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Prevalence of bedaquiline resistance in patients with drug-resistant tuberculosis: a systematic review and meta-analysis

Xinyang Hu[1†], Zhiwei Wu[2†], Jing Lei[1], Yanqin Zhu[1] and Jingtao Gao[1*]

Abstract

Background Drug-resistant tuberculosis (TB) remains a major global public health challenge. While bedaquiline (BDQ) offers improved treatment outcomes for patients with multi-drug resistant TB (MDR-TB), its widespread use has led to the emergence of BDQ resistance.

Methods This systematic review evaluated the prevalence of BDQ resistance among adult patients through searches of PubMed, Web of Science, and Embase databases. Sensitivity and subgroup analyses were performed to explore sources of heterogeneity and compare prevalence estimates across groups. The Joanna Briggs Institute's quality assessment checklist was used to evaluate the methodological quality of the included studies. Heterogeneity between studies was evaluated using Cochran's *Q* and I^2 tests.This study is registered with PROSPERO, CRD42024620791.

Results The weighted average prevalence of BDQ resistance was 5.7% (95% CI: 3.6–8.3), with acquired resistance reported at 5.4%. Geographic differences were observed, with South Africa showing a higher prevalence (10.4%) compared to China (2.4%).High-quality studies reported a prevalence of 5.2%, while fair-quality studies reported 7.7%. Mutations in the Rv0678 gene represented a significant proportion, reaching as high as 65.6%.

Conclusions Our findings highlight an increasing trend in acquired resistance to BDQ, offering critical insights for managing MDR-TB. The application of whole-genome sequencing shows promise for advancing understanding of drug resistance mechanisms in *Mycobacterium tuberculosis*.

Keywords Bedaquiline resistance, Acquired bedaquiline resistance, Tuberculosis, Systematic review, Meta-analysis

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Background

Tuberculosis (TB), particularly drug-resistant TB, remains a significant global public health challenge. The World Health Organization (WHO) estimates that approximately 400,000 new cases of multi-drug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB) occurred worldwide in 2023. China, a high-burden country for drug-resistant TB, ranks fourth globally, with an estimated 29,000 new cases annually [1]. Treating drug-resistant TB is challenging due to prolonged therapy, the use of multiple drugs, and frequent side effects, which hinder patient adherence and limit treatment success to only 68% of cases [1].

BDQ received accelerated approval from the U.S. Food and Drug Administration on December 28, 2012 [2]. In 2013, the WHO Expert Committee reviewed the trial data and issued the "*The Use of Bedaquiline in the Treatment of Multidrug-Resistant Tuberculosis: Interim Policy Guidance.*" The guidelines recommended that BDQ be included in the WHO-recommended regimen for treating MDR-TB patients (with a conditional recommendation and very low evidence level), provided the following conditions are met: (1) The drug is intended for adults aged ≥ 18 years. Due to limited safety and efficacy evidence, it should be used cautiously and is not recommended for individuals aged 65 and above or those co-infected with Human Immunodeficiency Virus (HIV). It is not recommended for use in pregnant women and children. (2) Treatment regimens containing BDQ should be administered under close monitoring, with active pharmacovigilance, especially electrocardiogram (ECG) monitoring, to prevent the risk of QT interval prolongation, which may occur due to the drug or interactions with other medications. (3) Informed consent must be obtained from the patient, ensuring that they are aware of both the benefits and risks associated with the use of the new drug BDQ [3].In 2014, the WHO published the "*Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*", which for the first time included BDQ in the group of anti-tuberculosis drugs. However, due to limited safety and efficacy data, it was placed in Group 5 [4].In 2016, the WHO launched the "Guidelines for the Treatment of Drug-Resistant Tuberculosis (2016 Update)" and reclassified drugs for drug-resistant tuberculosis into four groups: A, B, C, and D. The first three groups are core drugs, while Group D consists of non-core drugs. The WHO's recommendation for BDQ remained the same as in 2014 [5].From the end of 2018 to 2019, the WHO reclassified drugs for the treatment of drug-resistant tuberculosis into three groups. BDQ was elevated to the group A and was strongly recommended for use in long-term treatment regimens for MDR-TB [6].

In response to this pressing issue, the global community has accelerated the development of new drugs and treatment regimens. After a 70-year gap since the discovery of streptomycin in the 1940s, BDQ emerged as a novel anti-TB drug, offering hope for MDR/RR-TB patients. BDQ-containing regimens have demonstrated improved outcomes, with meta-analyses showing treatment success rates of 74.7% in observational studies and 86.1% in experimental studies [7].

BDQ, a diarylquinoline, inhibits the proton pump C subunit of the *M. tuberculosis* adenosine triphosphate (ATP) synthase, suppressing mycobacterial ATP production while sparing human ATP synthase function [8]. BDQ is primarily metabolised in the liver via cytochrome P450 isoenzyme 3A4 (CYP3A4), with CYP2C8 and CYP2C19 playing minor roles in BDQ metabolism. CYP3A4 converts BDQ into monodemethylated metabolites such as M2, which exhibits approximately five times the anti-TB activity of BDQ. BDQ has a long average half-life of 5.5 months and is primarily eliminated through the gastrointestinal tract [9, 10].

As evidence of BDQ's efficacy has grown, its use has gradually expanded, leading to its status as a first-line drug for MDR/RR-TB treatment [4, 11, 12]. However, with the widespread use of BDQ, drug resistance has emerged rapidly [13]. This underscores the urgent need for rapid and reliable drug susceptibility testing (DST) to enable personalised anti-TB drug regimens that optimise treatment outcomes while curbing the spread of drug-resistant TB, particularly of MDR/RR-TB [14].

BDQ resistance primarily arises through two mechanisms. The first involves mutations in *M. tuberculosis* ATP synthase-related genes, which prevent BDQ from targeting its site of action, often due to irregular or inadequate anti-TB treatment. The second mechanism involves mutations in the *Rv0678* gene, which encodes a transcriptional repressor that regulates the expression of *mmpS5* and *mmpL5* genes encoding key components of the *M. tuberculosis* efflux pump system. These mutations lead to overexpression of the MmpS5-MmpL5 efflux pump, reducing intracellular BDQ concentrations and rendering the drug less effective. In vitro studies have shown that *Rv0678* mutations increase BDQ's minimum inhibitory concentration (MIC) by 2- to 8-fold [15]. Other genes, including *atpE* and *pepQ*, have also been implicated in BDQ resistance [8, 16].

The WHO has cautioned that improper use of BDQ, such as administering it without susceptibility testing or as part of inadequate regimens, could accelerate the development of BDQ-resistant TB [17]. Thus, careful monitoring, adherence to treatment guidelines, and appropriate drug combinations are critical to maintaining BDQ's effectiveness and preventing the proliferation of resistant strains.

This study aims to summarize recent trends in BDQ resistance among adult patients, evaluate strategies for rapid diagnosis, and identify approaches to mitigate resistance.The findings will provide evidence-based insights to inform future diagnostic and therapeutic strategies for drug-resistant TB.

Methods

Materials and methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18].This study is registered with PROSPERO, CRD42024620791.

