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To assess the effectiveness of shorter MDR Regimen in tertiary care centre in Western UP

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Abstract---Background: In an attempt to reduce the length of conventional MDR TB regimen for 18months or more WHO updated its treatment guidelines in May 2016and included a recommendation on the use of Standardised Shorter MDR TB regimen with seven drugs and a treatment duration of 9to 12 months. The study explored the experience of the programmatic management of tuberculosis on a shorter injectable containing MDRTB regimen in a tertiary care centre in western Uttar Pradesh, India. Materials and Methods: Retrospective analysis of the data in a tertiary care centre in western up was carried out. The following attributes were included in outcome analysis: 1) Cured, 2) Treatment completed, 3) Treatment failure, Treatment regimen changed, 4) Died, 5) Lost to follow up. Results: Out of 87cases 43 are Male and 44 are female. Out Of the 87cases, 15 Cases were Cured ,57 Cases Treatment Completed, in 7 Patient treatment is changed or treatment is failed, 7 patients died in which 3 patients are female and 4 patients are male and 1 lost to follow up.

Keywords---Standardised Shorter Regimen (SSR), Multidrugresistant TB(MDRTB), Programmatic Management Of Drug Resistant TB(PMDT).

Introduction

WHO uses five categories to classify cases of drug-resistant TB: isoniazid-resistant TB, RR-TB and MDR-TB, plus pre-extensively drug-resistant TB (pre-XDR-TB) and XDR-TB.^[1] By definition, Multidrug-resistant tuberculosis (MDR-TB) is a disease caused by *Mycobacterium tuberculosis* that is resistant to at least both rifampicin and isoniazid with or without resistance to other anti-TB drug.

Detection of drug resistance requires bacteriological confirmation of TB and testing for drug resistance using rapid molecular tests, culture methods or

sequencing technologies. Treatment requires a course of second-line drugs for at least 9 months and up to 20 months,¹ supported by counselling and monitoring for adverse events. WHO recommends expanded access to all-oral regimens.

The currently recommended treatment for people with drug-susceptible TB disease is a 6-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide. The Global TB Drug Facility supplies a complete 6-month course. Treatment success rates for people enrolled on first-line treatment of at least 85% are regularly reported to WHO by its 194 Member States. Treatment for people diagnosed with rifampicin-resistant TB (RR-TB) and multidrug-resistant TB (MDR-TB, defined as resistance to isoniazid and rifampicin, the two most powerful anti-TB drugs) is longer, and requires drugs that are more expensive and that cause more side-effects. Nationally, treatment success rates for rifampicin-resistant TB are typically in the range of 50–75%.

Globally in 2020, 71% (2.1/3.0 million) of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, up from 61% (2.2/3.6 million) in 2019 and 50% (1.7/3.4 million) in 2018. Among these, 132 222 cases of MDR/RR-TB.

There are 10 countries that account for about 70% of the global gap between the estimated global incidence of MDR/RR-TB each year and the number of people enrolled in treatment in 2020: China, Democratic Republic of the Congo, India, Indonesia, Nigeria, Pakistan, Philippines, Russian Federation, South Africa and Viet Nam. Substantial gains in treatment coverage at the global level require particular efforts to improve testing and diagnosis of drug-resistant TB, and access to treatment, in these countries. More positively, there have been improvements in treatment success rates. Globally in 2018 (the latest patient cohort for which data are available, the treatment success rate for MDR/RR-TB was 59%, reflecting steady improvements in recent years from 50% in 2012. Among WHO regions, the treatment success rate in 2018 ranged from 56% in the European Region to 69% in the African Region.

