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- Evidence-based medicine - What does it mean to the average practitioner?
- Congenital scoliosis: What is new in the present decade?
- Prevalence of various fungal infections among HIV/AIDS patients
- Assessment of radiation exposure: An in-depth analysis of dose evaluation in contrast-enhanced computed tomography abdomen imaging
- NAMS task force report on breast cancer in India
- NAMS task force report on antimicrobial resistance

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Annals of the National Academy of Medical Sciences (India)

Editorial

Evidence-based medicine - What does it mean to the average practitioner?

Anil K Jain[1], Pragya Jain[2], Mohit Bhandari[3]

[1]Editor-in-chief, Annals of the National Academy of Medical Sciences (India); Ex-Principal and Director Professor & Head, Department of Orthopaedic, University College of Medical Sciences; Ex-Dean, Faculty of Medical Sciences, University of Delhi, [2]Associate Professor of Pathology, University College of Medical Sciences, New Delhi, [3]Department of Surgery, McMaster University, Chair of Surgery, Senior Tier Canada Research Chair in Surgery, Hamilton, Ontario, Canada; Editor-in-Chief, The Journal of Bone & Joint Surgery (Am) US.

The practice of medicine is an artistic application of science (knowledge). More and more knowledge based on scientific research reduces the guesswork and results in good treatment outcomes.[1,2] Medicine has evolved from a teacher-disciple lineage (observation transfer) to scientific and validated evidence based transfer of information.

The evolution of human beings from quadrupedal to the present stage suggests that biology is not stationary and continues to evolve. Medical science, being a biological science, has also evolved and will continue to evolve. The evolution in medicine has led to improvement in life expectancy. The life expectancy was 25 years in 1 AD (Roman Empire) to 40-45 years in Europe, the US, and Japan in 1900 AD. Around 2000 AD, the life expectancy was 80 years or more in Japan and the West. Even in India, the life expectancy has risen to around 70 years from 40 years at independence. Diseases like smallpox and polio have been eliminated. The outcomes of serious clinical problems like fracture, coronary heart diseases, oncology, tuberculosis, and many more have improved. Through medical research the life expectancy has improved, the death rate has declined, and all health indices have improved. Due to better diagnostics, treatment outcomes have improved. India is a country of contrast; we have amongst us, the wealthiest and the poorest people. There are *sheesh-mahal* mansions to slums. Even in the health sector, the best treatment facilities are available to 20% population, while a significant population is unable to access basic health facilities. As a result, India continues to see the natural history of disease, and we see the living biology. The clinicians are confronted by the most daunting to the most simple clinical problems.

HOW IS EVIDENCE GENERATED?

Science grows when a clinician is confronted with a clinical problem. The cause of the clinical problem is identified, and treatment strategies are executed. The outcome appraisal based on scientific criteria to differentiate whether the outcome is actual or a chance occurance gives us evidence. Definitive evidence is the result of a longitudinal collection of similar evidence with longer follow-ups. Practices in medicine can be categorized as good or not good on the basis of evaluation based on accepted scientific criteria.

EVIDENCE-BASED MEDICINE

Evidence-based medicine (EBM) is a term coined in 1990 by Gorden Gyuatt from Canada, and it was described as "an attitude of enlightened skepticism towards the application of diagnostic, therapeutic, and prognostic technologies".

The definition is simplified in the present time as "The conscientious use of current best evidence from clinical care research in making health care decisions". In other words, it is the integration of clinical expertise and patient value (suitability in a given patient/infrastructure) with the best available research evidence.[3]

SKILLS NEEDED TO PRACTICE EBM

The skills required to practice EBM include: (a) defining a research question-based on a given clinical problem; (b) Retrieval of best research evidence from vast pool of medical literatures; (c) Appraisal of the retrieved evidence for its

***Corresponding author:** Dr. Anil K Jain, MS, MAMS, FAMS, FIOA, FRCS (Eng.) profakjain@gmail.com

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robustness; (d) Deciding the applicability of the best available research evidence in a given patient (clinical expertise).

i) ***Defining the research question***

This step is the key to facilitate the retrieval of the best research evidence. While defining the research question, one has to describe a population and the intervention intended to be undertaken. It needs to be compared with another common option of management with well-defined outcome measures and a defined follow-up. Hence, PICO (Population (P), intervention (I), comparison (O), and outcome O) is the key to frame a research question. For example, in the case of a displaced fracture neck or femur in the elderly, the two treatment options available are internal fixation of fracture and replacement arthroplasty (hemiarthroplasty or total hip replacement). The reoperation rate at one year is taken as an outcome measure. So research question could be "effect of arthroplasty and internal fixation on one year reoperation rate at one year follow-up."