Data sources and study selection

A comprehensive search was conducted of PubMed, Embase, and Web of Science databases to identify relevant studies published up to November 2024. The following search strategy was used for PubMed: *(bedaquiline) AND (resistance)*. For Embase and Web of Science, equivalent terms were adapted to suit each database.

Studies were included if they met the following criteria: (i) reported phenotypic resistance to BDQ in bacterial strains; (ii) provided resistance rates or sufficient data to calculate these rates; and (iii) were published in English. Exclusion criteria included reviews, commentaries, case reports, studies involving animal subjects, editorials, conference papers, books, letters to the editor, and notes.

Data extraction and quality assessment

Two independent authors extracted relevant data from the selected studies, including the first author's name, study location, year of publication, number of bacterial strains included, number of resistant strains identified, corresponding prevalence rates, and whether DST and genomic sequencing were conducted.

Study quality was assessed using the Joanna Briggs Institute (JBI) quality assessment tool [19]. Each study's score was based on responses categorised as "Yes," "No," "Unclear," and "Not Applicable" to specific quality criteria. The assessment is conducted independently by HXY and WZW. If discrepancies arise, they first engage in a discussion to reach a consensus. If differences still persist after the discussion, LJ will act as the third independent reviewer to conduct the assessment.

Statistical analysis

Data analysis was performed using R version 4.4.1. Prevalence rates from individual studies were pooled using a random-effects meta-analysis model [20]. Heterogeneity across studies was assessed with the I^2 statistic, with thresholds of 25%, 50%, and 75% indicating low, medium, and high heterogeneity, respectively [21]. Potential sources of heterogeneity were explored based on study quality and country of origin. Publication bias was evaluated using Egger's regression test and visualised with funnel plots. Statistical significance was set at $P<0.05$ for all analyses. This methodology ensures a rigorous and systematic approach to synthesising evidence on BDQ resistance.

Results

Identification of relevant studies

The systematic search yielded 4106 studies, of which 1,974 were duplicates and subsequently removed. During title and abstract screening, an additional 2060 records were excluded for not meeting the inclusion criteria. After a full-text review of the remaining 72 articles, studies involving animal experiments, case reports, low-quality articles, and those lacking relevant data were excluded. Ultimately, 31 studies met the eligibility criteria and were included in this systematic review. The screening process is detailed in Fig. 1.

Characteristics of included studies

Key characteristics of the 31 studies included in this review and meta-analysis are shown in Table 1. Collectively, these studies investigated 17,128 *M. tuberculosis* strains, of which 648 were confirmed to exhibit phenotypic resistance to BDQ through DST. The studies were published between 2017 and 2024, with 14 originating from China and 6 from South Africa.

Quality of included studies

The quality and risk of bias for the included studies are presented in Table 2. Studies were assessed on a 9-point scale, with scores ≥ 7 classified as high quality, scores between 4 and 6 as medium quality, and scores ≤ 3 as low quality. Among the included studies, 22 were rated as high quality (≥ 7 points), while the remaining 9 scored between 4 and 6 points.

Prevalence of BDQ resistance

The pooled prevalence of BDQ resistance was estimated at 5.7% (*95% CI*: 3.6–8.3) (Fig. 2), with significant heterogeneity observed across studies ($I^2 = 93.95\%$; $P<0.001$). High-quality studies reported a prevalence of 5.2%, while fair-quality studies reported 7.7%; however, this difference was not statistically significant ($P=0.428$) (Fig. 3).

Subgroup analysis by country revealed geographic variation in BDQ resistance prevalence. South Africa reported the highest prevalence at 10.4%, compared to 2.4% in China (Fig. 4).We also conducted a subgroup analysis based on years to examine the trend of BDQ resistance over time, but due to significant bias in the study, no clear trend was observed (Fig. 5).Studies specifically examining acquired BDQ resistance indicated a prevalence of 5.5% (Fig. 6). We also found that among the

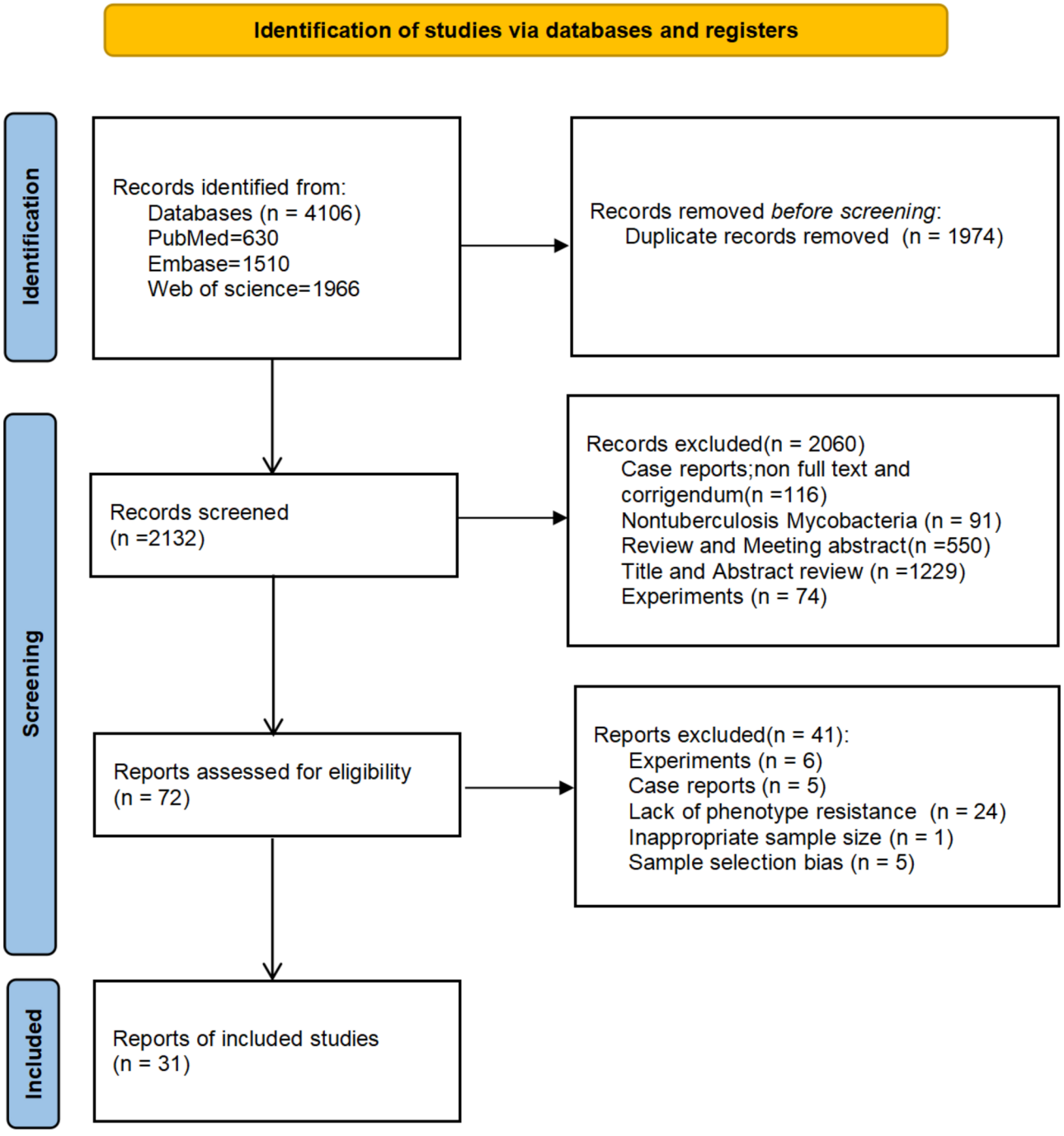

Fig. 1 PRISMA flow diagram of the studies selection process

gene mutations associated with BDQ resistance, mutations in the Rv0678 gene represented a significant proportion, reaching as high as 65.6% (Fig. 7).