Estimated number of MDR/RR-TB cases in India is 124 000 (9.1/lakh population). The first national anti-tuberculosis drug resistance survey (NDRS) revealed that 28% of TB patients were resistant to any drugs (22% among new and 36.82% among previously treated) and 6.19% had MDR-TB (2.84% among new and 11.62% among previously treated [PT]). Further, any Isoniazid (H) resistance (16% in all with 11.6% in new and 25% in PT being driver for RR-TB. 1.2. Status of drug-resistant TB. The treatment of MDR-TB is very expensive, requires at least 2 years of treatment with potentially toxic drugs.[\[1\]](#),[\[2\]](#),[\[3\]](#),[\[4\]](#),[\[5\]](#),[\[6\]](#)

Attempts to reduce the length of conventional MDR-TB regimens and to use a combination of drugs which is tolerable have been ongoing for several years through various studies. A standardized treatment regimen lasting less than 12 months has been used in a number of countries. It has shown promising results in selected MDR-TB patients. Based on data from these studies, WHO updated its treatment guidelines for drug-resistant TB in May 2016 and included a recommendation on the use of the shorter MDR-TB regimen under specific conditions. This recommendation expected to benefit, the majority of MDR-TB

patients worldwide; however, there are serious risks for worsening resistance if the regimen is used inappropriately (e.g., in XDR-TB patients). WHO encourages ongoing and future randomized controlled clinical trials to strengthen the evidence base for shorter and more effective regimens.

Features of the shorter mdr-tb regimen

- Standardized shorter MDR-TB regimen with seven drugs and a treatment duration of 9-12 months.
- Indicated conditionally in MDR-TB or rifampicin resistant-TB, regardless of patient age or HIV status.
- Monitoring for effectiveness, harms and relapse will be needed, with patient-centred care and social support to enable adherence.
- Programmatic use is feasible in most settings worldwide.
- Lowered costs and reduced patient loss expected.

Regimen Composition

4-6 Km, Mfx, Eto, Cfz, Z, Hhigh-dose, E / 5 Mfx, Cfz, Z, E
 Km=Kanamycin; Mfx=Moxifloxacin; Eto=Ethionamide;
 Cfz=Clofazimine; Z=Pyrazinamide;
 Hhigh-dose= high-dose Isoniazid; E=Ethambutol.

India also started with the shorter MDR regime. The study explores the advantages and disadvantages of the regimen in the Indian demography. The study also explores the fallouts and deaths due to various reasons and the percentage contribution of the reasons for the attrition. The study was done at LLRM Medical College.

The molecular biology of INH resistance in *M. tuberculosis* has been thoroughly studied. INH is a prodrug which undergoes an *in vivo* transformation to its active form. Catalase-peroxidase (KatG) encoded by *katG* performs this function in *M. tuberculosis*,^[7] and mutations in *katG*, at codon 315, confer INH resistance.^[8] The activated INH has a primary target. It is an Nicotinamide adenine dinucleotide (NAD) + hydrogen (H)-dependent enoyl-acyl carrier protein reductase, designated *InhA*.^[9]

Mutations within the *inhA* structural gene^{[10],[11],[12],[13]} or within the *inhA* promoter^{[12],[14],[15],[16],[17]} are associated with both INH and ETH resistance.^{[9],[14]} INH resistance occurs due to missense mutations within the *inhA* structural gene by reducing the NADH and protecting the enzyme from INH inactivation.^[18] The *inhA* promoter mutations upregulate the target expression, thereby rendering INH and ETH resistance.^{[9],[10]} The structural similarity and shared molecular target of INH and ETH led to the conjecture that ETH, such as INH, undergoes activation.^[19]

Materials and Methods

This is a retrospective analysis of patients put of shorter MDR regimen as per the diagnostic algorithm of a programmatic management of drug-resistant TB under the Revised National Tuberculosis Control Program. The sample of these patients was initially tested at the peripheral unit by Cartridge based Nucleic Acid

Amplification Test. RR cases were selected for shorter MDR regimen as per the criteria by the WHO. The patients selected for shorter MDR regimen are as follows:

Inclusion criteria

- All pulmonary and extrapulmonary cases only pleural effusion and lymph nodes
- RR TB or MDR TB patient regardless of patient age or HIV status.

Exclusion criteria

- All pregnant mothers
- Extrapulmonary cases other than pleural effusion and lymph nodes
- Previous exposure of more than 1 month to fluoroquinolones and second-line injectable group of drugs.