ii) ***Retrieval of research evidence***

The research evidence is to be collected for the research question framed. We have required to retrieve the best research evidence on a given research question. It must be ensured that the retrieved literature is comprehensive and not selective, where few articles have been retrieved from general search engines, such as Google. The proper keywords (MESH terms) should be used, and literature should be searched on PubMed, Cochrane Library, and other well-established search engines.

iii) ***Appraise the evidence***

The retrieved evidence is to be appraised for robustness of the studies and quality of evidence. Randomized control trials (RCTs) or Meta-analysis of RCTs are labelled as level 1 evidence, while Prospective Cohort Studies are level 2, Case Control Studies are level 3, and Retrospective Case Series are level 4. Individual opinion is described as the lowest level, 5. Level-1 studies have less bias while Level-5 evidence has the most bias. We also need to practice how to analyze these studies for their robustness. Bhandari and his team have published very simple checklists for randomized trials,[4] metanalysis,[5] prospective cohort study,[6] case series,[7] and diagnostic tests.[8]

Poorly conducted RCTs (Level-1) are inferior to well-conducted Cohort studies or level 4 retrospective studies. Robust RCT should have valid results. The interventionist should be well-trained in performing both types of interventions. It is important to know how subjects were randomized. Some questions to be asked are: Was the randomization concealed? Were they aware of allocation? Were the outcome assessors aware of allocation? Were the subjects analyzed? Were they initially randomized into enrolment? Was the follow-up completed? and How were the trial results measured? Similar criteria have been described for other types of studies. The clinician has to be confident about the quality of evidence to provide the expected outcome, only then it can be applied to a given patient.

iv) ***Patient value (applicability of evidence on a given patient)***

On retrieval of literature, we may get variable evidence. While making a decision on a patient, we need to assess the patient's expectations, available infrastructure, and the expertise of a surgeon/clinician to achieve the best treatment outcome. This is the clinical expertise of the clinician to use evidence for the best clinical outcome.

Above denotes that the evidence cycle starts with a patient where a question is asked about clinical problem, literature is acquired, and appraised. After assessing the patient's requirement and the feasibility of its applicability in a given circumstance, the treatment option is based on the best available evidence.

MYTHS AND BARRIERS TO IMPLEMENT EBM

Though EBM is almost 35 years old, some myths/false notions surround its universal acceptance. Some of the common myths and barriers to its implementations are:

1) High-quality evidence based on basic science and surrogate outcomes are used to practice EBM.
2) EBM is a method to suggest cookbook, overtly dogmatic, inflexible, and one-size-fits-all treatment options, and there is no place for clinical expertise.
3) EBM is only research evidence, only RCT or just percent, P value and other statistic tests.
4) EBM can be based on any evidence available.

These myths have no basis. To practice EBM, studies on patient-oriented factors, such as morbidity, mortality, and quality of life, are used to make a clinical decision. The disease-oriented evidence, such as physiologic variables and blood tests, are not used for clinical decisions. The EBM practice provides an opportunity to tailor best research evidence to a patient based on clinical judgement by a capable physician and not a cookbook option of treatment. EBM practice is based on the best available evidence that requires evaluation of all available evidence and grading its quality and its applicability in a given patient and not any evidence

Barriers to practice EBM

The most common barrier is the availability of too many articles on the digital platform. It is to be understood that data available on the internet may not be authentic and instead may be industry-driven. We have to learn how to identify the best quality evidence. We have to practice how not only to retrieve but also to appraise the best available evidence.

Another common barrier to implementing EBM is a lack of adequate outcome effectiveness studies, particularly in developing/resource-crunch countries. In India, we face a vast variety of clinical challenges and see complex clinical conditions to be treated in variable infrastructures and with variable expertise. For many clinical problems, we do not have research-based evidence generated from the West, and not too many Indian researchers are publishing research. **Unless we create evidence on clinical conditions unique to our country, we will not have the best available evidence. We have to publish to generate evidence of clinical conditions unique to us**. It is important that we publish our data. In certain clinical situations where we do not have robust data, we need to use guidelines developed by government agencies or WHO.

We should continue to be updated about literature and be prepared to change the practice as evidence changes. One such platform is OrthoEvidence, for example, bringing best evidence summaries in surgery to help surgeons and clinicians stay up to date. There are similar platforms in medicine.[9]

To conclude, evidence-based medicine allows us an opportunity to rationalize the best treatment option to a patient by integrating the best available research evidence.

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Annals of the National Academy of Medical Sciences (India)

Review Article

Congenital scoliosis: What is new in the present decade?

