

# **Technical Report on critical concentrations for drug susceptibility testing of isoniazid and the rifamycins (rifampicin, rifabutin and rifapentine)**



WHO Collaborating Centre for  
Tuberculosis Laboratory Strengthening  
and Diagnostic Technology Evaluation



# **Technical Report on critical concentrations for drug susceptibility testing of isoniazid and the rifamycins (rifampicin, rifabutin and rifapentine)**



WHO Collaborating Centre for  
Tuberculosis Laboratory Strengthening  
and Diagnostic Technology Evaluation

Technical report on critical concentrations for drug susceptibility testing of isoniazid and the rifamycins (rifampicin, rifabutin and rifapentine).

ISBN 978-92-4-001728-3 (electronic version)

ISBN 978-92-4-001729-0 (print version)

**© World Health Organization 2021**

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo> ).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (<http://www.wipo.int/amc/en/mediation/rules/> ).

**Suggested citation.** Technical report on critical concentrations for drug susceptibility testing of isoniazid and the rifamycins (rifampicin, rifabutin and rifapentine). Geneva: World Health Organization; 2021. Licence: [CC BY-NC-SA 3.0 IGO](#).

**Cataloguing-in-Publication (CIP) data.** CIP data are available at <http://apps.who.int/iris> .

**Sales, rights and licensing.** To purchase WHO publications, see <http://apps.who.int/bookorders> . To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing> .

**Third-party materials.** If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

**General disclaimers.** The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

## Contents

Acknowledgements.....	vii
Abbreviations .....	x
Glossary of terms.....	xi
Executive summary.....	xiv
<b>SECTION 1: Introduction.....</b>	<b>1</b>
1.0 Background .....	2
1.1 Scope of the Technical Expert Consultation Meeting .....	3
1.2 Systematic review .....	3
1.2.1 <i>Search methodology</i> .....	3
1.2.2 <i>Inclusion criteria</i> .....	4
1.2.3 <i>Studies identified through the systematic review</i> .....	4
1.3 Data presentation .....	6
1.3.1 <i>Format of this report</i> .....	6
1.3.2 <i>Format of MIC tables</i> .....	6
<b>SECTION 2: Isoniazid .....</b>	<b>9</b>
2.0 INH resistance mechanisms .....	10
2.1 Current statements and policies regarding genotypic markers of INH resistance .....	11
2.2 INH MIC data stratification and current breakpoints .....	12
2.A.1 INH MIC data on LJ.....	14
2.A.1.1 <i>INH MICs for pWT isolates on LJ</i> .....	14
2.A.1.2 <i>INH MICs for mutated isolates on LJ</i> .....	14
2.A.1.3 <i>Conclusion for INH CC for LJ</i> .....	17
2.A.2 INH MIC data on 7H10 .....	18
2.A.2.1 <i>INH MICs for pWT isolates on 7H10</i> .....	18
2.A.2.2 <i>INH MICs for mutated isolates on 7H10</i> .....	18
2.A.2.3 <i>Conclusion for INH CC for 7H10</i> .....	21
2.A.3 INH MIC data on 7H11 .....	22
2.A.3.1 <i>INH MICs for pWT isolates on 7H11</i> .....	22
2.A.3.2 <i>INH MICs for mutated isolates on 7H11</i> .....	22
2.A.3.3 <i>Conclusion for INH CC for 7H11</i> .....	23
2.A.4 INH MIC data in MGIT .....	24
2.A.4.1 <i>INH MICs for pWT isolates in MGIT</i> .....	24
2.A.4.2 <i>INH MICs for mutated isolates in MGIT</i> .....	24
2.A.4.3 <i>Conclusion for INH CC in MGIT</i> .....	28
2.3 INH conclusions and comments .....	29
2.4 References for INH MIC studies .....	30
<b>SECTION 3: Rifamycins .....</b>	<b>35</b>
3.0 Rifamycin resistance mechanisms .....	36
3.1 Current statements and policies regarding genotypic markers of rifamycin resistance .....	37
3.2 Rifamycin MIC data stratification and current breakpoints .....	41
3.A.1 RIF MIC data on LJ.....	43
3.A.1.1 <i>RIF MICs for pWT isolates on LJ</i> .....	43
3.A.1.2 <i>RIF MICs for mutated isolates on LJ</i> .....	43
3.A.1.3 <i>Conclusion for RIF CC for LJ</i> .....	45
3.A.2 RIF MIC data on 7H10 .....	47
3.A.2.1 <i>RIF MICs for pWT isolates on 7H10</i> .....	47
3.A.2.2 <i>RIF MICs for mutated isolates on 7H10</i> .....	47
3.A.2.3 <i>Conclusion for RIF CC for 7H10</i> .....	51
3.A.3 RIF MIC data on 7H11 .....	52

