An overview of Programmatic Management of Drug Resistance Tuberculosis (PMDT) in India

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Introduction:

Tuberculosis (TB) is a major public health concern in India, accounting about one-fourth of the world's annual incidence of TB cases. Each year, about 2.8 million people develop TB in India and an estimated 4.8 lakh people die from the disease. As per the Global TB Report 2016, about 1.3 lakh multi-drug resistant TB patients emerge annually in India. The Revised National TB Control Programme (RNTCP) till date has treated over 19 million patients and thus saved an additional three million lives. The cure rates under RNTCP have consistently been above 85%. TB Millennium Development Goals of 50 per cent reduction in the prevalence of TB and reducing TB death by 50 per cent have been achieved.

India is now stepped into National Strategic Plan and is a signatory to "The End TB Strategy" that calls for a world free of tuberculosis, with measurable aims of a 50% and 75% reduction in incidence and related deaths, respectively, by 2025, and corresponding reductions of 90% and 95% by 2035. Sustainable Development Goals (SDGs) which came into effect from 1st January 2016 require that all three dimensions of sustainable development i.e. economic, social and environmental, are addressed in an integrated manner to ensure that "no one is left behind". As a step towards achieving the SDGs and End TB Strategy, the RNTCP is adopting newer strategies and tools to ensure universal access to quality TB care.

However, despite a comprehensive national TB control program-guiding states for implementation of TB diagnosis and treatment there is still a long way to go. The decline in TB incidence has been slow, mortality remains unacceptably high and the emergence of drug-resistant TB has become a major challenge.

The reasons why drug resistance continues to emerge and spread are mismanagement of TB treatment and person-to-person transmission. Most people with TB can be cured by a strictly followed, 6-month treatment provided to patients with support and supervision. Inappropriate or incorrect use of antimicrobial drugs, or use of ineffective formulations of drugs (such as use of single drugs, inappropriate dosage, poor quality medicines or bad storage conditions), and premature treatment interruption can cause drug resistance, which can then be transmitted, especially in crowded settings like ours.

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The two most potent anti – TB drugs of strains resistant viz. isoniazid (H) and rifampicin (R) (multidrug resistant-tuberculosis, MDR-TB). The response of patients with MDR-TB to treatment is poor and the mortality rate is usually high. Since these patients need to be treated with expensive and toxic second line drugs, and may require hospitalization to manage their toxic reactions and other complications, they require a sizeable proportion of health care resources.

Further, an alarming increase in infection due to the human immunodeficiency virus (HIV) has accelerated this situation. There is a concern in India regarding the increase in HIV-associated TB and the emergence of MDR-TB in both magnitude and severity of TB epidemic.

Classification of TB based on drug resistance:

- **Mono-resistance (MR):** A TB patient, whose biological specimen is resistant to one first-line anti-TB drug only.
- **Poly-Drug Resistance (PDR):** A TB patient, whose biological specimen is resistant to more than one first-line anti-TB drug, other than both INH and Rifampicin.
- **Multi Drug Resistance (MDR):** A TB patient, whose biological specimen is resistant to both isoniazid and Rifampicin with or without resistance to other first line drugs, based on the results from a quality assured laboratory.
- **Rifampicin Resistance (RR):** resistance to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs excluding INH. Patients, who have any Rifampicin resistance, should also be managed as if they are an MDR TB case.
- **Extensive Drug Resistance (XDR):** A MDR TB case whose biological specimen is additionally resistant to a fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin) and a second-line injectable anti TB drug (kanamycin, amikacin, or capreomycin) from a quality assured laboratory.

Programmatic Management of Drug-resistant Tuberculosis:

PMDT, earlier referred to as DOTS-Plus, is provided as a specialized service under the expanded framework of the DOTS package for management of MDR-TB. The implementation of DOTS is to be accorded higher priority over PMDT with the view that effective implementation of DOTS would reduce the emergence of drug-resistant TB cases. India began services for diagnostic and treatment for MDR-TB in the year 2007 and achieved complete coverage in the year 2013. Till 2016, 1,39,369 persons with MDR-TB/RR TB were diagnosed and 91% of these patients were put on treatment under PMDT of RNTCP.

