than 1 billion people in the world. BQT is not available in countries such as Nigeria, Malaysia, Indonesia, Republic of Korea, Japan and Brazil, as shown in table 3.

In many countries, clarithromycin-based triple therapy is retained as a first-line option. Guidelines have long recommended the empirical use of PPI triple only if clarithromycin

resistance is<15% and is properly monitored.[5 9 17 47] However, because, clarithromycin resistance rates are significantly higher than 15% in numerous countries, clarithromycin-based triple should no longer be empirically prescribed.[17]

There are two opposing views concerning the role of AST in the management of *H. pylori* infection. One view is that the choice of treatment regimen should always be based on an individual strain's AST. The opposing position is that the preferred strategy is to choose an effective empirical therapy that is typically unaffected by AR surveilled on a population level. There was general agreement among the experts on the broader use of AST if certain antibiotics are intended to be used. Current recommendations for antibiotic (clarithromycin and levofloxacin) resistance testing vary between guidelines, with some recommending that AST has already been used in the first line,[6 35] and others only after treatment failure[20] (online supplemental file 1 and 2).[6] According to this survey, AST is currently available routinely in only a few countries (table 2). AST in most countries depends on successful bacterial culture obtained from gastric biopsies (phenotypic AR testing). In most parts of the world, molecular testing is rarely or not at all available for use in clinical practice[7 8 10 48 49]). A change towards broader use of molecular AST would benefit the strategy of selecting eradication regimens based on antibiotic resistance because phenotypic culture-based AST is cumbersome and not always successful, and it requires gastric biopsies (and therefore an invasive procedure to obtain these), and specialised microbiological laboratories, resulting in high costs (table 4). Genotypic AST (PCR-based or NGS-based) is more convenient and can be applied to gastric aspirates, gastric biopsies, and, much less invasively stool samples, though further validation is required for the latter.[7 8 50] Molecular tests are not currently accessible in many parts of the world and are often not reimbursed by national healthcare systems even when they are available. Access to and reimbursement for molecular tests for clarithromycin and levofloxacin resistance are only currently available in Japan and Chile (table 4). In addition, the time delay for additional diagnostic measures before initiating treatment and the necessity of additional visits might hamper the broad implementation of AST in general management.

The concept of selecting an effective empirical therapy that is not compromised by AR based on regional AR rates requires AR surveillance programmes. To date, only a few countries have national antibiotic resistance/susceptibility registries. Japan, Korea, Spain and Germany are running joint or individual prospective programmes to collect resistance data. In the UK, only isolates following treatment failure are centrally analysed, but the service was just put on hold due to capacity issues. AR data are often used to draw conclusions from an epidemiological perspective, and these are only available in the selective context of therapy studies or single-centre studies.[51] More structured efforts are needed to gain a representative insight into *H. pylori* resistance among the world's population and the need to implement AST-based treatment recommendations (online supplemental file 2). The lack of such data prevents adequate recommendations for first-line combinations, which is expected to lead to a further reduction in successful eradication rates.

Antimicrobial stewardship measures need to be consequently included in *H. pylori* management strategies. According to the selected principles of antimicrobial stewardship, BQT is the most suitable regimen and thus recommended in first line. The reason for this is that the efficacy of standard BQT with tetracycline and metronidazole is not jeopardised by antibiotic resistance and safety concerns. The contrary holds true for clarithromycin and levofloxacin-containing regimens in triple- and non-bismuth-quadruple therapies, and thus they should not be used in first line except when their efficacy can be predicted by a positive AST. However, from the responses in our survey, AST is only available in a few, mostly specialised centres only, and thus their use lacks in practicality.[52]

AR data are of crucial importance in laying the foundation for evidence-guided strategies and successful management of *H. pylori* infections. Currently available data on molecular AST are based on small sample numbers, and in addition, there is a lack of comparability of methods used in different settings. The majority of data are still obtained via culture-based methods, but their major complexities in handling and logistics limit broader use. Molecular testing holds greater promise for more widespread implementation[7 8 10 48 49].

There are relevant limitations of our survey, including incomplete epidemiological data from large parts of the world, heterogenous measures used for AST in different studies and frequently small cohorts analysed. It results from our survey that phenotypic testing is still the gold standard for the detection of antibiotic resistance and the only one available in most countries. However, there are important limitations for its use, as apart from challenges in the management of logistics, in the majority of countries (pretherapeutic) testing is not reimbursed.

Molecular testing for AST in most countries is neither available nor reimbursed with the exception of a few Asian countries (Korea, Japan). Molecular testing in stool samples, although reported from some centres as an attractive way to be included in non-invasive testing of antibiotic resistance is at present insufficiently validated for use in clinical practice and not ready for general implementation.

Conclusions and future directions

Our study documents high rates of *H. pylori* AR, which are further increasing at pace in many parts of the world. The greatest concerns relate to the use of clarithromycin and levofloxacin, and require urgent revision of current therapeutic strategies. The options are to either select individually effective antibiotics via regular use of AST, or to use empirical therapies that are minimally or not affected by AR. In view of these circumstances, it is unclear why clarithromycin-resistant *H. pylori* was removed from the WHO's list of high-priority organisms[53] for which urgent additional research is needed.[54]

Effective antibiotics for first-line treatment and alternatives in case of first-line failure are still missing in certain parts of the world and need to be made universally available. Bismuth-based combinations, which are currently the least influenced by AR, are not yet available in many countries.[55–57] There is an urgent need for the supply of such therapies to keep eradication effective and to stop further uncontrolled progression of AR. Integrating antimicrobial stewardship measures into *H. pylori* management could reduce antimicrobial resistance, improve patient outcomes, optimise the use of effective antibiotics and lower healthcare costs.[53] There is a need to extend measures for AR surveillance measures which are running only in 4/26 countries surveyed.

In this context, the identification of novel combinations and/or doses of existing drugs or the inclusion of novel drugs in eradication regimens deserves sustained effort. The introduction of new potent acid suppressive agents has already influenced development positively, and the search for novel selective anti-*H. pylori* agents and vaccinations continues to be important goals for the immediate future.

International and national guidelines remain important drivers in setting the basic framework for the management of *H. pylori* infections. However, regional surveillance of AR development and monitoring the efficacy of locally used therapies needs to be an integral part of future guidelines in order to deliver the most appropriate treatment to patients.

The information collected in our survey aims to raise awareness among healthcare authorities around the world for the establishment of programmes for *H. pylori* AR testing and surveillance, to pay attention to the availability of effective and safe drugs in *H. pylori*.

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