SMGroup

**Title: Tuberculosis Control: An Indian Perspective**

**Author: Saurabh Shrivastava**

**Published by SM Online Publishers LLC**



**ISBN: 978-0-9962745-1-7**



**First published October, 2014**

**Online Edition available at www.smgebooks.com**

**For reprints, please contact us at ebooks@esciencemedicine.com**

SMGroup

CHAPTER 4

# Drug Resistant Tuberculosis

## INTRODUCTION

Globally, owing to the emergence of resistance to first line anti-tubercular drugs, a remarkable rise in the incidence of drug resistant forms of TB drugs has been observed [1,2]. In India, this has been identified as a major obstacle in the government initiative to ensure effective TB control [2,3].

## MULTIDRUG RESISTANT TB (MDR-TB) SUSPECT

A patient suspected of drug-resistant tuberculosis, based on RNTCP criteria for submission of specimens for drug-susceptibility testing (described later in this Chapter) [3].

**MDR-TB Case:** A TB patient whose

- Sputum is culture positive for Mycobacterium tuberculosis
- It is resistant in-vitro to isoniazid and rifampicin with or without other anti-tubercular drugs and
- Provided drug sensitivity testing (DST) results are obtained from an Revised National TB Control Program (RNTCP) -certified Culture & DST laboratory [3].

## EXTENSIVELY DRUG RESISTANT TB (XDR TB)

An MDR TB case whose recovered M. tuberculosis isolate is resistant to at least isoniazid, rifampicin, a fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin) and a second-line injectable antiTB drug (kanamycin, amikacin, or capreomycin) at a RNTCP-certified Culture & DST laboratory [3].

As per the estimates of drug resistance surveillance conducted in three states (viz. Gujarat, Maharashtra, Andhra Pradesh), it has been revealed that almost 2-3% of newly detected cases and 12-17% of the previously-treated cases of TB suffer from multi-drug resistant TB (MDR-TB) [3]. Although, the rate of MDR-TB is relatively low in India, but owing to a very high burden of TB cases, this is equivalent to a large number of MDR-TB cases [3]. In-fact, the findings of Global TB report-2013 suggest that India is one among the high burden countries with regard to MDR-TB and a persistent rise in such cases has been observed over the years [2]. Almost 60% of the reported global burden of MDR-TB is provided by India and China [1]. However, exact burden

of MDR-TB is not yet clear as often most of the cases go unreported because of ignorance by the private practitioners and poor awareness among the community [1,2,4].

## ETIOLOGY AND PREVENTION OF DRUG-RESISTANT TB

In general, MDR-TB is a man-made phenomenon – poor treatment, poor drugs and poor adherence lead to the development of MDR-TB [3]. However, the drug-resistant TB can result because of the providers/program related factors (viz. inappropriate guidelines, non-adherence to guidelines, inadequate training of health team, no monitoring; poorly organized TB control programs); drugs (viz. non-availability of certain drugs, delivery disruptions, poor quality of supplied drugs, poor storage conditions, wrong dosages or combination); and patient related determinants (viz. poor adherence to DOT, poor knowledge about different aspects of TB, non-availability of free drugs, adverse drug effects, socio-economic constraints, and substance abuse) [3-9].

As already discussed, most of the cases of drug resistance result because of poor treatment practices and thus delivery of a quality assured treatment is a pre-requisite for the prevention of emergence of the resistance [3,7,10]. In other words, RNTCP recognizes that implementation of a good quality DOTS program is the chief priority for TB control in the country [6]. In-fact, ensuring prevention of emergence of MDR-TB in the community is more crucial than its treatment as

- Second line drugs are used in management of DR-TB whose efficacy and effectiveness in curing the disease is inferior to first line drugs
- More expensive (viz. Full course of category-I ATT cost around Rs 1500 per patient as compared to Category IV ATT used for treatment of MDR-TB which approximately costs Rs. 4-4.5 Lacs {in private sector} or Rs 2-2.5 Lacs {under the RNTCP})
- Long duration of therapy (viz. Category I ATT – 6 months / Category II ATT – 8 months versus Category IV ATT – 24-27 months & Category V – 24-30 months)
- More risk of adverse drug reactions (as the number of drugs consumed in category IV / V – ATT are more their toxicity is also more)
- Special need for continuous psychological and social support [3,5,11,12].