The diagnostic tools, diagnostic algorithms and treatment practices under PMDT are briefed as under**:**

Diagnosis tools:

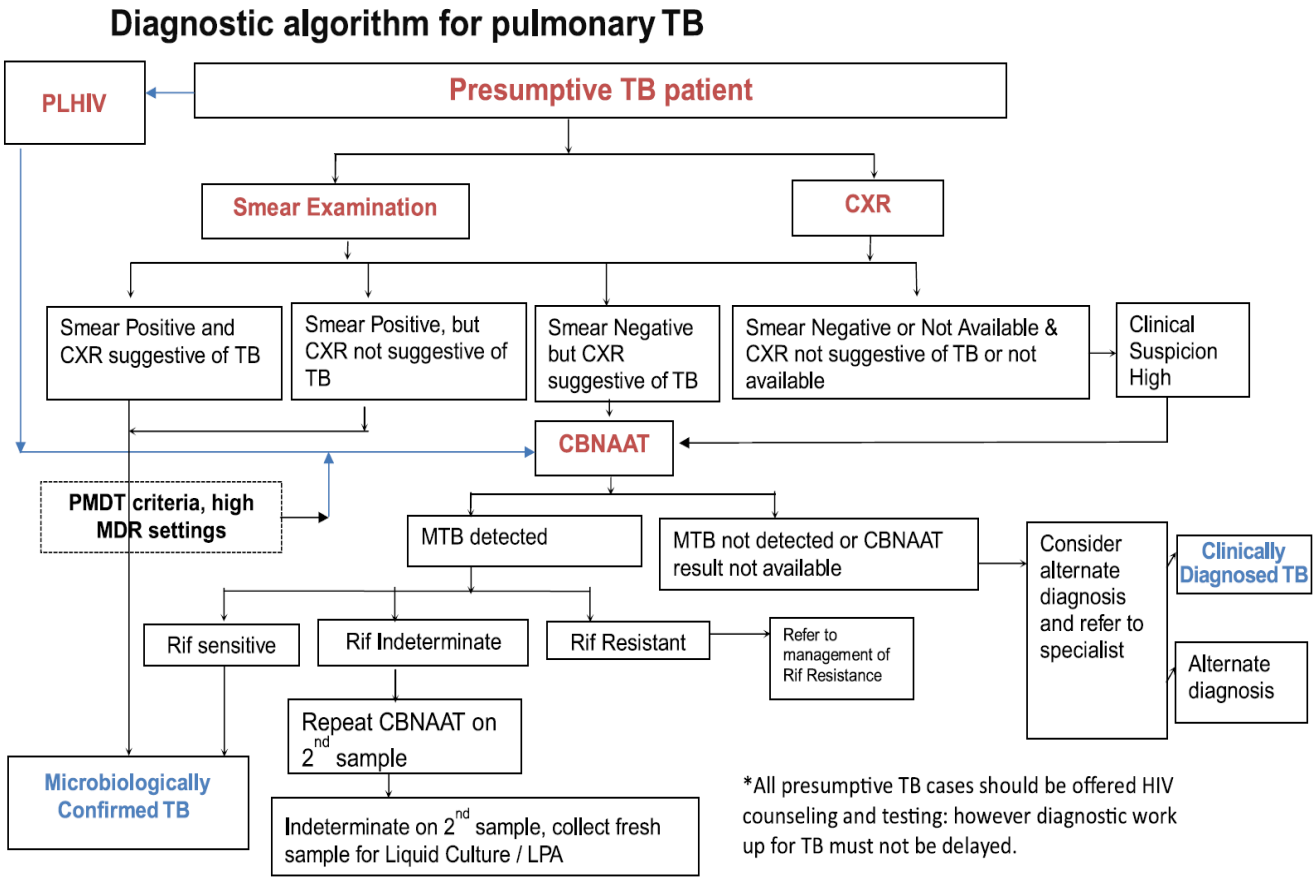
All efforts should be undertaken for microbiologically confirming the diagnosis in presumptive TB patients. Under RNTCP, the acceptable methods for microbiological diagnosis of TB are:

- ***Sputum Smear Microscopy(for AFB):***
    - Zeihl -Neelson Staining
    - Fluorescent Staining