3.A.3.1 RIF MICs for pWT isolates on 7H11.....	52
3.A.3.2 RIF MICs for mutated isolates on 7H11 .....	52
3.A.3.3 Conclusion for RIF CC for 7H11 .....	53
3.A.4 RIF MIC data in MGIT .....	54
3.A.4.1 RIF MICs for pWT isolates in MGIT .....	54
3.A.4.2 RIF MICs for mutated isolates in MGIT .....	54
3.A.4.3 Conclusion for RIF CC for MGIT .....	58
3.A.5 References for RIF MIC studies .....	60
3.B.1 RFB MIC data on LJ.....	64
3.B.1.1 RFB MICs for pWT isolates on LJ .....	64
3.B.1.2 RFB MICs for mutated isolates on LJ .....	64
3.B.1.3 Conclusion for RFB CC for LJ.....	64
3.B.2 RFB MIC data on 7H10 .....	65
3.B.2.1 RFB MICs for pWT isolates on 7H10.....	65
3.B.2.2 RFB MICs for mutated isolates on 7H10 .....	65
3.B.2.3 Conclusion for RFB CC for 7H10 .....	67
3.B.3 RFB MIC data on 7H11 .....	68
3.B.3.1 RFB MICs for pWT isolates on 7H11.....	68
3.B.3.2 RFB MICs for mutated isolates on 7H11 .....	68
3.B.3.3 Conclusion for RFB CC for 7H11 .....	69
3.B.4 RFB MIC data in MGIT .....	70
3.B.4.1 RFB MICs for pWT isolates in MGIT .....	70
3.B.4.2 RFB MICs for mutated isolates in MGIT .....	70
3.B.4.3 Conclusion for RFB CC for MGIT .....	73
3.B.5 References for RFB MIC studies .....	74
3.C.1 RPT MIC data on LJ.....	76
3.C.1.1 RPT MICs for pWT isolates on LJ .....	76
3.C.1.2 RPT MICs for mutated isolates on LJ .....	76
3.C.1.3 Conclusion for RPT CC for LJ.....	76
3.C.2 RPT MIC data on 7H10 .....	77
3.C.2.1 RPT MICs for pWT isolates on 7H10.....	77
3.C.2.2 RPT MICs for mutated isolates on 7H10.....	77
3.C.2.3 Conclusion for RPT CC for 7H10 .....	78
3.C.3 RPT MIC data on 7H11 .....	79
3.C.3.1 RPT MICs for pWT isolates on 7H11.....	79
3.C.3.2 RPT MICs for mutated isolates on 7H11.....	79
3.C.3.3 Conclusion for RPT CC for 7H11 .....	79
3.C.4 RPT MIC data in MGIT .....	80
3.C.4.1 RPT MICs for pWT isolates in MGIT.....	80
3.C.4.2 RPT MICs for mutated isolates in MGIT .....	80
3.C.4.3 Conclusion for RPT CC for MGIT .....	80
3.C.5 References for RPT MIC studies .....	81
3.3 Rifamycin conclusions and comments .....	82
Rifampicin.....	82
Rifabutin .....	86
Rifapentine .....	87

## List of figures

FIGURE 1. PRISMA DIAGRAM FOR ISONIAZID SEARCH RESULTS AND EXCLUSION CRITERIA .....	5
FIGURE 2. PRISMA DIAGRAM FOR RIFAMYCIN SEARCH RESULTS AND EXCLUSION CRITERIA.....	6