Thus, basic TB diagnostic and treatment services should be prioritized with the view that DOTS reduce the emergence of MDR-TB [6]. In addition, promoting rational use of anti-TB drugs, and implementing appropriate infection control measures in health care establishments can also reduce the risk of transmission of the MDR-TB [3,5].

## PROGRAMMATIC MANAGEMENT OF DRUG RESISTANT TB (PMDT)

Under the flagship Revised National Tuberculosis Control Program, specific measures have been taken to address the public health concern of MDR-TB by ensuring appropriate management of patients and invoking strategies to prevent the propagation and dissemination of MDR-TB [3]. In order to strengthen the country's capacity to diagnose MDR-TB cases, equally matched with

ensuring uninterrupted supply of quality assured drugs, Programmatic Management of Drug Resistant TB (previously known as DOTS Plus) component was launched in 2007 [3]. The PMDT has laid down standardized guidelines to facilitate integration of basic TB control and PMDT activities under the RNTCP, so that patients with TB are adequately evaluated for drug-resistance and placed on the recommended anti-TB regimen (MDR-TB & XDR-TB) at the earliest [11]. These guidelines also integrate the identification and treatment of more severe forms of drug resistance, such as extensively drug resistant TB [3,11]. In addition, a management information system has also been established to allow systematic, comprehensive data collection and analysis to facilitate appropriate supervision and monitoring of the PMDT activities and formulation of future policies and recommendations [3,12].

To ensure success of PMDT component special attention is needed towards efficient and timely identification of patients who require DST; expansion of quality-assured laboratory services (sputum, culture-DST, rapid molecular test); efficient drug procurement and supply chain management; adherence to difficult-to-take regimens for long periods; prompt identification and management of side-effects; human and financial resources; and recording and reporting [10,13,14].

## MDR-TB CASE FINDING

It has been acknowledged that most of the high burden countries tend to have a weak public health care delivery system and thus have scarce resources – administrative & monetary support / limited number of level-3 bio-safety laboratories / trained health care providers [15,16]. Thus, to ensure detection of the maximum number of MDR-TB cases within the available resources, MDR-TB suspects (or high risk groups) have to be identified in order to interrupt the transmission of the disease as early as possible [1,2,6].

When the PMDT component was launched initially the strategy was to screen only high risk patients, but gradually the range of services has been expanded to the entire country [5,6]. To upscale the expansion uniformly, RNTCP has devised MDR suspect criteria – A, B, and C [3]. These criteria were framed to run in tandem with the strengthening of the laboratory services so that the existing RNTCP certified laboratories can carry out the culture & DST services without being overburdened [8,16]. Hence, Criteria-A was first implemented in most of the parts of the country and depending upon the load of MDR-TB cases, Criteria-B and Criteria-C was subsequently either implemented or would be implemented in a time-bound manner to geographically cover the entire nation [3].

### MDR Suspect Criteria A:

- Category – I failure at the end of 5th month of treatment
- Category – II sputum positive at the end of 4th month of treatment or onwards and
- All pulmonary TB cases (sputum positive and sputum negative) who are contact of known MDR-TB case

The main limitation of the Criteria-A was that despite the availability of documented evidence that 2-3% of the newly treated TB patients and 12-17% of previously-treated TB cases are bound to be resistant to first line drugs even before initiation of treatment, these are still treated with anti-TB drugs which are ineffective and thus, patients lose out on five months and four months in category-I and category-II respectively [3,6]. From the public health perspective, such patients remain a potential source of transmission of MDR-TB for almost four to five months during which they were inadequately managed to all of their possible contacts [3].

Furthermore, the criteria-A does not permit inclusion of patients who have been previously treated under private health sector [3]. This is quite an important aspect as almost 70% of the country population access private health sector and thus the number of people not eligible for MDR suspect could be huge [18,19].