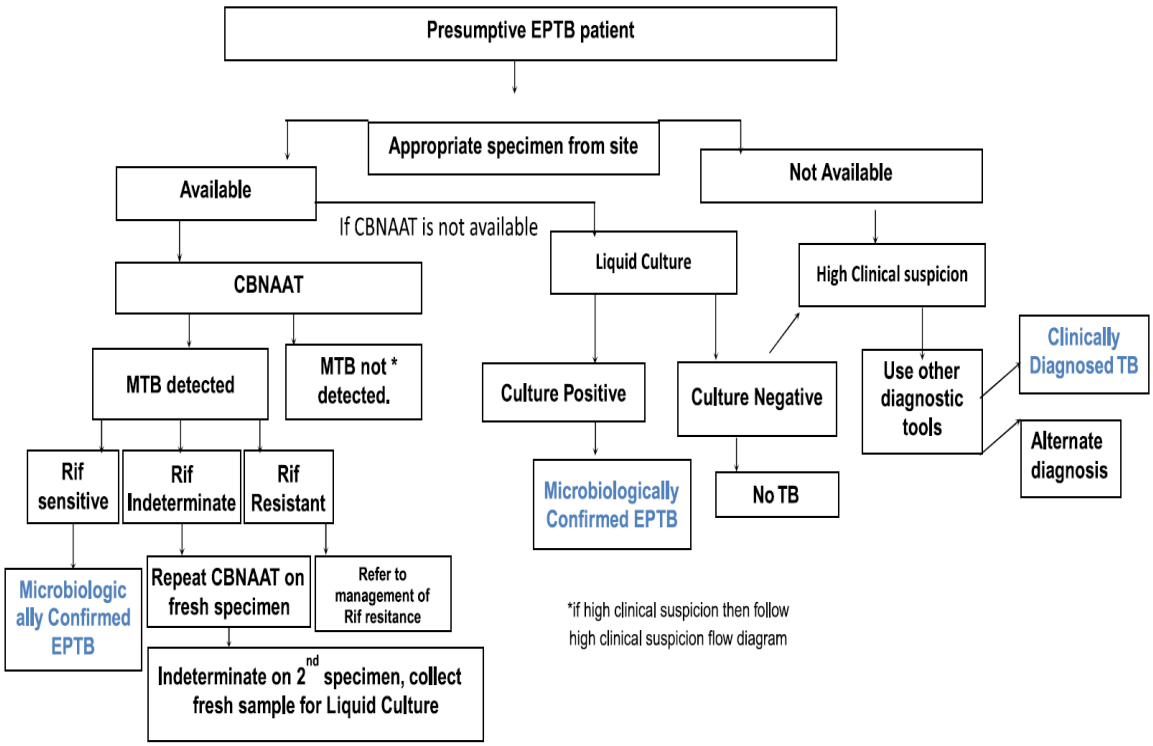
- ***Culture& DST:***
    - Liquid culture
    - Solid(Lowenstein Jensen) media
    - Automated Liquid Culture System e.g. BACTEC MGIT 960, BacTAlert, Versatrek etc.

- ***Rapid Molecular diagnostic testing:***
    - Line Probe Assay for M.TB complex and detection of Rif and INH resistance
    - Nucleic Acid Amplification testing (NAAT) Xpert MTB/RIF testing using GeneXpert System (CBNAAT)