## List of tables

TABLE 1. CRITICAL CONCENTRATIONS FOR INH AND THE RIFAMYCINS. ....	XV
TABLE 2. OVERVIEW OF MIC DATA PRESENTATION. ....	7
TABLE 3. PROBE-BINDING REGIONS AND <i>KATG</i> AND <i>INHA</i> PROMOTER MUTATION COVERAGE OF WHO-ENDORSED LPAs.....	11
TABLE 4. OVERVIEW OF CURRENT INH CCs.....	13
TABLE 5. INH MICs FOR PWT ISOLATES ON LJ. ....	14
TABLE 6. INH MICs FOR CLINICAL <i>KATG</i> S315 MUTANTS ON LJ. ....	15
TABLE 7. INH MICs FOR CLINICAL <i>INHA</i> PROMOTER MUTANTS ON LJ. ....	15
TABLE 8. INH MICs FOR CLINICAL <i>INHA</i> CODING MUTANTS ON LJ.....	16
TABLE 9. INH MICs FOR CLINICAL <i>OXYR-AHPC</i> INTERGENIC REGION MUTANTS ON LJ. ....	16
TABLE 10. INH MICs FOR CLINICAL <i>KATG</i> S315, <i>INHA</i> PROMOTER AND <i>INHA</i> CODING DOUBLE MUTANTS ON LJ.....	17
TABLE 11. INH MICs FOR PWT ISOLATES ON 7H10. ....	18
TABLE 12. INH MICs FOR CLINICAL <i>KATG</i> S315 MUTANTS ON 7H10. ....	19
TABLE 13. INH MICs FOR CLINICAL <i>INHA</i> PROMOTER MUTANTS ON 7H10.....	19
TABLE 14. INH MICs FOR CLINICAL <i>INHA</i> CODING MUTANTS ON 7H10. ....	20
TABLE 15. INH MICs FOR CLINICAL <i>KATG</i> S315, <i>INHA</i> PROMOTER AND <i>INHA</i> CODING DOUBLE MUTANTS ON 7H10. ....	21
TABLE 16. INH MICs FOR PWT ISOLATES ON 7H11. ....	22
TABLE 17. INH MICs FOR CLINICAL <i>KATG</i> S315 MUTANTS ON 7H11. ....	22
TABLE 18. INH MICs FOR CLINICAL <i>INHA</i> PROMOTER MUTANTS ON 7H11.....	22
TABLE 19. INH MICs FOR CLINICAL <i>KATG</i> S315, <i>INHA</i> PROMOTER AND <i>INHA</i> CODING DOUBLE MUTANTS ON 7H11. ....	23
TABLE 20. INH MICs FOR PWT ISOLATES IN MGIT. ....	24
TABLE 21. INH MICs FOR CLINICAL <i>KATG</i> S315 MUTANTS IN MGIT.....	25
TABLE 22. INH MICs FOR CLINICAL <i>INHA</i> PROMOTER MUTANTS IN MGIT.....	26
TABLE 23. INH MICs FOR CLINICAL <i>INHA</i> CODING MUTANTS IN MGIT. ....	26
TABLE 24. INH MICs FOR CLINICAL <i>OXYR-AHPC</i> INTERGENIC REGION MUTANTS IN MGIT. ....	26
TABLE 25. INH MICs FOR CLINICAL <i>KATG</i> S315, <i>INHA</i> PROMOTER AND <i>INHA</i> CODING DOUBLE MUTANTS IN MGIT..	27
TABLE 26. OVERVIEW OF CONFIDENCE-GRADED <i>RPOB</i> RIF RESISTANCE MUTATIONS, INCLUDING THE SEVEN BORDERLINE RESISTANCE MUTATIONS. ....	39
TABLE 27. PROBE-BINDING REGIONS AND <i>RPOB</i> MUTATION COVERAGE OF WHO-ENDORSED GDST ASSAYS. ....	40
TABLE 28. OVERVIEW OF CURRENT RIFAMYCIN CCs.....	42
TABLE 29. RIF MICs FOR PWT ISOLATES ON LJ. ....	43
TABLE 30. RIF MICs FOR <i>RPOB</i> S450 (S531) MUTANTS ON LJ. ....	43
TABLE 31. RIF MICs FOR <i>RPOB</i> BORDERLINE RRDR MUTANTS ON LJ. ....	44
TABLE 32. RIF MICs FOR OTHER <i>RPOB</i> RRDR MUTANTS ON LJ. ....	45
TABLE 33. RIF MICs FOR <i>RPOB</i> MUTANTS OUTSIDE THE RRDR ON LJ. ....	45
TABLE 34. EFFECT OF INTRODUCING AN ATU FOR RIF DST ON LJ. ....	46
TABLE 35. RIF MICs FOR PWT ISOLATES ON 7H10. ....	47
TABLE 36. RIF MICs FOR <i>RPOB</i> S450 (S531) MUTANTS ON 7H10. ....	48
TABLE 37. RIF MICs FOR <i>RPOB</i> BORDERLINE RRDR MUTANTS ON 7H10. ....	49
TABLE 38. RIF MICs FOR OTHER <i>RPOB</i> RRDR MUTANTS ON 7H10. ....	50
TABLE 39. RIF MICs FOR <i>RPOB</i> MUTANTS OUTSIDE THE RRDR ON 7H10. ....	50
TABLE 40. EFFECT OF CHANGING THE CC FOR RIF DST ON 7H10 FOR DETECTION OF <i>RPOB</i> MUTANTS.....	51
TABLE 41. RIF MICs FOR PWT ISOLATES ON 7H11. ....	52
TABLE 42. RIF MICs FOR <i>RPOB</i> S450 (S531) MUTANTS ON 7H11. ....	52
TABLE 43. RIF MICs FOR OTHER <i>RPOB</i> RRDR MUTANTS ON 7H11. ....	53
TABLE 44. RIF MICs FOR PWT ISOLATES IN MGIT. ....	54