Sensitivity analysis

To explore heterogeneity, stratified analyses were performed based on study quality and country of origin. A statistically significant difference in prevalence between countries was observed ($P = 0.0016$) (Fig. 4). A leave-one-out sensitivity analysis confirmed that the pooled estimates were robust and not influenced by any single study (Table 3).

Publication bias

Potential publication bias in BDQ resistance prevalence was indicated by funnel plot asymmetry and Egger's regression test results ($B = 3.9252$, $SE = 1.1155$, $P = 0.018$) (Fig. 8). These findings highlight the widespread nature of

Table 1 The characteristics of studies included in the systematic review and meta-analysis

Author	Country	Year	Sample size	Cases	Prevalence(%)	DST[a]	Sequencing
Jian Xu et al [22]	China	2017	90	4	4.44	Y[b]	Sanger sequencing
Yu Pang et al [23]	China	2017	90	3	3.33	Y	WGS[c]
Camus Nimmo et al [24]	South Africa	2019	92	10	10.87	Y	spoligotyping
Hasan Ghajavand et al [25]	Iran	2019	24	12	50	Y	WGS
Jian Yang et al [26]	China	2020	518	10	1.93	Y	spoligotyping
Huiwen Zheng et al [27]	China	2021	88	2	2.27	Y	Sanger sequencing
Cong Yao et al [28]	China	2021	425	10	2.35	Y	Sanger sequencing
Sheng-Han Wu et al [29]	China	2021	898	28	3.12	Y	Sanger sequencing
Yuhong Liu et al [30]	China	2021	277	6	2.17	Y	WGS
Guirong Wang et al [31]	China	2021	391	28	7.16	Y	WGS
Wencong He et al [32]	China	2021	1603	6	0.37	Y	NA[d]
Helen Pai et al [33]	South Africa	2022	383	19	4.96	Y	WGS
Helen Pai et al-baseline [33]	South Africa	2022	142	5	3.52	Y	WGS
Max R O'Donnell et al [34]	South Africa	2022	58	7	12.07	Y	NA
P. Nair et al [35]	Uzbekistan	2022	523	31	5.93	Y	WGS
Nazir Ahmed Ismail et al-baseline [36]	South Africa	2022	2023	76	3.76	Y	WGS
Nazir Ahmed Ismail et al [36]	South Africa	2022	695	16	2.30	Y	WGS
Elena Chesov et al [37]	Moldova	2022	26	5	19.23	Y	WGS
B. Derendinge et al [38]	South Africa	2022	40	22	55.00	Y	WGS
Kanwara Trisakul et al [39]	Multicentre	2022	513	69	13.45	Y	WGS
Enyu Tong et al [40]	China	2023	245	5	2.04	Y	NA
S. Moe et al [41]	Uzbekistan	2023	1930	64	3.32	Y	WGS
Yan Hu et al [42]	China	2023	205	9	4.39	Y	NA
Yinjuan Guo et al [43]	China	2023	1572	63	4.01	Y	WGS
Juliano Timm et al-baseline [44]	Multicentre	2023	648	13	2.01	Y	WGS
Juliano Timm et al [44]	Multicentre	2023	43	3	6.98	Y	WGS
Christian Utpatel et al [45]	Peru	2024	171	6	3.51	Y	WGS
Tatiana Umpeleva et al [46]	Russia	2024	239	5	2.09	Y	NA
L. Mikiashvil et ali-baseline [47]	Georgia	2024	89	6	6.74	Y	NA
L. Mikiashvili et al [47]	Georgia	2024	21	5	23.81	Y	WGS
Tyler S. Brown et al [48]	South Africa	2024	147	24	16.33	Y	WGS
Ivan Barilar et al [49]	Mozambique	2024	704	61	8.66	Y	WGS
Andriansjah Rukmana et al [50]	Indonesia	2024	60	3	5.00	Y	WGS
Wenfeng Gao et al [51]	China	2024	278	8	2.88	Y	WGS
Shanshan Li et al [52]	China	2024	1877	4	0.21	Y	Sanger sequencing

[a]drug susceptibility testing;[b]yes;[c]Whole Genome Sequencing;[d]not applicable

BDQ resistance and the regional and temporal variations, emphasizing the need for targeted strategies to address this emerging challenge.

Discussion

This review analysed 31 studies from 11 countries, with a significant proportion originating from China and South Africa, to estimate the prevalence of BDQ resistance. The global prevalence of BDQ resistance was estimated at 5.7% (3.6–8.3), with regional variations observed, including 2.4% in China and 10.4% in South Africa. The prevalence of acquired BDQ resistance (ABR) was 5.5%, consistent with previous findings, including a 2022 systematic review that reported median phenotypic and genotypic frequencies of 2.2% (1.1-4.6%) and 4.4% (1.8-5.8%), respectively. Although this study did not distinguish between phenotypic and genotypic resistance, it highlights an increasing trend in ABR, raising concerns regarding future treatment outcomes [53].

BDQ is metabolized by the CYP3A4 into its M2. Therefore, it is important to avoid co-administration with strong CYP3A4 inducers (such as rifampin, rifabutin, and rifapentine) or inhibitors [8, 9]. The half-life of BDQ is approximately 5.5 months, and it is recommended to discontinue its use 4 to 5 months before stopping other drug regimens to reduce or avoid prolonged exposure to low drug concentrations, which could lead to acquired resistance [54].

Despite prioritising BDQ resistance monitoring since the drug's introduction, resistance has emerged [55]. Interestingly, MDR-TB patients with low-level BDQ resistance (0.25–0.5 μg/mL) can still achieve sputum