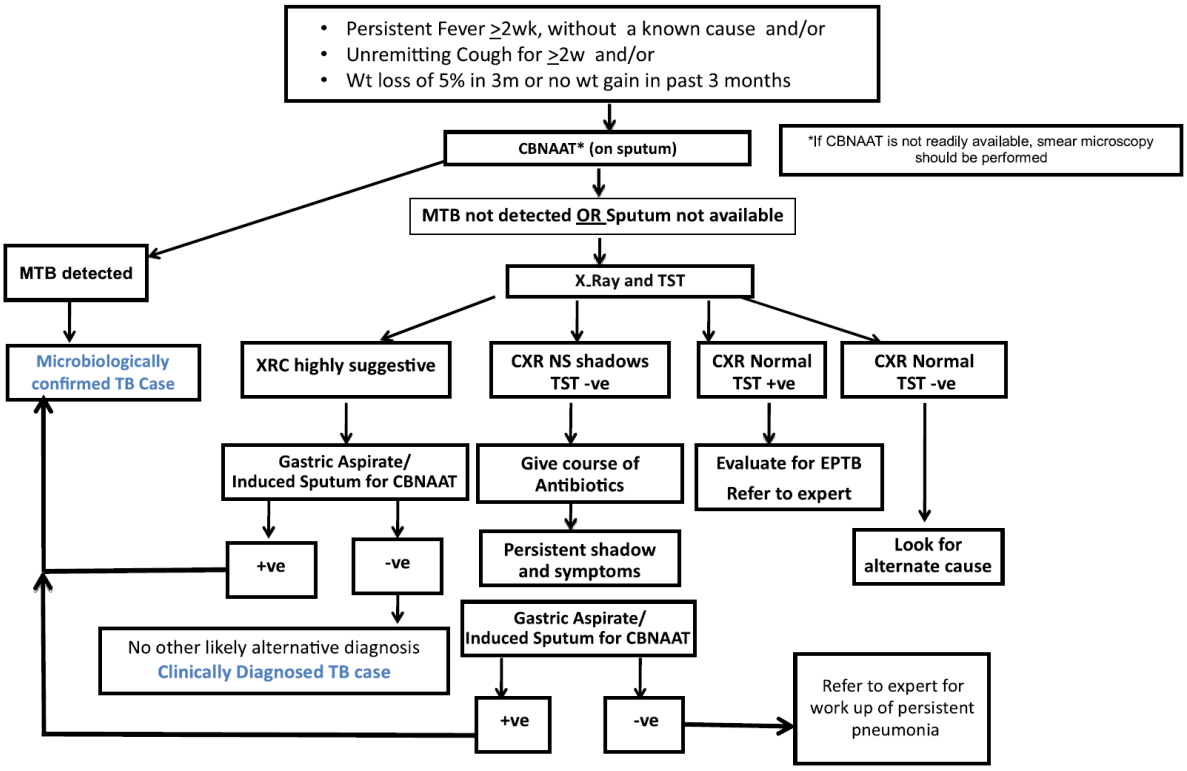
Diagnostic algorithms:



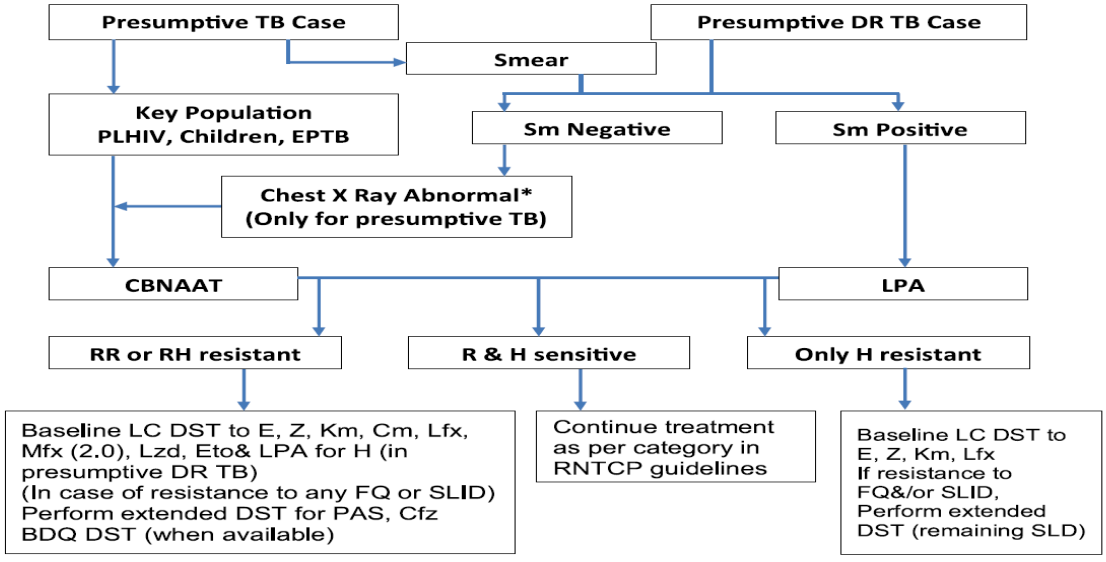
Diagnostic Algorithm for Extra Pulmonary TB