Smear examination of the patient selected for shorter MDR is done on a monthly basis in the intensive phase to guide decision-making to move to continuation phase. Smear examination is continued in the extended intensive phase only if the previous month smear is positive up to a maximum of 6 months. Follow-up cultures are done at the end of intensive phase, extended intensive phase, and at the end of treatment regime, and if found positive are subjected to first- and second-line LPA for the assessment of resistance, and if found resistance, modification regime is offered to the patient.

The outcomes of the treatment for all patients are declared only on the basis of follow-up culture. During the course of treatment, samples of the patient are tested at specified intervals as follow-ups to assess the prognosis and outcome of the disease.

Results

This is a retrospective analysis of data with a total of 87 cases which were subjected to shorter MDR regimen. Among these 43 Patient are male and 44 females. Of the 87 Cases 15 Case cured ,57 cases treatment completed, in 7 Patient Treatment is changed or treatment is failed, 7 patients died in which 3 patients are male and 4 patients are female and 1 lost to follow up. As given in Table 1,2 and Figure 1,2.

Table 1
Sex Distribution

Sex	No of patients
Male	43
Female	44
Total	87

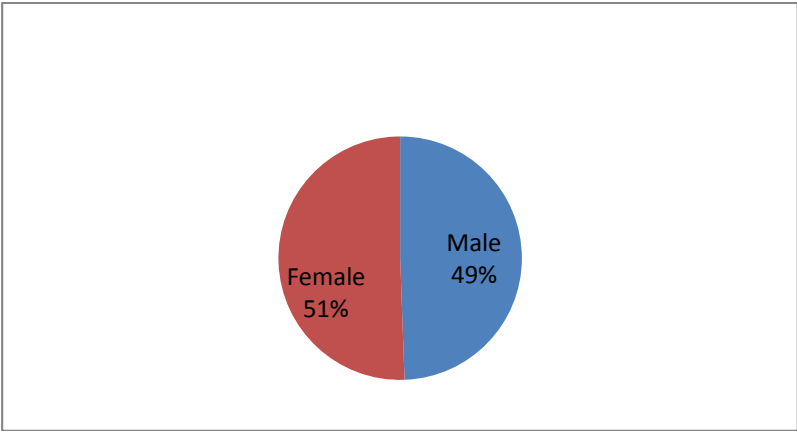


Figure 1. Sex Distribution

Table 2
Status of the patients after following the prescribed treatment

Status	No of patients
Cured	15
Treatment Completed	57
Treatment Changed or failed	7
Died	7
Lost to follow up	1
Total	87

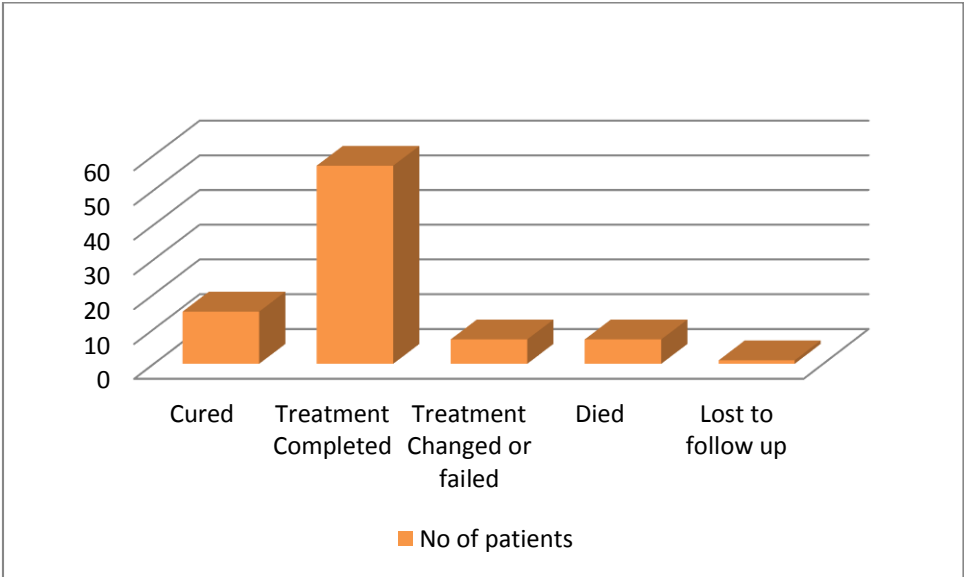


Figure 2. Patients Status after treatment

Outcome definitions

Treatment failed. A patient whose treatment regimen needs to be terminated or permanently changed¹ to a new regimen option or treatment strategy. Cured. A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response² and no evidence of treatment failed. Treatment completed. A patient who completed treatment as recommended by the national policy whose outcome does not meet the definition for cure or treatment failed. Died. A patient who died³ before starting or during the course of treatment. Lost to follow-up. A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