Athanasios I Tsirikos[1]

[1]Consultant Orthopaedic and Spine Surgeon and Honorary Clinical Senior Lecturer, University of Edinburgh/Royal Hospital for Children and Young People, Edinburgh, United Kingdom

ABSTRACT

Congenital anomalies of the spine occur due to faults in the embryological development of the immature vertebrae as an isolated defect or in association with a systemic condition. The result of the presence of these abnormalities is an asymmetrical growth affecting the longitudinal development of the spine and often producing an aggressive deformity involving the coronal and/or the sagittal planes. Recognition of the anatomical nature of the vertebral anomalies, their location along the spine and relationship to adjacent levels can predict the risk of deformity development and curve deterioration. Treatment is recommended at an early stage for those vertebral defects that are likely to produce a progressive deformity. The key to successful treatment in congenital spinal deformity is to diagnose in a timely manner those patients who are at risk to develop a severe deformity and apply early, prophylactic surgical treatment when the associated risks of major complications are more limited.

Key words: Congenital kyphosis, Congenital scoliosis, Growing rods, Hemivertebra resection, Surgical treatment, Vertical expandable prosthetic titanium rib, Vertebral anomaly

INTRODUCTION

The aim of this review article is to provide an update and present essential guidelines that can be helpful for clinicians treating patients with congenital spinal deformities.

Embryology: Congenital scoliosis can develop due to a range of congenital vertebral abnormalities that produce an imbalance in the longitudinal growth of the immature spine.[1-3] The congenital anomalies impacting on the development of the vertebral column can affect one or multiple levels and carry a varying prognosis. These congenital defects occur during the first 6-8 weeks of embryologic growth and are caused by disruption of the notochord and somites that are responsible for the development of skeletal muscles, dorsal dermis, tendon, ligaments but also play a role in the respiratory, cardiac and genito-urinary system formation. It should, therefore, be appreciated that a multidisciplinary assessment of a patient with congenital vertebral abnormalities is required in order to identify medical co-morbidities beyond the development of the spinal column.

Classification: Having a classification system for congenital spinal deformities can determine the prognosis of the pathological curvature on the basis of the type, number and location of congenital vertebral anomalies, as well as their relation to the adjacent levels of the spine and the presence of contralateral spinal growth that acts as the deforming force that precipitates the deformity. The classification of vertebral abnormalities into failures of formation, failures of segmentation and mixed anomalies provides a useful tool to define the natural history and risk of progression of the curve and communicate treatment outcomes.[4,5]

Assessment: The use of prenatal ultrasound or magnetic tomography imaging (MRI) can allow early diagnosis of congenital vertebral anomalies and timely referral to specialist services. Post-natal assessment involves plain radiographs, computer tomography scans with 3D reconstruction to define the nature of bony defects affecting the vertebral bodies and posterior arches, and MRI to evaluate for intraspinal anomalies.[6,7] The spinal MRI can provide imaging of the kidneys and if any abnormality is identified a renal ultrasound is recommended. A cardiac evaluation including echocardiogram and cardiac ultrasound can be organised to exclude congenital heart disease. In the presence of congenital rib fusions or complex rib abnormalities a respiratory review is advised.[8] A genetic review should also be done to rule out an

***Corresponding author:** Dr. Athanasios I Tsirikos, MD FRCS PhD, Consultant Orthopaedic and Spine Surgeon and Honorary Clinical Senior Lecturer, University of Edinburgh/Royal Hospital for Children and Young People, Edinburgh, United Kingdom. atsirikos@hotmail.com

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underlying syndromic condition such as VATER, VACTERL, Goldenhar, spondylocostal/spondylothoracic dysplasia, Alagille.[9] In the presence of a congenital vertebral anomaly that is likely to produce a progressive deformity these tests should be performed at the time of index review so that there is no delay if surgical treatment is indicated.[10]

Prognosis: A fully **segmented hemivertebra** (most common failure of vertebral formation) is likely to produce a progressive scoliosis, kyphosis or kyphoscoliosis and require surgical treatment. The presence of 2 ipsilateral hemivertebrae produces a more progressive scoliosis and need prophylactic treatment. Two contralateral hemivertabrae (hemimetameric shift), especially those affecting transitional areas such as the thoracolumbar or lumbosacral spine create an unbalanced deformity and necessitate surgery. A semi-segmented hemivertebra produces a slowly progressive scoliosis and treatment may not be required for small curves unless these affect the lumbosacral junction. Lumbosacral hemivertebrae (fully or semi-segmented) create an oblique take-off of the spine and a structural compensatory curve in the lumbar spine that often progresses more than the congenital scoliosis. Early surgical treatment is commonly required to balance the congenitally abnormal spine before a compensatory curve develops.