Table 2 Qualities of studies included in the systematic review and meta-analysis

Study name	Response									
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	total
Jian Xu	U[a]	U	Y[b]	N[c]	Y	Y	Y	U	Y	5
Yu Pang	U	Y	Y	N	Y	Y	Y	U	Y	6
Camus Nimmo	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Hasan Ghajavand	Y	Y	N	U	Y	Y	Y	N	Y	6
Jian Yang	U	U	Y	N	Y	Y	Y	U	Y	5
Huiwen Zheng	U	Y	Y	N	Y	Y	Y	N	Y	6
Cong Yao	Y	Y	Y	N	Y	Y	Y	N	Y	7
Sheng-Han Wu	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Yuhong Liu	Y	Y	Y	N	Y	Y	Y	N	Y	7
Guirong Wang	Y	Y	Y	N	Y	Y	Y	N	Y	7
Wencong He	Y	Y	Y	N	Y	Y	Y	N	Y	7
Helen Pai	Y	Y	Y	Y	Y	Y	Y	N	N	7
Max R O'Donnell	Y	Y	Y	Y	Y	Y	Y	Y	N	8
P. Nair	Y	Y	Y	Y	Y	Y	Y	N	N	7
Nazir Ahmed Ismail	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Elena Chesov	Y	Y	N	Y	N	Y	Y	N	N	5
B. Derendinger	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Kanwara Trisakul	Y	U	Y	N	Y	Y	Y	N	U	5
Enyu Tong	Y	Y	Y	Y	Y	Y	Y	N	Y	8
S. Moe	Y	Y	Y	N	Y	Y	Y	N	Y	7
Yan Hu	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Yinjuan Guo	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Juliano Timm	Y	Y	Y	Y	Y	Y	Y	N	N	7
Christian Utpatel	Y	Y	Y	Y	Y	Y	Y	U	Y	8
Tatiana Umpeleva	U	Y	Y	N	Y	Y	Y	U	Y	6
L. Mikiashvili	Y	Y	Y	Y	Y	Y	Y	N	N	7
Tyler S. Brown	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Ivan Barilar	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Andriansjah Rukmana	U	U	Y	N	Y	Y	Y	U	Y	5
Wenfeng Gao	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Shanshan Li	Y	Y	Y	Y	Y	Y	Y	Y	U	8

Keys:

Q1–Q9 represents questions used to assess the quality of included studies, which are listed below

Q1. Was the sample frame appropriate to address the target populations?

Q2. Were the study participants sampled appropriately?

Q3. Was the sample size adequate?

Q4. Were the study subjects and setting described in detail?

Q5. Was the data analysis conducted with sufficient coverage of the identified sample?

Q6. Was a valid method used in the identification of conditions?

Q7. Was the condition measured in a standard, reliable way for all participants?

Q8. Was there an appropriate statistical analysis?

Q9. Was the response rate adequate, and if not, was the low response rate managed appropriately?

[a]unclear;[b]yes; [c]no

culture conversion with BDQ-containing regimens, suggesting that BDQ may retain therapeutic efficacy even in cases of low-level resistance [30]. However, alternative treatment options remain crucial, as similar conversion rates have been observed with non-BDQ regimens [56]. Therefore, a comprehensive approach integrating BDQ with other anti-TB drugs is recommended to optimise outcomes and mitigate resistance development.

According to a report from the Drug-Resistant TB Scale-up Treatment Action Team (DR-TB STAT), by March 2017, only 8,195 patients worldwide had been reported to receive BDQ treatment, with the vast majority (59.6%) receiving treatment in South Africa alone [55]. South Africa started using Bedaquiline much earlier than China. Additionally, the co-infection of HIV and tuberculosis is more severe in South Africa than in China, and

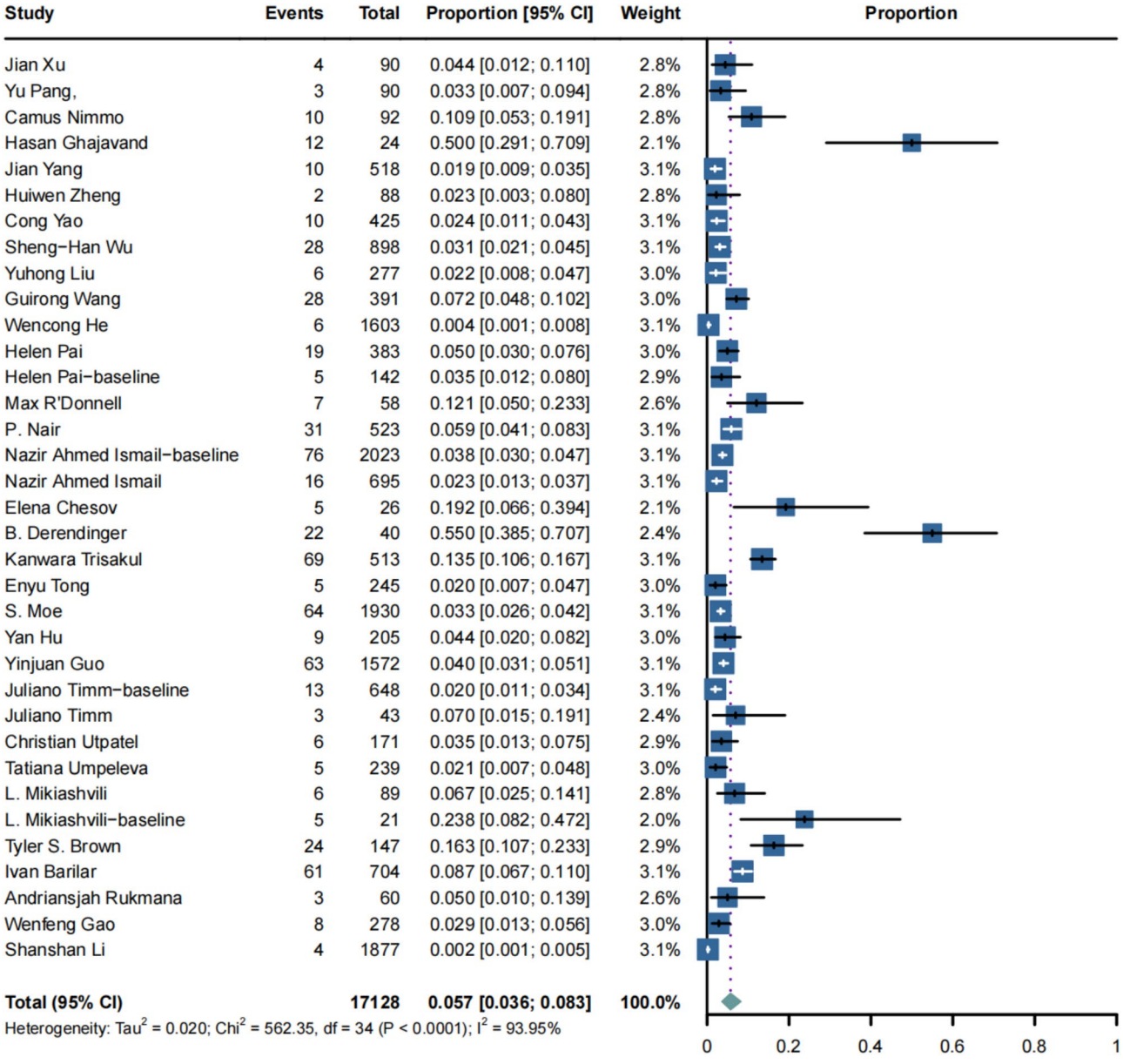

Fig. 2 The prevalence of BDQ resistance in study periods

drugs interacting with BDQ in antiretroviral therapy may contribute to an increased BDQ resistance rate [57].

Consistent with the results of a previous meta-analysis, the *Rv0678* mutation plays a major role in BDQ resistance [53]. Notably, exposure to clofazimine may also induce *Rv0678* mutations, resulting in cross-resistance between the two drugs, with approximately one-third of clofazimine-resistant isolates exhibiting BDQ resistance [58–60], with many *Rv0678* mutations conferring resistance to both drugs [61]. To address this issue, sensitivity testing for BDQ is advised before initiating treatment, particularly in patients previously treated with clofazimine.