### MDR Suspect Criteria B:

- All sputum positive re-treatment pulmonary TB cases at diagnosis
- Any sputum positive follow-up of new cases at the end of intensive phase / later or re-treatment cases, in addition to Criteria A

In order to extend the coverage of PMDT services and to improve upon the limitations of Criteria-A, Criteria-B was implemented [3,11]. From the patient perspective, three months (Category I) and four months (Category II) can be saved [3]. From the community perspective, because drug resistant patients will be issued appropriate treatment since the beginning, the potential transmission to contacts can be interrupted [3]. In-fact, all re-treatment cases will be considered as MDR-TB suspect right at the time of diagnosis. In addition, regions of the country where criteria-B is implemented, free diagnostic / therapeutic services will be offered to even those patients who have previously taken anti-TB treatment from the private sector [3]. The only limitation of Criteria-B was that no provision exists to include sputum negative retreatment TB cases [3].

### MDR Suspect Criteria C:

- Sputum negative re-treatment pulmonary TB cases at the time of diagnosis; and
- HIV-TB co-infected cases, in addition to Criteria B

The criteria-C has been suggested to achieve geographical expansion of PMDT services [3]. However, nothing has been incorporated regarding people who will be diagnosed with pulmonary TB for the first time [20]. It is anticipated that all districts in the country would be implementing Criteria-C by 2015 [3,20].

## DIAGNOSIS

All identified MDR-TB suspect will be referred for culture and drug sensitivity testing (C & DST) from a RNTCP certified laboratory and based on the results patient will be started on

Category-IV or V anti-TB treatment [3]. Over the last decade, the diagnostic modalities for drug-resistant TB has extensively expanded to such an extent that a diagnosis can be available within two hours as compared to more than three months in earlier days [3]. All the expansion related aspects will be dealt in Chapter 5.

## DRUG RESISTANT TB CENTER (DR-TB CENTER)

Findings of studies done across heterogeneous settings have identified multiple factors (viz. poor counseling of the patient, absence of continuous motivation, adverse drug reactions, complications of the disease, etc.) which eventually affect the outcome of MDR-TB treatment [12,21,22]. Realizing the long duration of treatment, PMDT advocates for decentralization of treatment. However, to assure adequate supervision and to guide the program managers, an expert resource center called as Drug-resistant TB (DR-TB) center has been established [3].

As far as population norms are concerned, one DR-TB center is expected to extend therapeutic services to 10 million people [3]. These DR-TB centers are preferably started in government medical college hospital (with a one-time financial assistance of Rs. 1 million) under the supervision of the department of pulmonology or general medicine [11]. The DR-TB center functions through a DR-TB center committee, chaired by the Medical Superintendent / institute director; Vice-chairperson – Head of department of respiratory medicine / general medicine; nodal officer; member secretary - DR-TB center senior medical officer; clinicians – Heads of Psychiatry / Gynecology / ENT / Microbiology; one chest physician from NGO/private sector; and local district TB officers of the districts catered by the DR-TB center [3,23].

A DR-TB center plays significant role in the management of drug resistant TB like pre-treatment evaluation; initiation of category – IV / V treatment; airborne infection control measures in wards; adverse drug reaction management; free laboratory investigations; alterations in the line of management based on the drug sensitivity test results during the course of treatment; shifting patient from intensive phase to continuation phase; transfer-in and transfer-out of patients; management of records; outcome declaration; and as a clinical expert resource for guidance to the program managers and the health care providers [1-3].

## PRE-TREATMENT EVALUATION & INITIATION OF TREATMENT

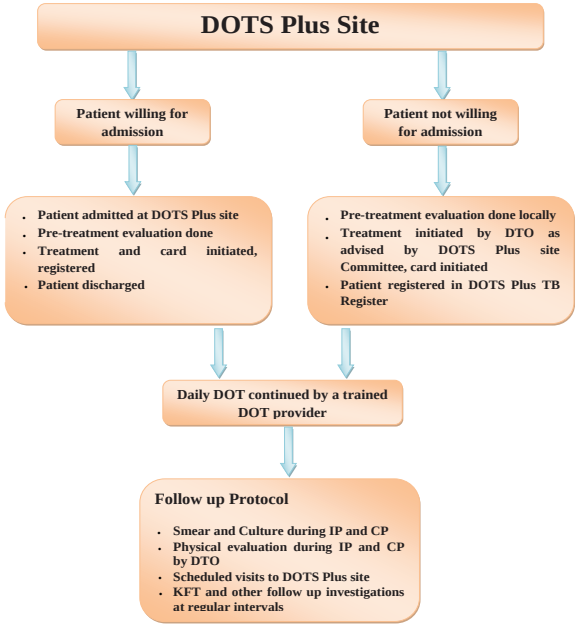
Considering the life threatening nature of the MDR-TB, poor treatment success rate, high default / complication rate and the potential risk of transmission of the disease to a susceptible contact, early diagnosis and initiation of the patient on second-line anti-TB drugs is of prime public health importance [24-27]. In-fact, one of the most important elements to ensure a positive outcome is to initiate the treatment regimen based on the pre-treatment evaluation (PTE) done at the drug resistant TB centre (DR-TB centre) by an expert DR-TB centre committee [28]. The idea behind a comprehensive PTE is to identify those high-risk patients who are at risk of developing adverse effects owing to consumption of MDR-TB drugs during the course of treatment [28].