A **posterior hemivertebra** or a posterolateral quadrant vertebra causing a congenital kyphosis or kyphoscoliosis carries an increased risk of spinal cord compression as the hemivertebra can grow towards the spinal canal producing neurological damage.[4,5] When radiographic imaging is organised during clinical follow-up it is, therefore, critical to include a lateral erect scoliosis view in order to assess for the presence or progression of congenital kyphosis as in this case surgical treatment should be offered before neurological symptoms develop. Congenital kyphosis due to a failure of formation can produce a displaced spinal canal. This occurs as a step-off deformity at the level of a subluxed or dislocated vertebral segment due to the hypoplastic vertebra. This type of deformity is progressive with the spine being highly unstable in the sagittal and axial planes resulting in greater risk of neural damage.

A **unilateral unsegmented bar** (most common failure of vertebral segmentation) produces a rapidly progressive scoliosis due to its tethering effect that impacts on the longitudinal spinal growth in the presence of normal contralateral end plates. The combination of a unilateral unsegmented bar with contralateral hemivertebra (most common mixed anomaly) at the same level carry the worst prognosis in regard to curve deterioration as the tethering impact of the bar is enhanced by accelerated growth in the presence of one or more hemivertebrae on the opposite side. Similarly, rapid curve progression is expected in the presence of an anterolateral unsegmented bar with or without contralateral hemivertebra producing a kyphoscoliosis.

Mixed congenital vertebral anomalies can affect large segments or different areas of the spine combining failures of formation and segmentation. Advances in imaging techniques allow better definition of the anatomy of these vertebral defects which can be very difficult to categorise. There is commonly an association with rib and chest wall abnormalities producing tethering of both the spinal and thoracic growth.

An **unsegmented or incarcerated hemivertebra** or a block vertebra carry very limited or no growth potential and do not create a deformity. An anterior unsegmented bar produces a congenital kyphosis with slow progression that often requires no treatment.

Conservative treatment: Observation is recommended in patients with non-progressive deformities in 6-12 month intervals depending on the stage of skeletal development. Children in their first 3 years of life and teenagers who are in their adolescent growth spurt are at maximum risk of curve deterioration and need to be monitored closely.

Bracing or casting is not effective to control congenital curves or impact on their long-term prognosis as these are usually rigid in the presence of vertebral abnormalities.[11] These treatment modalities are useful to prevent progression of structural compensatory scoliotic curves that develop at the levels proximal or distal to the congenital vertebral defects in an attempt to achieve global coronal spinal balance. Brace treatment can occasionally be used in patients with hemivertebra after resection and segmental fusion or in those with a unilateral bar after a convex fusion when the apical deformity has been controlled if the residual scoliosis extends to longer segments above and below the congenital anomaly.

Surgical treatment: Spinal surgery is indicated in the presence of a progressive deformity. Timing of surgery is of outmost importance and age of the patient is not necessarily a restrictive factor if the deformity is rapidly deteriorating. Prophylactic surgical treatment is recommended when dealing with a type of congenital vertebral abnormality which is expected to produce a highly progressive curve such as when a unilateral or anterolateral unsegmented bar with or without contralateral hemivertebra or a posterior/posterolateral hemivertebra exists. The location of congenital scoliosis in transitional areas of the spine can produce severe spinal imbalance and a deteriorating deformity necessitating early surgery.

Posterior in situ fusion is indicated in the presence of mixed congenital anomalies affecting transitional areas of the spine such as the cervico-thoracic and upper thoracic region and producing a mild scoliosis. This can stabilise the spine across the area of the vertebral defects and prevent progression of the congenital curve, as well as the development of a structural compensatory scoliosis at the levels below. A localised posterior fusion can also be performed when addressing a congenital kyphosis due to a posterior hemivertebra. In this case, the kyphosis should ideally be up to 50o and the child less than 5 years of age.[10] In the presence of residual anterior vertebral growth the posterior bony tether can allow for progressive gradual improvement of the kyphosis occurring with subsequent spinal growth. There should be a low threshold to consider a re-grafting procedure in order to address a non-union or reinforce the posterior fusion mass.

Anterior convex in situ fusion can be performed with the use of an autologous rib strut graft with the aim to stabilise the spine in the presence of a unilateral unsegmented bar. This will convert the congenitally abnormal area in a block segment that will stop deformity progression.