Reasons for the change include: a) No clinical and/or bacteriological response b) Adverse drug reactions (ADRs) c) Evidence of additional drug resistance to medicines in the regimen:

- 1) 1 Bacteriological response – bacteriological conversion with no reversion.
- 2) 2 Bacteriological response – bacteriological conversion with no reversion.
- 3) 3 Patient died of any reason
- 4) 4 This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown and excludes lost to follow up.

Discussion

Out Of the 87 CASES 15 CASES (17.27%) CURED, 57 CASES (66.27%) TREATMENT COMPLETED, IN 7 PATIENT (8.13%) TREATMENT IS CHANGED OR TREATMENT IS FAILED, 7 PATIENT (8.13%) DIED IN WHICH 3 PATIENTS ARE MALE AND 4 PATIENT ARE FEMALE. And 1 case lost to follow up. Programmatic management of drug resistant TB (PMDT) is complex and requires a perfect blend of clinical and programmatic interventions. India has gathered experience of nearly two decades in planning and implementation diagnosis and clinical management of DR-TB.

- Patients with drug resistant TB are managed with the support of a nation-wide network of DR-TB centres, NTEP staff, general health system staff, community volunteers and the private health facilities.
- Treatment follows a pre-treatment evaluation to identify potential risk factors.
- The DST results, history of previous treatment and adverse reaction to drugs are taken into account to further guide the selection of the regimen.
- Treatment may be initiated in the ward or on an out-patient basis depending on the clinical conditions, access to services and patient preferences.

The treatment regimen consisted of seven drugs in the intensive phase: pyrazinamide (Z), ethambutol (E), high-dose isoniazid (H), moxifloxacin (Mfx), capreomycin (Cm) or kanamycin (Km), Ethionamide (Eto) and clofazimine (Cfz) for 4 to 6 months. This was followed by a fixed 5-month continuation phase with Z, E, Mfx, Eto and Cfz, after documentation of sputum-smear microscopy conversion and at least one negative culture. Dosing was weight-based and all treatment was provided under routine programmatic conditions, cost-free to the patient.

Determination of the end of treatment outcome followed WHO definitions for MDR-TB programmes, adapted for changes relevant to the shortened duration of treatment. At the end of treatment, successful outcomes were defined as cure or treatment completion, whereas LTFU, death and treatment failure were considered as unsuccessful. Whole-genome sequencing of isolates was not available, so differentiating relapse from re-infection was not possible. Recurrence was defined as any successfully treated patient who was culture-positive for RR-TB during 12 months of post-treatment follow-up

INH inhibits the process of mycolic acid synthesis.^[20] Mutations in the *katG* gene or the *inhA* regulatory regions leads to INH resistance. INH is rendered ineffective for the treatment of *M. tuberculosis* if encountered mutation.^[8] The *inhA* regulatory region which encodes the primary target of active INH is nicotinamide adenine dinucleotide-dependent enoyl-acyl carrier protein reductase,^{[21],[22]} ETH and prothionamide. *inhA* mutations cause low-level resistance to the molecule meaning that higher doses may be effective. ^[23]

As ETH is a structural analog of INH, cross-resistance occurs between INH and ETH;^{[14],[19]} thus, ETH and low-level INH show cross-resistance. A clinical trial has shown adding high-dose INH systematically to a standard MDR-TB regimen which has been effective. ETH is judiciously used in case of MDR- or XDR-TB strains with *katG* mutations. Of those who had failed to get cured on shorter MDR regimens were further subjected to first-line LPA based on sputum microscopy, and those which were smear negative in between the course of treatment were put on liquid culture and subsequently subjected to first-line LPA.