TABLE 45. RIF MICs FOR <i>RPOB</i> S450 (S531) MUTANTS IN MGIT.....	55
TABLE 46. RIF MICs FOR <i>RPOB</i> BORDERLINE RRDR MUTANTS IN MGIT.....	56
TABLE 47. RIF MICs FOR OTHER <i>RPOB</i> RRDR MUTANTS IN MGIT.....	57
TABLE 48. RIF MICs FOR <i>RPOB</i> MUTANTS OUTSIDE THE RRDR IN MGIT.....	58
TABLE 49. EFFECT OF CHANGING THE CC FOR RIF DST ON MGIT FOR DETECTION OF <i>RPOB</i> MUTANTS.....	59
TABLE 50. RFB MICs FOR PWT ISOLATES ON 7H10.....	65
TABLE 51. RFB MICs FOR <i>RPOB</i> S450 (S531) MUTANTS ON 7H10.....	65
TABLE 52. RFB MICs FOR <i>RPOB</i> BORDERLINE RRDR MUTANTS ON 7H10.....	66
TABLE 53. RFB MICs FOR OTHER <i>RPOB</i> RRDR MUTANTS ON 7H10.....	66
TABLE 54. RFB MICs FOR <i>RPOB</i> MUTANTS OUTSIDE THE RRDR ON 7H10.....	67
TABLE 55. EFFECT OF ADOPTING A CC FOR RFB DST ON 7H10 FOR DETECTION OF <i>RPOB</i> MUTANTS.....	67
TABLE 56. RFB MICs FOR PWT ISOLATES ON 7H11.....	68
TABLE 57. RFB MICs FOR <i>RPOB</i> S450 (S531) MUTANTS ON 7H11.....	68
TABLE 58. RFB MICs FOR OTHER <i>RPOB</i> RRDR MUTANTS ON 7H11.....	69
TABLE 59. RFB MICs FOR PWT ISOLATES IN MGIT.....	70
TABLE 60. RFB MICs FOR <i>RPOB</i> S450 (S531) MUTANTS IN MGIT.....	70
TABLE 61. RFB MICs FOR <i>RPOB</i> BORDERLINE RRDR MUTANTS IN MGIT.....	71
TABLE 62. RFB MICs FOR OTHER <i>RPOB</i> RRDR MUTANTS IN MGIT.....	72
TABLE 63. RFB MICs FOR <i>RPOB</i> MUTANTS OUTSIDE OF RRDR IN MGIT.....	72
TABLE 64. EFFECT OF ADOPTING A CC FOR RFB DST ON MGIT FOR DETECTION OF <i>RPOB</i> MUTANTS.....	73
TABLE 65. RPT MICs FOR PWT ISOLATES ON 7H10.....	77
TABLE 66. RPT MICs FOR <i>RPOB</i> S450 (S531) MUTANTS ON 7H10.....	77
TABLE 67. RPT MICs FOR <i>RPOB</i> BORDERLINE RRDR MUTANTS ON 7H10.....	77
TABLE 68. RPT MICs FOR OTHER <i>RPOB</i> RRDR MUTANTS ON 7H10.....	78
TABLE 69. RPT MICs FOR PWT ISOLATES ON 7H11.....	79

预览已结束，完整报告链接和二维码如下：

[https://www.yunbaogao.cn/report/index/report?reportId=5\\_24106](https://www.yunbaogao.cn/report/index/report?reportId=5_24106)