Anterior convex hemiepiphysiodesis (growth arrest procedure) is recommended in young children in the presence of a fully segmented hemivertebra involving the thoracic spine where hemivertebra resection can be associated with increased risks.[12] This should extend to include one level proximal and distal to the congenital anomaly. By preserving anterior concave vertebral growth gradual improvement of the scoliosis is expected to occur over time.

Posterior hemivertebra resection is the treatment of choice when addressing a deteriorating congenital deformity due to the presence of a lateral, posterior or posterolateral hemivertebra.[13,14] This involves complete excision of the hemivertebra (including the posterior elements at the affected level), contralateral disc, as well as the discs and adjacent end plates at the levels cephalad and caudal to the hemivertebra. The benefit of this procedure is that it removes completely the deforming force and can achieve rebalancing of the spine that is usually sustained over skeletal growth with no need for further surgery.

Instrumented posterior spinal correction and fusion can be done in patients who present at an older age with long-standing congenital deformities of any anatomical aetiology and normal neurology. The aim is to balance the spine by using adjacent level spinal flexibility above and below the level of the congenital vertebral abnormality. If the congenital deformity is more severe and rigid the addition of an anterior spinal release can improve the ability to correct the curve; this can also control the risk of crankshaft effect that can occur due to remaining anterior vertebral growth in young patients.

Complex spinal reconstruction *with the use of spinal osteotomies or vertebral column resection* may be required when dealing with severe neglected congenital curves that cause significant spinal decompensation often associated with neurological damage. These techniques will also be needed during revision surgery in the presence of an established fusion mass in order to treat residual or recurrent deformities. The risk of neurological and life-threatening (related to intraoperative blood loss) complications of such procedures is considerable and cannot be underestimated during decision making. The neurological risk is related to segmental mechanical instability produced at the level of vertebral column resection and resulting in spinal cord injury. Neural injury can also occur due to disruption of the vascular supply to the spinal cord at the level of the osteotomy/vertebrectomy.

Growth preserving techniques can be used in isolation in the treatment of congenital scoliosis or alongside the previously described techniques. The aim is to control the deformity at a young age and preserve spinal growth which corresponds to chest development. Good indications for using growing rods in the context of congenital scoliosis is as an adjunct to anterior convex fusion in patients with a unilateral bar (with or without contralateral hemivertebra) or anterior convex epiphysiodesis in patients with a fully segmented hemivertebra. In these cases, the growing rod can control residual adjacent level scoliosis at the levels above and below the congenital abnormality and guide spinal growth during skeletal development which can further improve the remaining deformity. The development of the magnetically controlled growing rods that can limit the number of repeat surgeries has made this technique more attractive but the currently available results have not met the initial high expectations. In addition, growing rod techniques either traditional or magnetically lengthened have a number of inherent complications which can be technical related to implant failure, associated with infection, reduced ability to lengthen the construct over time (so called 'law of diminishing returns'), as well as the development of crankshaft effect or proximal junctional kyphosis.

The vertical expandable prosthetic titamium rib was originally developed as a rib-to-rib construct to address thoracic insufficiency in young children with severe congenital scoliosis and rib fusions.[15] A rib-to-spine construct was subsequently used as an alternative to traditional growing rods as primary treatment of congenital scoliosis with controversial results and limited acceptance.

Hybrid growth preservation techniques have been introduced in the last few years as part of clinical trials. These are based on a combined concept of concave distraction using a growing rod or the spring system and convex growth guidance.[16,17] Even though the initial results are very promising more data is required to allow wider use of these techniques.

CONCLUSION

Successful treatment of congenital spinal deformity requires an early diagnosis and understanding of the nature of congenital abnormalities that carry increased risk to produce a progressive deformity. Surgical treatment depends on factors that include patient's age, remaining spinal growth, type and site of vertebral anomaly, type and size of curvature, as well as the development or impending risk of spinal cord compression. Anticipating deformity progression will allow selecting the correct procedure and applying it at the appropriate time. It is not possible to create vertebral growth where this does not exist. However, early surgery can balance spinal growth and prevent the development of a severe deformity and spinal cord compression which then require much more complex surgery associated with increased risks for major morbidity and potential mortality.

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Original Article

Prevalence of various fungal infections among HIV/AIDS patients

Nirmala Kumari[1], Shalini Malhotra[1], Ankit Kumar Chauhan[1], Neha Chauhan[1], Nirmaljit Kaur Bhatia[1]

[1]Department of Microbiology, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi, India

ABSTRACT

Objectives: Human immunodeficiency virus (HIV)-associated opportunistic fungal infections (OFI) are a major cause of mortality and morbidity in HIV-seropositive patients. This prospective study aimed to isolate various fungal pathogens from HIV seropositive patients and to identify and characterize these fungal pathogens at the species level in India.