The sequencing methods for determining BDQ resistance primarily include Sanger sequencing and Whole Genome Sequencing (WGS). Sanger sequencing provides accurate sequence information, making it suitable for directly detecting known drug resistance gene mutations with high accuracy. However, it has high costs for large-scale, automated genomic analysis and lower throughput [62]. On the other hand, WGS can detect all known resistance-associated genes and also identify unknown mutations related to drug resistance. However, the high cost of sequencing and the lack of standardized interpretation for the results remain challenges [63]. That's why one site may use different sequencing techniques.

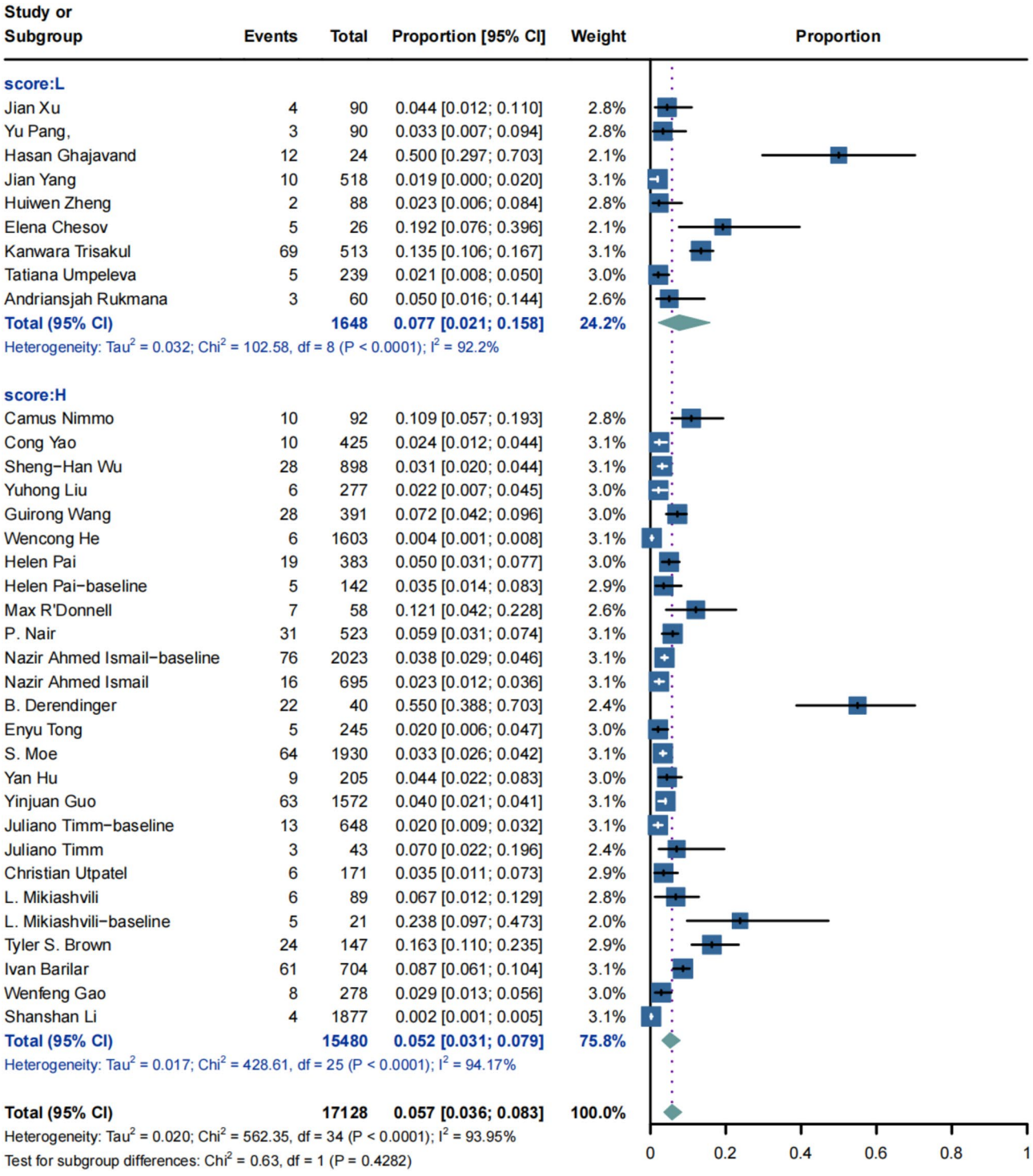

Fig. 3 The prevalence of BDQ resistance in studies of different qualities

WGS was utilised in over half of the studies reviewed, highlighting its value in detecting drug resistance. Since the first *M. tuberculosis* genome was published in 1998, WGS has revolutionised our understanding of TB drug resistance mechanisms, their evolution within individual patients and populations, and their transmission pathways [63], and additional virulence factors contributing to the dissemination of drug-resistant TB [64]. Its adoption in TB surveillance, particularly in high-risk populations in Europe, demonstrates its potential for broader clinical application [65]. Furthermore, by providing comprehensive