Diagnostic algorithm for Pediatric Pulmonary TB



Diagnostic Algorithm for Bedaquiline containing and optimized treatment regimen



- If RR by CBNAAT, in addition to other drugs, H resistance (by LPA) to be done and treatment modified accordingly.
- For samples reported by LPA – report must mention H- resistance by Kat G or INH A mutation.
- For new patients (those who do not fit in the definition of presumptive DR-TB case diagnosed as TB with RR by CBNAAT – a second CBNAAT test will be offered along with liquid culture DST

** Those who do not fit in the definition of presumptive DR-TB case*

Treatment regimens:

Treatment regimen for MDR/RR-TB cases without additional resistance

These patients are to be treated with standard treatment regimen for MDR-TB that contains 6 to 9 months of IP with Kanamycin, Levofloxacin, Ethambutol, Pyrazinamide, Ethionamide and Cycloserine and 18 months of CP with Levofloxacin, Ethambutol, Ethionamide and Cycloserine.

Type of TB Case	Treatment regimen in IP	Treatment regimen CP
Rifampicin resistant + Isoniazid sensitive or unknown	(6-9) Km Lfx Eto Cs Z E H	(18) Lfx Eto Cs E H
MDR TB	(6-9) Km Lfx Eto Cs Z E *(Modify treatment based on the level of INH resistance as per the footnote)*	(18) Lfx Eto Cs E

- *All MDR TB isolates would be subjected to LC DST at baseline for Kanamycin and Levofloxacin.*
- *The results would be received after 6-8 weeks.*
- *Appropriate medications of the treatment regimens can be done in the presence of additional resistance.*

Treatment regimen for XDR TB

- XDR TB cases will be treated with the STR for XDR TB comprising of Injection Capreomycin, Moxifloxacin, Linezolid, PAS, Clofazimine High Dose INH & Co-Amoxyclav.
- The duration of IP will be for 6-12 months.
- Only the injectables will be stopped in CP and the remaining medicines will continue for another 18 months in CP.
- All DR TB treatment regimens are to be given on daily basis under supervision.

Type of TB Case	Treatment regimen in IP	Treatment regimen CP
XDR	(6-12) Cm, PAS, Mfx, High dose-H, Cfz, Lzd, Amx/Clv	(18) PAS, Mfx, High dose-H, Cfz, Lzd, Amx/Clv

- *Whenever DST pattern of extended panel of drugs would be available to guide the treatment like at six sites where Bedaquiline is introduced initially.*
- *The management protocol will follow essentially optimized regimen in case patients are diagnosed with drug resistance other than or in addition to MDR and XDR.*

Treatment regimen for Mono/Poly DR TB

- **Mono Drug Resistant TB-** The treatment regimen is consisting of Injectable SLD + FQ + Rifampicin + two out of the first line drugs (from H,E & Z) to which the patient is sensitive to make a total of 5 effective drugs regimen given daily.
- In case of **reported baseline additional resistance to other FLDs**, the regimen is Inj SLD + FQ + Rifampicin + any FLD to which patient is sensitive + one of the remaining Group 4 drugs (Ethionamide, Cycloserine, and PAS).
- In addition High Dose INH is added to the regimen if LPA shows inhA mutation or culture reports show low level INH resistance
- The total duration of treatment will be 9 to 12 months. The Intensive Phase (IP) is for 3 months with scope for extension to a maximum of 6 months.
- The Continuation phase (CP) is for a fixed duration of 6 months.
- The patient is initiated on treatment at DR-TB Centre, and then sent back for ambulatory treatment to the DTO for continuation of treatment regimen and regular follow-up.

Type of TB Case	Treatment regimen in IP	Treatment regimen CP
Rifampicin Sensitive, INH Resistant TB & DST of SEZ not known	(3-6) Km, Lfx R E Z *(Modify treatment based on baseline DST report to E, Z, KM, CM, Lfx, Mfx)*	(6) Lfx R E Z