Conclusion

Initiating a MDR regimen requires a modified selection criteria. The criteria should exclude isoniazid resistant cases owing to its cross resistance with Ethionamide. As ETH is one of the challenging drugs selected in the shorter MDR regime, a simultaneous detection of RR status by CBNAAT at periphery and putting these samples for first-line as well as second-line LPA needs to be implemented prior to the selection of shorter MDR regime. 8% of cases which were culture positive after the initiation of treatment with shorter MDR regime found to be resistant to fluoroquinolones groups or second-line injectable class resistance or both and lead to modification of treatment. Furthermore, to note that the patient receiving the regimen were compelled to change the injectable kanamycin due to intolerability in the initial course of therapy have varied symptoms.

Even extensive studies are required for detecting the well-known drug targets (new drugs for TB) such as *InhA*, *RpoB*, *FabC*, *FabD*, *KasA*, *Ndh*, *Glfx*, *EfpA*, *EmbB*, *ES31*, *Cyp125*, and *InhA*. FASII enoyl-ACP reductase (*InhA*) is the only well-validated target of the TB drug INH and has been a target of the rational drug design. Generally, the cost per diagnosis of using GeneXpert has proved to be very cost-effective among the elderly but the study included project samples which were facilitated by free drugs and diagnostic services; the cost-effectiveness for the patients was not very significant.

Overall success with a standardised shorter MDR-TB regimen was moderate with treatment failure and fluoroquinolone and/or SLID resistance observed. Recently, the WHO has announced changes to the treatment of drug-resistant TB, recommending shorter, all-oral, bedaquiline-containing regimens in place of the injectable-containing SSR. In the primary analysis on which the WHO guidelines decision was based, treatment success rates for the all-oral bedaquiline-containing regimen were 73% *versus* 60% in the SSR. Uncertainty exists over whether those with isolates resistant to ethambutol, pyrazinamide or ethionamide should be excluded from SSR treatment, particularly in the absence of an accurate rapid diagnostic test for these drugs, or treated with alternative medications.

Newer treatment regimen

- NTEP provides simplified regimen for various types of DR-TB including shorter oral Bedaquiline-containing MDR/RR-TB regimen and longer oral M/XDR-TB regimen based on DST/DRT results with scope in difficult patients to extend Bdq beyond 6 months, combined use of Bdq and Dlm and Bdq use in pregnancy
- As the fully oral regimens get scaled up nationwide, the current shorter MDR-TB regimen with injectable SLDs will be phased out.
- Injectable SLDs will be available for use under PMDT to substitute oral SLDs based on DST and ADR.
- Guidance is also provided for using Bdq for children above 5 years and Dlm for children above 6 years.
- Use of BPaL regimen consisting of Bdq, pretomanid (Pa) & linezolid (Lzd) are ongoing in select group of patients on a research mode.

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Conflicts of interest

There are no conflicts of interest.

References

- [1] World Health Organization. Global Tuberculosis Report 2021: Geneva, Switzerland: World Health Organization; 2021
- [2] Crofton JP, Chaulet D, Maher J, Grosset W, Harris H, Norman M, *et al.* Watt. Guidelines for the Management of Multidrug Resistant Tuberculosis. Geneva, Switzerland: World Health Organization; 1997.
- [3] World Health Organization. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug Resistant Tuberculosis. Geneva: World Health Organization; 2014.
- [4] Central TB Division. Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India. New Delhi: Directorate of General Health Services, Ministry of Health and Family Welfare, Government of India; 2021.