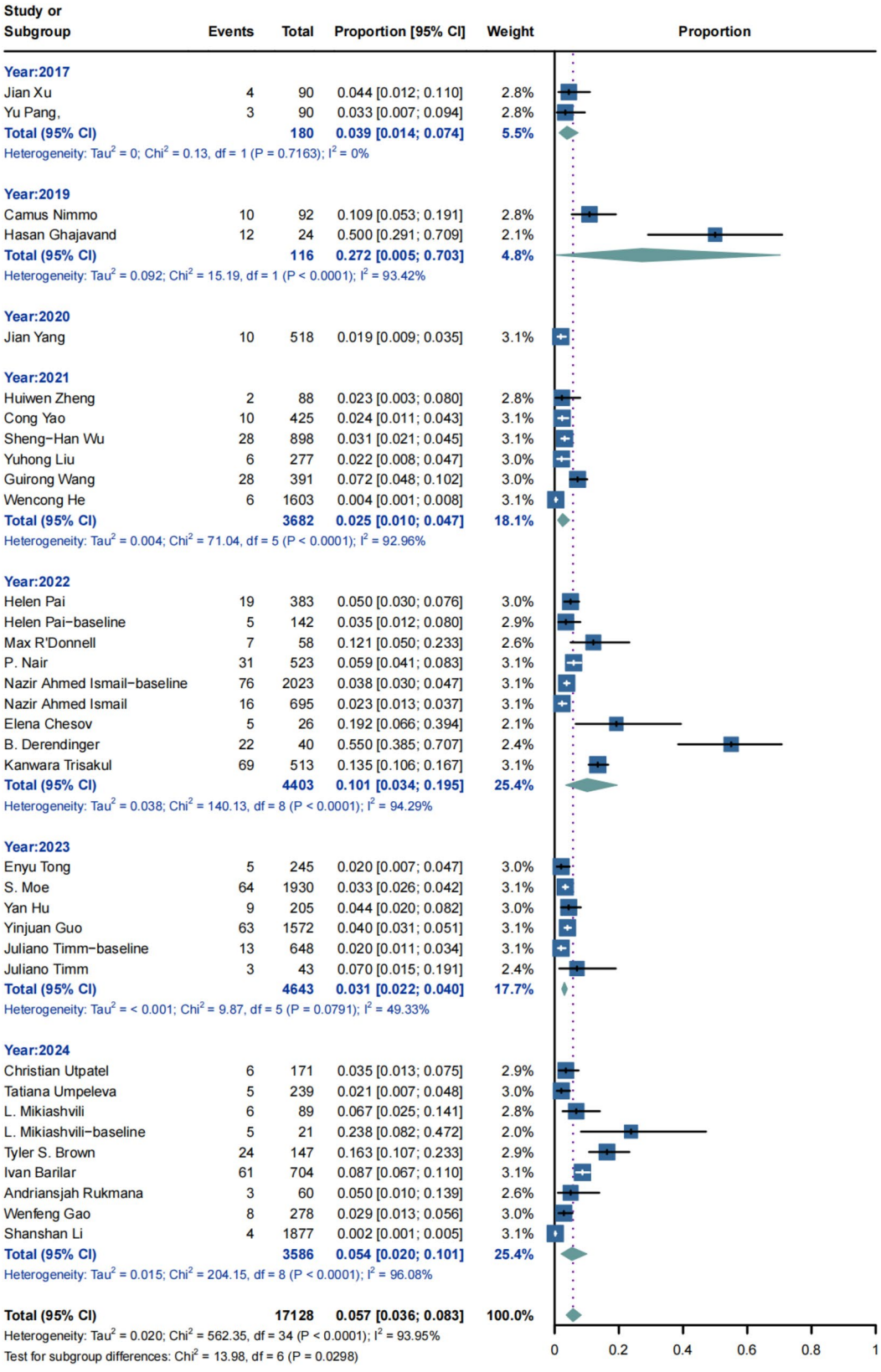

Fig. 4 The prevalence of BDQ resistance in studies of different years

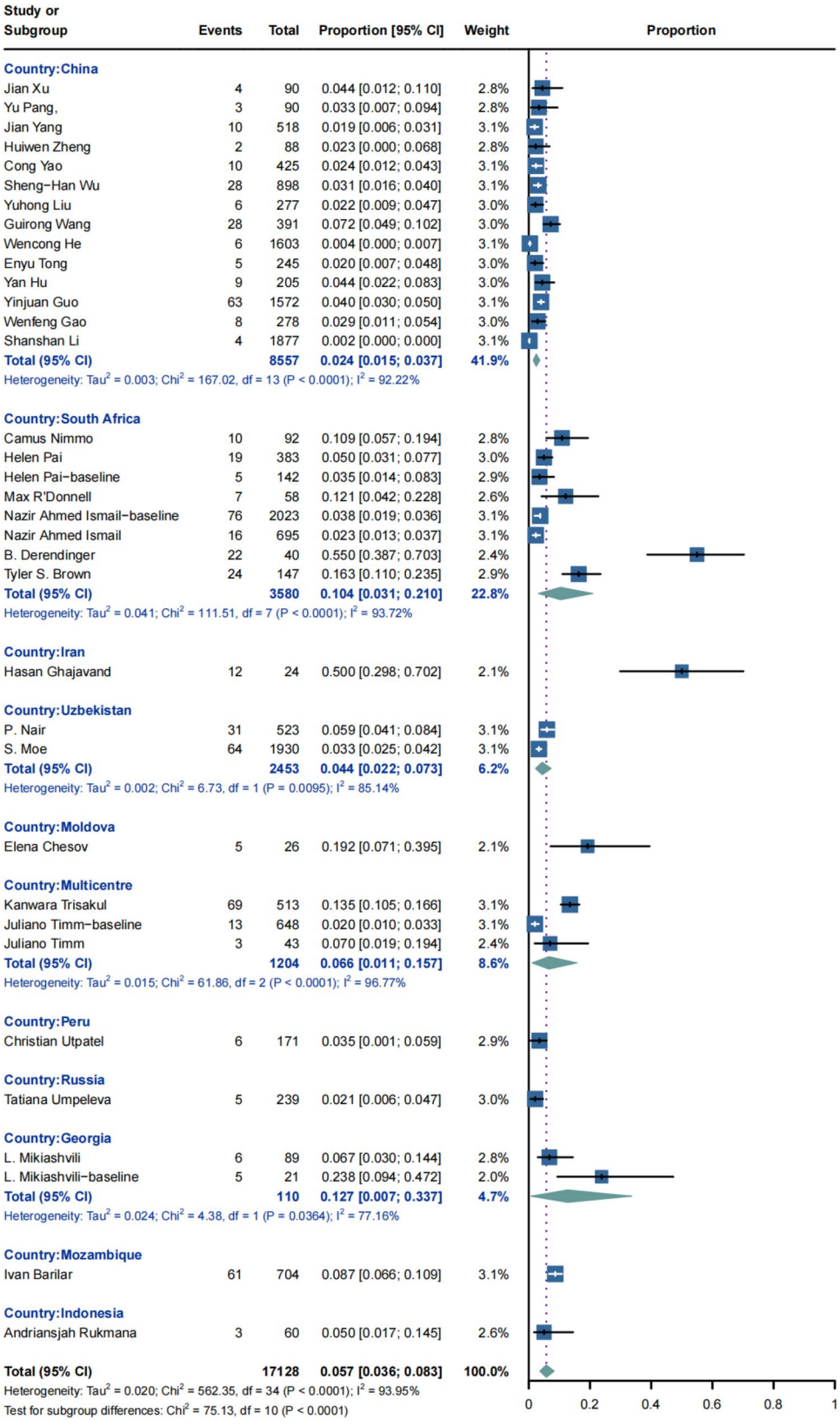

Fig. 5 The prevalence of BDQ resistance in studies of different countries

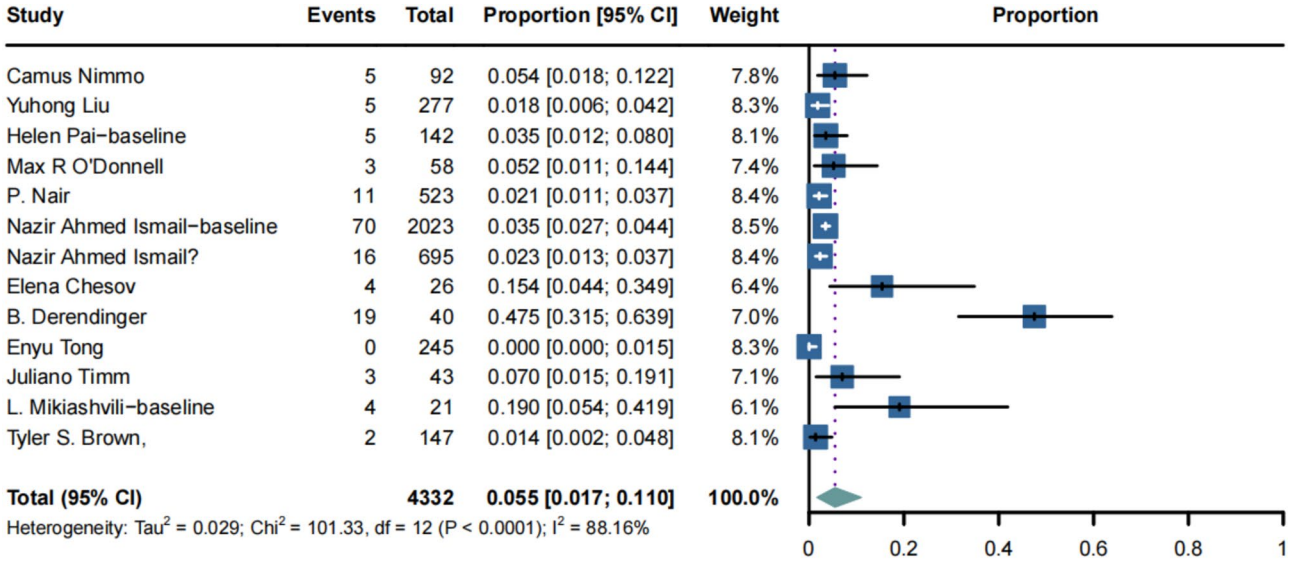

Fig. 6 The prevalence of acquired BDQ resistance in studies

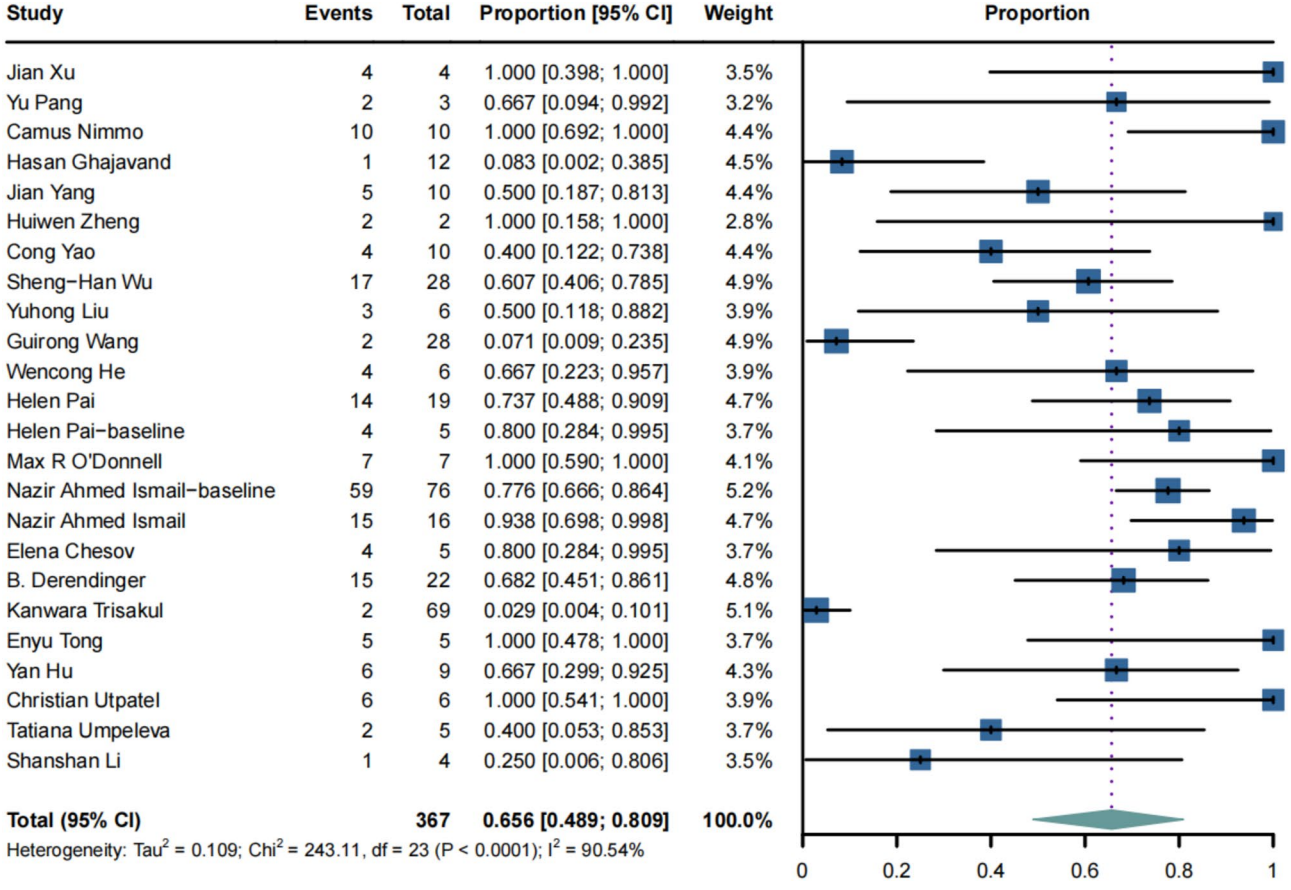

Fig. 7 The prevalence of *Rv0678* gene mutation in studies

genomic insights, WGS enables rapid and precise resistance profiling, guiding the development of personalised treatment regimens [66]. WGS has a sensitivity of over 80% for detecting drug resistance to tuberculosis medications, whereas the sensitivity of phenotypic drug testing is less than 80% [67].Multiple studies have shown that the genetic resistance rate to BDQ is higher than the phenotypic resistance

Table 3 Sensitivity analysis of all studies

Study	Estimate	95% confidence interval	
Jian Xu	0.0581	0.0359	0.0847
Yu Pang	0.0584	0.0362	0.0851
Camus Nimmo	0.0563	0.0347	0.0824
Jian Yang	0.0513	0.0334	0.0724
Huiwen Zheng	0.0592	0.0369	0.0858
Cong Yao	0.0590	0.0367	0.0857
Sheng-Han Wu	0.0587	0.0364	0.0855
Yuhong Liu	0.0590	0.0367	0.0857
Guirong Wang	0.0573	0.0352	0.0839
Wencong He	0.0601	0.0382	0.0863
Helen Pai	0.0580	0.0357	0.0847
Helen Pai-baseline	0.0584	0.0362	0.0851
Max R O'Donnell	0.0562	0.0346	0.0821
P. Nair	0.0576	0.0355	0.0844
Nazir Ahmed Ismail-baseline	0.0584	0.0361	0.0852
Nazir Ahmed Ismail	0.0590	0.0367	0.0857
Elena Chesov	0.0554	0.0345	0.0805
B. Derendinger	0.0483	0.0329	0.0662
Kanwara Trisakul	0.0555	0.0341	0.0812