The Pre-treatment evaluation for MDR-TB consists of

- Obtaining thorough history
- Detailed clinical examination
- Height (for estimation of doses of renal-toxic drugs) and weight (for selecting an appropriate weight band of treatment) measurement
- Complete blood count
- Blood sugar to rule out diabetes
- Liver function tests
- Renal function tests - blood urea and serum creatinine
- Thyroid stimulating hormone levels (to adjust the dosage of ethionamide)
- Urine routine
- Chest X-ray
- HIV counseling and testing services (if the status is unknown / previous results are more than six months old)
- Pregnancy test (for all women in the childbearing age-group)
- Psychiatric assessment (if patient is suffering from mental illness or is addicted to drugs/alcohol)

However, for XDR-TB patients – PTE also includes electrocardiogram, serum electrolytes, and surgical evaluation. However, the role of counseling to the patient and family members (regarding nature and duration of treatment; the need for regularity; probable side effects; and consequences of irregular treatment) is once again a key element [3,28].

Under the PMDT, the only provision available for performing PTE was to admit the patient at the DR-TB centre for an initial period of minimum seven days to check for the response and then subsequently discharge them for Directly Observed Treatment near to the patient local residence [3]. This initial period of hospitalization was recommended to alter the treatment regimen based on any adverse effects [3]. However, owing to the lack of availability of the beds at the DR-TB centre and the unwilling nature of patients to get admitted at the DR-TB centre, PMDT introduced the strategy of out-patient PTE (Flowchart 2) [3]. This strategy was introduced to guarantee that none of the diagnosed TB patient should be refused treatment for any reason [5,6]. In such cases, the local District TB Officer is made accountable to ensure that all the necessary laboratory and biochemical investigations (required for pre-treatment evaluation) are performed, patient visits the DR-TB centre for PTE on a out-patient basis [28].




**Flowchart 2: Patient flow, treatment, and follow-up**

## TREATMENT OF DRUG RESISTANT TB

The treatment duration and choice of drugs vary depending on the type of TB [3]. Different weight bands are available and depending on the weight of the patient appropriate weight band can be selected for the patient [11]. All the prescribed drugs have to be administered as a single daily dosage under DOT on six days of the week [11]. On Sundays patient takes drug at his home and there is no injection scheduled [11].

**A) Multi-Drug Resistant TB:** The overall duration of treatment ranges from 24-27 months, consisting of

**I. Intensive phase (6-9 months):** Kanamycin, Levofloxacin, Cycloserine, Ethionamide, PZA, Ethambutol; and

**II. Continuation phase (18 months):** Levofloxacin, Cycloserine, Ethionamide, Ethambutol

***Weight bands available:*** <16kgs, 16-25kgs, 26-45kgs, 46-70kgs, >70kgs.

**B) Extensively Drug Resistant TB:** The overall duration of treatment ranges from 24-30 months, consisting of

**I. Intensive phase (6-12 months):** Capreomycin, Para-amino salicylic acid, Moxifloxacin, High dose-Isoniazid, Clofazimine, Linezolid, & Amoxyclav; and

**II. Continuation phase (18 months):** Para-amino salicylic acid, Moxifloxacin, High dose-Isoniazid, Clofazimine, Linezolid, and Amoxyclav

***Weight bands available:*** ≤45 Kgs and >45 Kgs

In case, patient gains weight during treatment and crosses the weight bands range the DOTS Plus site may consider moving the patient to higher weight band drug dosages [3]. Finally, during the course of treatment, periodic sputum culture & DST, chest X-ray, renal function tests, and other laboratory investigations will be done to assess the adverse impact on metabolic functions and clinical improvement of the patient [3].