Introduction of newer anti-TB drug -

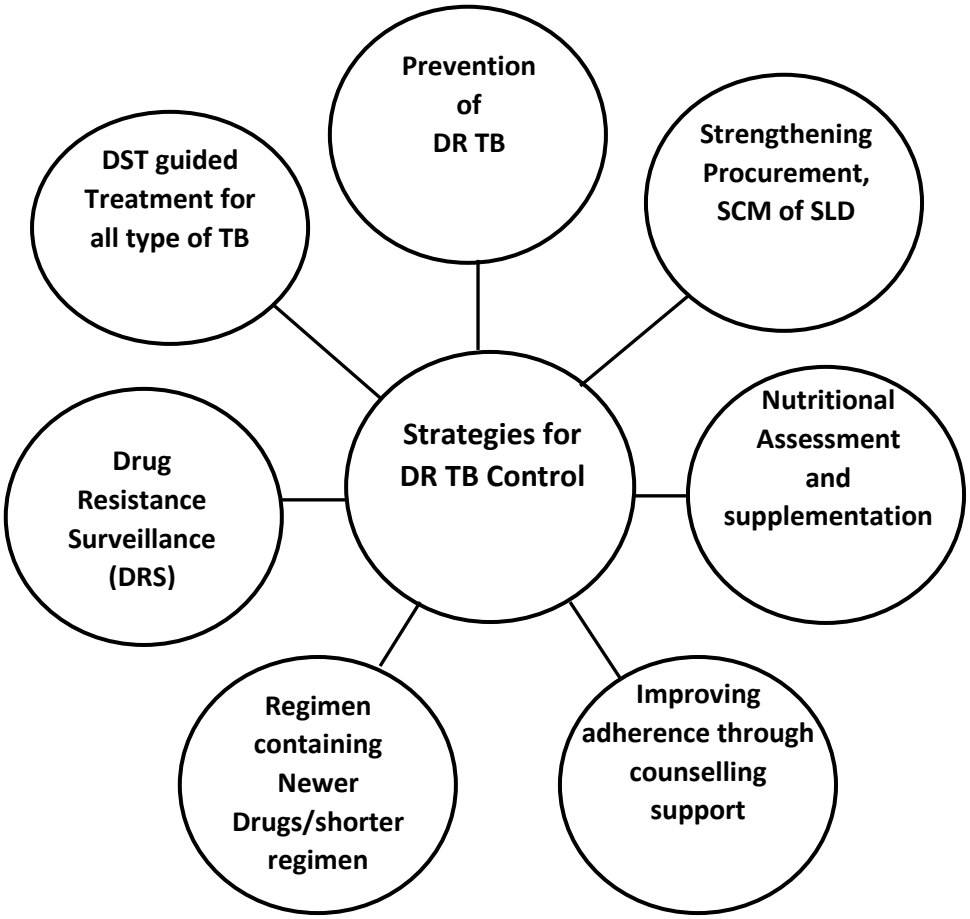
Bedaquiline

After 40 years, the new drug Bedaquiline has been introduced at six sites in 5 states in the country in March, 2016. The drug is currently being used under RNTCP for MDR/RR-TB patients with resistance to fluoroquinolone and or second line injectable, mixed pattern of drug resistance. The Bedaquiline is used along with optimum background regimen designed based on drug susceptibility testing. Being a new drug, a national level committee is monitoring its safety as per the global guidelines on use of Bedaquiline.

Delamanid

Delamanid belong to the nitroimidazole class of antibiotics, they inhibit the synthesis of mycolic acids, which are components of the cell envelope of *M. tuberculosis*. RNTCP is in the process of including this drug under PMDT services of RNTCP.

Strategies for Drug Resistance TB Control:



Conclusions:

There are many challenges for TB control in India. Prompt, accurate diagnosis and effective treatment of TB are not only essential for good patient care, but they are also the key elements in the public health response to tuberculosis and the cornerstone of any initiative for tuberculosis control. The private sector holds a factual predominance of health care service delivery in India. There is very little information about the TB patient from the private sector available to the programme and little is known about their quality of treatment, including treatment outcomes.

The vision of India's national TB control programme is that the people suffering from TB receive the highest standards of care and support from healthcare providers of their choice. The programme has now adopted WHO's "**The End TB Strategy**" under **National Strategic Plan** towards Ending TB in India by adopting the following pillars:

1. Integrated, patient – centred care and prevention.
   - *Precision in TB diagnosis and treatment*
   - *Precision in TB preventive therapy*
   - *TB digital health application for monitoring and evaluation*

- *ICT to support patients*

2. Bold policies and supportive system
3. Intensified research and innovation

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