Enyu Tong	0.0590	0.0368	0.0857
S. Moe	0.0586	0.0363	0.0854
Yan Hu	0.0581	0.0359	0.0849
Yinjuan Guo	0.0583	0.0360	0.0851
Juliano Timm-baseline	0.0591	0.0369	0.0858
Juliano Timm	0.0574	0.0355	0.0837
Christian Utpatel	0.0584	0.0362	0.0852
Tatiana Umpeleva	0.0590	0.0368	0.0857
L. Mikiashvili	0.0574	0.0354	0.0839
L. Mikiashvili-baseline	0.0551	0.0345	0.0798
Tyler S. Brown	0.0549	0.0339	0.0801
Ivan Barilar	0.0568	0.0348	0.0833
Andriansjah Rukmana	0.0579	0.0358	0.0844
Wenfeng Gao	0.0587	0.0364	0.0855
Shanshan Li	0.0603	0.0385	0.0863
Pooled estimate	0.0575	0.0360	0.0831

rate. WGS can detect resistance mutations earlier, but there is still no clear genotype-phenotype correlation for BDQ resistance. As a result, using genomics alone to fully diagnose BDQ resistance remains challenging. It is crucial to improve phenotypic testing standards to ensure more accurate and reliable identification of BDQ resistance [53, 68, 69].Although WGS has significant advantages in DST, its widespread application still faces several challenges. These include high costs, complex data analysis, and the need for advanced laboratory equipment and skilled personnel. These factors hinder the large-scale implementation of WGS in routine clinical settings, despite its potential to provide more comprehensive and early detection of resistance mutations. Compared to WGS, DST may be relatively conservative in detecting resistance rates, especially in the early stages of resistance mutations. Future research needs to combine DST and genetic sequencing technologies to more comprehensively monitor the dynamics of BDQ resistance.