## TOTAL DRUG RESISTANT TB - MYTH OR REALITY

In the month of January 2012, it was reported that twelve cases of Total drug resistant (TDR) TB had been diagnosed in Mumbai owing to the resistance of the bacilli strain to anti-TB drugs [23]. The patients were resistant to all first-line and second-line drugs (kanamycin, amikacin, capreomycin, ofloxacin, moxifloxacin, ethionamide and para-amino salicylic acid) [24]. It was even reported that this phenomenon has emerged due to the failure of the overall health system as these patients have received irrational, unsupervised second line drugs, in incorrect dosages, from multiple private practitioners [23,24].

However, Government of India and Brihanmumbai Municipal Corporation denied the existence of such cases. Eventually on analysis of the laboratory reports of these patients, it was realized that these patients were not tested for all drugs which have anti-tubercular properties (like clofazamine, etc.) [25]. In-fact, what all happened next is worth mentioning – a set of major reforms were introduced not only in Mumbai but even on the national level by the Union Ministry of Health. These included:

- All of a sudden, TB was in the front page of every Indian newspaper, and this proved to be a blessing in disguise giving extra attention which was very much needed for this chronic disease
- TB was made a notifiable disease on 7 May 2012 to encourage reporting from all practitioners / laboratories network, etc.
- Rapid expansion in the laboratory capacity of the public health sector with introduction of Molecular tests and GeneXpert machines
- Human resource related changes – appointment of additional 24 RNTCP managers in 24 municipal wards of Mumbai
- Massive hike in the budgetary allocation to the RNTCP (in Mumbai alone –six time hike was observed)
- Action plans were laid to upscale the PMDT in the entire state [23,24].

The moral of this incident is that the prescription of second-line drugs should always be done by a trained medical practitioner and regulation must be implemented to prevent the relentless amplification of resistance.

## CONCLUSION

To conclude, MDR-TB is a man-made phenomenon resulting because of the poor treatment,

poor drugs and poor treatment adherence. Although, RNTCP has launched a special initiative in the form of PMDT to address to the concern of drug resistant TB, it still recommends implementation of a good quality DOTS program is the chief priority for TB control in the country.

## SUMMARY

Globally, owing to the emergence of resistance to first line anti-tubercular drugs, a remarkable rise in the incidence of drug resistant forms of TB drugs has been observed. In India, this has been identified as a major obstacle in the government initiative to ensure effective TB control. In general, MDR-TB is a man-made phenomenon – poor treatment, poor drugs and poor adherence lead to the development of MDR-TB. Under the flagship Revised National Tuberculosis Control Program, specific measures have been taken to address the public health concern of MDR-TB by ensuring appropriate management of patients and invoking strategies to prevent the propagation and dissemination of MDR-TB. To upscale the expansion uniformly, RNTCP has devised MDR suspect criteria – A, B, and C. All identified MDR-TB suspect will be referred for culture and drug sensitivity testing (C & DST) from a RNTCP certified laboratory and based on the results patient will be started on Category-IV or V anti-TB treatment. To conclude, MDR-TB is a man-made phenomenon resulting because of the poor treatment, poor drugs and poor treatment adherence. Although, RNTCP has launched a special initiative in the form of PMDT to address to the concern of drug resistant TB, it still recommends implementation of a good quality DOTS program is the chief priority for TB control in the country.