Material and Methods: Based on clinical signs and symptoms, various clinical specimens (n=323) were collected from (n=200) HIV-seropositive patients in the adult age group of either sex and underwent direct microscopy and fungal culture. Fungal isolates were identified and specified according to a standard protocol. Statistical analysis: All data were collected and analyzed using Microsoft Excel.

Results: Out of 323 samples from 200 HIV-seropositive patients with a suspected fungal infection, fungal isolates were found in 89 cases, or 27.56% of cases. The most frequently isolated fungal organism was *Candida* species (75.28%), followed by *Cryptococcus neoformans* (17.97%), *Aspergillus* species (4.48%), *Alterneria* species (1.12%), and *Trichophyton* mentagrophyte (1.12%). Amongst 67 *Candida* species, *Candida albicans* had the highest isolation rate (88.05%), followed by *Candida tropicalis* (5.97%), *Candida parasilosis* (2.98%), and *Candida auris* (2.98%).

Conclusion: Oropharyngeal candidiasis followed by cryptococcal meningitis was the most common OFI among other fungal infections. This study would help clinicians in the proper diagnosis and early treatment of these infections to prevent their devastating effects in developing countries like India.

Keywords: *Aspergillus*, *Candida*, Cryptococcus, Opportunistic infections

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is an immune system disorder that affects humans, leading to a loss of CD4 cells below 200 cells/mm^3 and a decrease in immunity.[1,2]

In 2016, one million people died from AIDS-related diseases globally.[3] According to the United Nations Programme on HIV/AIDS (UNAIDS), an estimated 38 million people were living with human immunodeficiency virus (HIV) infection worldwide in 2019. It has been observed that opportunistic infections, particularly fungal infections, are the leading cause of morbidity and mortality in HIV-infected patients due to the progressive decline in CD4+ T cells.[4]

With an estimated 2.6 million HIV-infected individuals, India has the third-largest population of HIV-positive patients in the world.[2] Opportunistic infections in people with late-stage HIV infection are primarily caused by fungi.[3,4] A rapid decline in peripheral blood CD4+T cells is a key mechanism associated with the occurrence and progression of opportunistic fungal infections (OFI) in HIV seropositive patients.[5-7] Opportunistic respiratory infections are major causes of morbidity and mortality in HIV patients, and pulmonary involvement is the first manifestation in approximately 65% of cases.[8]

The spectrum of fungal infections ranges from asymptomatic mucosal candidiasis to disseminated infections, fungal pneumonia, and meningitis.[6] Fungal infections by *Candida albicans, Cryptococcus neoformans, and Aspergillus fumigatus* are the most prevalent mycoses in immunocompromised individuals.[5] Systemic infections include *Pneumocystis jirovecii* (pneumocystosis), *Cryptococcus neoformans* (cryptococcosis), *Histoplasma capsulatum* (histoplasmosis), and *Talaromyces*, previously known as *Penicillium marneffei* (talaromycosis).[1] The purpose of the present study was to characterize the various fungal pathogens found in HIV-positive patients and their susceptibility to different antifungal drugs.

***Corresponding author:** Dr. Shalini Malhotra, Department of Microbiology, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, Delhi, India. drshalinimalhotra@yahoo.com

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MATERIAL AND METHODS

Study population and design

This cross-sectional observational study was carried out from November 01, 2019, to March 31, 2021, after obtaining approval and ethical clearance from the Institutional Ethics Committee (No. TP (MD/MS) 34/2019/IEC/ABVIMS/RMLH 698/19). According to various studies, the isolation rate of fungal infections in HIV-positive patients was 41.1%. Based on this figure, a minimum sample size of 166 samples was determined for analysis, allowing a 7.5% margin of error and a 5% significance level. The calculation was performed using the formula,

$$N \geq (p\ (1\text{-}p)\ /(ME/Z_{\alpha})^2$$

Where Z_{α} = Value of Z at two-sided alpha error of 5%

ME = Margin of error

P = Isolation rate

Two hundred HIV seropositive patients in the adult age group (>18 years) of either sex, with suspected fungal infection, were enrolled in the study. The CD4 cell count was conducted at the Integrated counseling and testing center using the flow cytometry method. A total of 323 different clinical specimens were received from these 200 HIV seropositive patients who exhibited relevant clinical signs and symptoms while attending the antiretroviral therapy (ART) clinic or being admitted to the department of medicine.