This study has several strengths. First, it provides robust global and China-specific estimates of BDQ resistance, identifying an upward trend in ABR. Second, subgroup and sensitivity analyses addressed potential biases, improving the reliability of the findings. Third, the inclusion of a substantial sample size across numerous studies strengthens the statistical power of the meta-analysis.

However, limitations must also be acknowledged. Most included studies were observational, contributing to significant heterogeneity and potential publication bias, likely driven by regional variations in BDQ resistance rates. Additionally, the focus on high-burden TB countries, particularly China and South Africa, limits the generalisability of findings to low-burden settings. The exclusion of non-English studies may also have led to the omission of relevant research. The period of some studies are concentrated and might not reflect the trend of BDQ resistance evolution. Future multi-center, large-scale clinical trials could be conducted to reduce bias and expand the scope of research, especially in low-burden countries, in order to gain a more comprehensive understanding of BDQ resistance. Similarly, studies could focus on different populations, such as various age groups or those with comorbidities, to better understand BDQ resistance in diverse groups.Despite these limitations, this review provides valuable insights into the prevalence and mechanisms of BDQ resistance, emphasising the need for continued monitoring, personalised treatment strategies, and further research to optimise TB management globally.

Conclusions

This study highlights an increasing trend in both overall and acquired resistance to BDQ among adult patients,, raising concerns about its long-term efficacy in treating MDR-TB. The findings emphasise the potential of verapamil to enhance BDQ efficacy and delay resistance development, offering a promising adjunctive strategy. Additionally, the critical role of WGS in advancing TB research and management is underscored, particularly in identifying resistance mechanisms and guiding personalised treatment. Future research should focus on elucidating the mechanisms of BDQ resistance and developing targeted strategies to prevent and mitigate its emergence. These efforts are crucial to sustaining BDQ's effectiveness and improving outcomes for patients with drug-resistant TB.

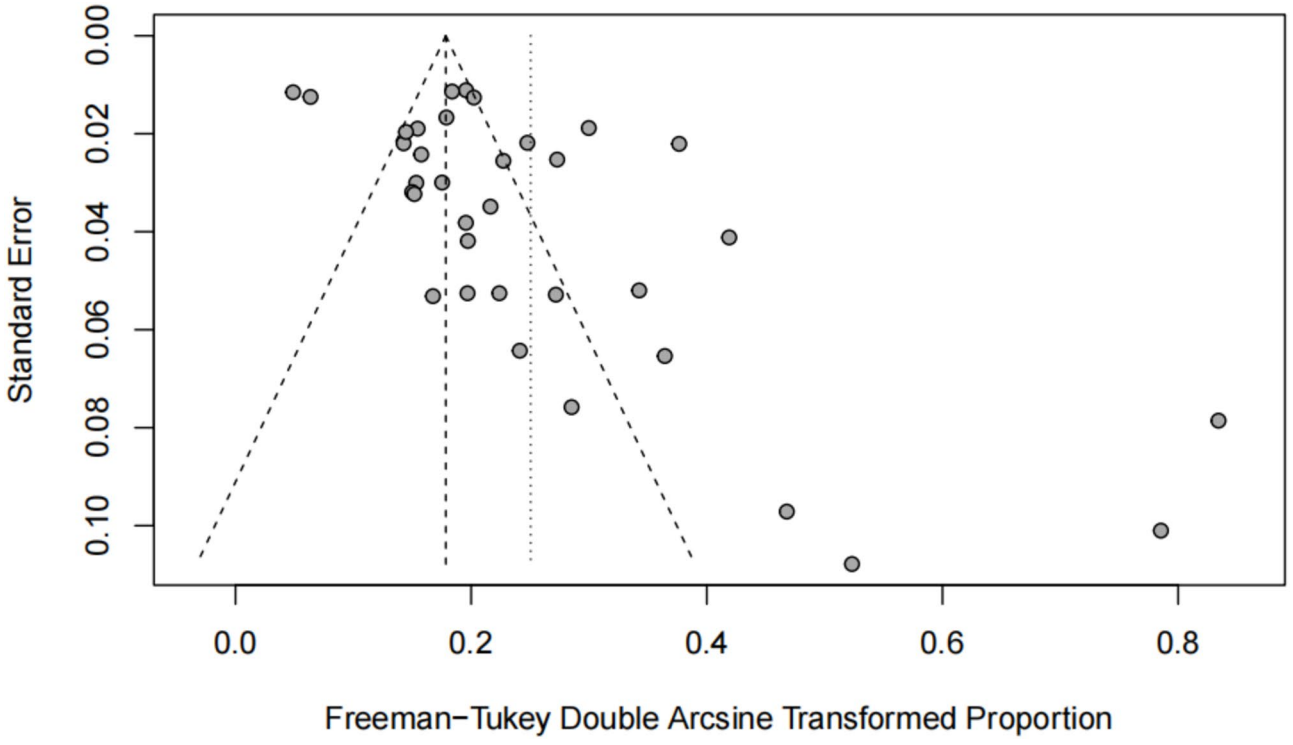

Fig. 8 Funnel plot of the risk of publication bias

Abbreviations

TB	Tuberculosis
BDQ	Bedaquiline
MDR-TB	Multi-drug resistant TB
RR-TB	Rifampicin-resistant TB
WHO	World Health Organisation
HIV	Human Immunodeficiency Virus
ECG	Electrocardiogram
ATP	Adenosine triphosphate
CYP3A4	Cytochrome P450 isoenzyme 3A4
MIC	Minimum inhibitory concentration
PRISMA	The Preferred Reporting Items for Systematic Reviews and Meta-Analyses
JBI	The Joanna Briggs Institute
ABR	Acquired BDQ resistance
WGS	Whole genome sequencing
DST	Drug susceptibility testing

Supplementary Information

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Supplementary Material 1

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Author contributions
All authors contributed to the study conception and design. The first draft of the manuscript was written by HXY and WZW. Material preparation, data collection and analysis were performed by LJ and ZYQ. GJT rigorously supervised proposal development, data collection, and data analysis and reviewed the manuscript for submission.All authors read and approved the final manuscript.HXY and WZW are the co-first authors and contributed equally to this study.All authors read and approved the final manuscript. GJT is the corresponding author for this article.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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