### References


1. World Health Organization. Global Tuberculosis Control Report 2012. Geneva: WHO press, 2012.
2. World Health Organization. Global Tuberculosis Control Report 2013. Geneva: WHO press. 2013.
3. TBC India. Guidelines for PMDT in India. New Delhi: TBC India. 2012.
4. Travasso C. Detection and treatment of multidrug resistant TB in India remains low. BMJ. 2013; 347: f5414.
5. TBC India. Managing the RNTCP in your area - A training course (Modules 1-4). 2011.
6. Park K. Epidemiology of communicable diseases. Park K, editor. In: Text Book of Preventive and Social Medicine. 21st edn. Jabalpur: Banarsidas Bhanot Publishers. 2011; 164-181.
7. Kapata N, Chanda-Kapata P, Bates M, Mwaba P, Cobelens F. Multidrug-resistant TB in Zambia: review of national data from 2000 to 2011. Trop Med Int Health. 2013; 18: 1386-1391.
8. Portero JL, Rubio M. Multidrug-resistant TB in the Philippines: totem and taboo. PLoS Med. 2006; 3: e539.
9. Akksilp S, Wattanaamornkiat W, Kittikraisak W, Nateniyom S, Rienthong S, et al.. Multidrug-resistant TB and HIV in Thailand: overlapping, but not independently associated, risk factors. Southeast Asian J Trop Med Public Health. 2009; 40: 1264-1278.
10. Nardell EA. Impact of DOTS and DOTS-plus on multidrug resistant TB: DOTS-plus strengthens, not weakens, DOTS programmes. BMJ. 2003; 327: 164.
11. Sarin R. Programmatic management of multidrug resistant TB. Indian J Tuberc. 2009; 56: 171-173.
12. Alexander PE, De P. The emergence of extensively drug-resistant tuberculosis (TB): TB/HIV co-infection, multidrug-resistant TB and the resulting public health threat from extensively drug-resistant TB, globally and in Canada. Can J Infect Dis Med Microbiol. 2007; 18: 289-291.
13. Strâmbu I. Practical, recommendation for the approach of multidrug-resistant TB. Pneumologia. 2004; 53: 36-42.
14. Schmid ML, McKendrick MW, Green ST, Ridgway EJ. More financial resources must be provided for multidrug resistant TB. BMJ. 1999; 318: 1076.

15. Verma R, Khanna P, Mehta B. Revised national tuberculosis control program in India: the need to strengthen. Int J Prev Med. 2013; 4: 1-5.

16. Chavez Pachas AM, Blank R, Smith Fawzi MC, Bayona J, Becerra MC. Identifying early treatment failure on category I therapy for pulmonary tuberculosis in Lima Ciudad, Peru. Int J Tuberc Lung Dis. 2004; 8: 52-58.

17. John TJ, Vashishtha VM, John SM, Sudarsanam TD. Tuberculosis control must be scientifically defined & soundly designed. Indian J Med Res. 2010; 132: 4-8.

18. Ministry of Health and Family Welfare (2006) National family health survey (NFHS-3), 2005-06. 2006.

19. Ramachandran R, Muniyandi M, Gopi PG, Wares F. Why do tuberculosis suspects bypass local services to attend tuberculosis sanatorium? Lung India. 2010; 27: 111-114.

20. TBC India. National PMDT scale-up plan – India 2011-12. 2011.

21. Hirpa S, Medhin G, Girma B, Melese M, Mekonen A. Determinants of multidrug-resistant tuberculosis in patients who underwent first-line treatment in Addis Ababa: a case control study. BMC Public Health. 2013; 13: 782.

22. Sagar T, Singh NP, Kashyap B, Kaur IR. Current status of multidrug resistant tuberculosis in a tertiary care hospital of East Delhi. J Postgrad Med. 2013; 59: 173-176.

23. Shrivastava SR, Shrivastava PS, Ramasamy J. Exploring the role of drug resistant tuberculosis centre in the programmatic management: An Indian perspective. MRIMS J of Health Sci. 2013; 1: 64-65.

24. García de la Osa Mde L, García Silvera E, Solano Leal M, Milanés Virelles MT. Response to therapy in multiple drug resistant tuberculosis patients. Rev Cubana Med Trop. 2012; 64: 153-162.

25. Unsal E, Güler M, Ofluoglu R, Capan N, Cimen F. Factors associated with treatment outcome in 64 HIV negative patients with multidrug resistant tuberculosis. J Thorac Dis. 2013; 5: 435-439.

26. Podewils LJ, Gler MT, Quelapio MI, Chen MP. Patterns of treatment interruption among patients with multidrug-resistant TB (MDR TB) and association with interim and final treatment outcomes. PLoS One. 2013; 8: e70064.

27. Chien JY, Chen YT, Shu CC, Lee JJ, Wang JY. Outcome correlation of smear-positivity for acid-fast bacilli at the fifth month of treatment in non-multidrug-resistant TB. Chest. 2013; 143: 1725-1732.

28. Shrivastava SR, Shrivastava PS, Ramasamy J. Pre-treatment evaluation: Setting a foundation in the management of drug resistant tuberculosis. El Mednifico Journal. 2014; 2: 164-165.