- [5] Prasad R, Srivastava DK. Multidrug and extensively drug resistant TB (M/XDR TB) management: Current issues. *Clin Epidemiol Glob Health* 2013;1:124-8.
- [6] Prasad R. Multidrug and extensively drug-resistant tuberculosis management: Evidences and controversies. *Lung India* 2012;29:154-9.
- [7] Zhang Y, Heym B, Allen B, Young D, Cole S. The catalase-peroxidase gene and isoniazid resistance of *Mycobacterium tuberculosis*. *Nature* 1992;358:591-3.
- [8] Blanchard JS. Molecular mechanisms of drug resistance in *Mycobacterium tuberculosis*. *Annu Rev Biochem* 1996;65:215-39.
- [9] Larsen MH, Vilchèze C, Kremer L, Besra GS, Parsons L, Salfinger M, *et al*. Overexpression of *inhA*, but not *kasA*, confers resistance to isoniazid and ethionamide in *Mycobacterium smegmatis*, *M. bovis* BCG and *M. tuberculosis*. *Mol Microbiol* 2002;46:453-66.
- [10] Banerjee A, Dubnau E, Quemard A, Balasubramanian V, Um KS, Wilson T, *et al*. *InhA*, a gene encoding a target for isoniazid and ethionamide in *Mycobacterium tuberculosis*. *Science* 1994;263:227-30.
- [11] Basso LA, Zheng R, Musser JM, Jacobs WR Jr., Blanchard JS. Mechanisms of isoniazid resistance in *Mycobacterium tuberculosis*: Enzymatic characterization of enoyl reductase mutants identified in isoniazid-resistant clinical isolates. *J Infect Dis* 1998;178:769-75.
- [12] Kapur V, Li LL, Hamrick MR, Plikaytis BB, Shinnick TM, Telenti A, *et al*. Rapid *Mycobacterium* species assignment and unambiguous identification of mutations associated with antimicrobial resistance in *Mycobacterium tuberculosis* by automated DNA sequencing. *Arch Pathol Lab Med* 1995;119:131-8.
- [13] Ristow M, Möhlig M, Rifai M, Schatz H, Feldmann K, Pfeiffer A. New isoniazid/ethionamide resistance gene mutation and screening for multidrug-resistant *Mycobacterium tuberculosis* strains. *Lancet* 1995;346:502-3.
- [14] Lee H, Cho SN, Bang HE, Lee JH, Bai GH, Kim SJ, *et al*. Exclusive mutations related to isoniazid and ethionamide resistance among *Mycobacterium tuberculosis* isolates from Korea. *Int J Tuberc Lung Dis* 2000;4:441-7.
- [15] Morris S, Bai GH, Suffys P, Portillo-Gomez L, Fairchok M, Rouse D. Molecular mechanisms of multiple drug resistance in clinical isolates of *Mycobacterium tuberculosis*. *J Infect Dis* 1995;171:954-60.
- [16] Musser JM, Kapur V, Williams DL, Kreiswirth BN, van Soolingen D, van Embden JD. Characterization of the catalase-peroxidase gene (*katG*) and *inhA* locus in isoniazid-resistant and -susceptible strains of *Mycobacterium tuberculosis* by automated DNA sequencing: Restricted array of mutations associated with drug resistance. *J Infect Dis* 1996;173:196-202.
- [17] Rouse DA, Li Z, Bai GH, Morris SL. Characterization of the *katG* and *inhA* genes of isoniazid-resistant clinical isolates of *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 1995;39:2472-7.
- [18] Zhang Y, Yew WW. Mechanisms of drug resistance in *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis* 2009;13:1320-30.
- [19] Müller B, Streicher EM, Hoek KG, Tait M, Trollip A, Bosman ME, *et al*. *InhA* promoter mutations: A gateway to extensively drug-resistant tuberculosis in South Africa? *Int J Tuberc Lung Dis* 2011;15:344-51.

- [20] Moulding TS. Should isoniazid be used in retreatment of tuberculosis despite acquired isoniazid resistance? *Am Rev Respir Dis* 1981;123:262-4.
- [21] Katiyar SK, Bihari S, Prakash S, Mamtani M, Kulkarni H. A randomised controlled trial of high-dose isoniazid adjuvant therapy for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2008;12:139-45.
- [22] Jena L, Harinath BC. Anti-tuberculosis therapy: Urgency for new drugs and integrative approach. *Bio Biotech Res J* 2018;2:16-9.
- [23] Sookaromdee P, Wiwanitkit V. Cost-effectiveness analysis of classical sputum examination versus molecular diagnosis by genexpe. *Bio Biotech Res J* 2019;3:210-1.