Isolation and identification of fungal isolates

Oral and throat swabs were obtained by swabbing the oropharyngeal mucosa. cerebrospinal fluid (CSF), sputum, urine, and blood samples were collected according to the protocol and placed directly into sterile containers. Strict confidentiality was maintained throughout the study. A standard procedure was followed to process the samples.

Microscopy

Depending on the type of specimen and the suspected fungal infection, all samples were examined directly under a microscope using Gram stains, potassium hydroxide preparations/Wet preparations, and India ink preparations.

Fungal culture

Fungal cultures were grown on sabouraud dextrose agar (SDA) (with and without antibiotics) and blood agar as appropriate. Chloramphenicol (50 mg/L), cycloheximide (500 mg/L) (Hi-media), and gentamicin (40 mg/L) were added to prepare SDA with antibiotics. Samples were streaked in duplicate on slants, incubated at 25°C and 37°C, and examined for growth after 48 hours, then weekly for up to 6 weeks until being discarded as negative. Specimens inoculated onto blood agar were incubated for 24–48 hours.[5] Cream-colored, smooth pasty colonies grown on SDA slant or blood agar were Gram-stained and processed further for the identification of yeast. Molds were identified based on morphological appearances and microscopic features under lactophenol cotton blue stain and Riddles Slide culture in accordance with standard procedures.[9] Yeast isolates were identified and classified based on germ tube formation, Calcofluor White Staining, morphology on corn meal agar with Tween 80 (Hi-Media), Hi-Crome *Candida* agar (Hi-Media), and automated VITEK 2 compact system (BioMerieux) according to standard protocol.[9,10]

RESULTS

Among the 200 HIV-positive individuals, 144 (72%) were predominantly male. Most patients, 105 (52.50%), were between the ages of 30 and 45 years, with 59 (29.50%) under 30 years [Table 1].

Among the 200 HIV-seropositive patients, weight loss (50.56%) was the most prevalent clinical symptom, followed by oral ulceration (46.06%), fever (37.07%), and cough (29.21%) [Figure 1].

A total of 323 specimens were received from 200 HIV seropositive patients with suspected fungal infections. Among these, 89 specimens (27.56%) tested positive for various fungal infections.

The CD4 levels of the patients in this study ranged from 5 to 927 cells/mm^3. The mean CD4 cell count among the 200 patients with suspected fungal infection was 221.20 cells/mm^3. Specifically, 18% showed a count of less than 50, 35.5% had counts between 50 and 199, 36.5% had counts between 200 and 500, and 10% had a CD4 cell count above 500 cells/mm^3. In the 89 confirmed fungal-positive patients, the mean CD4 cell count was 140.8, with 24.71% having a count of less than 50, 48.31% between 50 and 199, 23.59% between 200 and 500, and only 3.37% of having a count above 500 cells/mm^3.

Table 1: Age-wise distribution of HIV seropositive patients with suspected fungal infections

Age category	Number of patients	Male	Female	Percentage
<30 Years	59	41	18	29.50
31-45 Years	105	79	26	52.50
ears	28	18	10	14.0
>60 Years	8	6	2	4.0
Total	200	144	56	

HIV: Human immunodeficiency virus

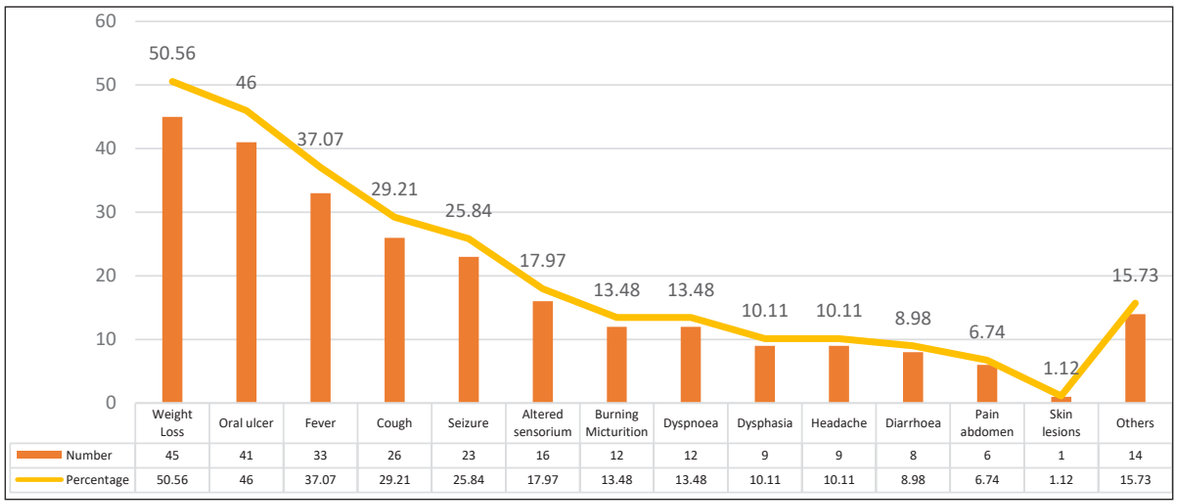

Figure 1: Clinical profile of patients with confirmed fungal infections.

The most common specimens in the study were CSF (62), followed by oral swabs (59), urine (57), sputum (51), and blood (45). Oral swabs (66.10%) and sputum samples (45.10%) had the highest positivity rate for fungal isolates [Table 2].

Candida albicans was the most frequently isolated fungal species in oral swabs (97.43%) and sputum samples (78%). It was also seen that CSF samples (88%) were primarily positive for *Cryptococcus neoformans.*

Candida species were the most frequently isolated fungi, accounting for 75.28%, followed by *Cryptococcus neoformans*, which was identified in 16 patients (17.97%). Among the 67 *Candida* species isolated, *Candida albicans* had the highest isolation rate (88.05%), followed by *Candida tropicalis* (5.97%) [Figure 2].

Table 2: Distribution of fungal isolates from various samples

Sample type	No. of samples	No. of fungal isolates	Isolated fungal species
Oral swab	59	39	*C. albicans*: 38 *C. tropicalis*: 01
Sputum	51	23	*C. albicans*: 18 *C. parasilosis*: 01 *A. niger*: 02 *A. flavus*: 01 *A. fumigatus*: 01
CSF	62	15	*C. neoformans*: 15
Urine	57	7	*C. albicans*: 03 *C. tropicalis*: 02 *C. parasilosis*: 01 *C. auris*: 01
Blood	45	1	*C. neoformans*: 01
Throat swab	02	1	*C. tropicalis*: 01
Skin scrapping	02	1	*T. mentagrophyte*: 01
Axilla/Groin swab	01	1	*C. auris*: 01
Nail	01	1	*Alternaria spp:* 01
Total	280	89	

CSF: Cerebrospinal fluid

DISCUSSION

In developing countries, opportunistic fungal infections (OFI) in HIV-positive patients are the most important cause of mortality and morbidity.[2-5] While there is extensive literature on the spectrum of OFIs (OFIs) in HIV seropositive patients worldwide, data from India remains inadequate.

In our study, 200 HIV-positive patients from different age groups were included, with a male predominance of 72%. Most patients (52.50%) were in the age group of 30-45 years, followed by 29.50% who were under 30 years. Similar results in the most sexually active and economically productive age male preponderance of 67% and 73.2% was observed by Kaur *et al.*, (2016) and by Harikrishna *et al.*, (2017) respectively.[5,11] Our findings are consistent with other studies on HIV-seropositive patients in India and Iran.[12,13] Men often migrate away from their homes in search of work, leading to prolonged separations from their wives and visits to brothels, which are significant contributors to HIV infection and the observed male preponderance. Additionally, many women in Indian society are housewives and may not receive treatment due to social stigma and lack of family support.[14,15]

Among the 200 HIV-seropositive patients with suspected fungal pathogens, the most prominent clinical features in our study were weight loss (50.56%) followed by oral ulcer (46.06%), fever (37.07%), and cough (29.21%). Similarly, a

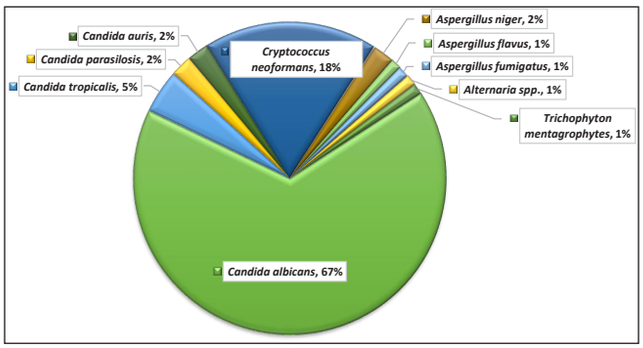

Figure 2: Distribution of fungal species in human immunodeficiency virus (HIV) patients.

study from New Delhi, India, reported weight loss (78.2%) and oral ulcers (74.6%) as the prominent clinical features in HIV-positive patients.[5] In a different study from Nepal, Joshi *et al.*, (2004) also identified weight loss (58.8%) as the most common clinical feature, consistent with our findings.[16] However, Chakravorty *et al.*, (2006) reported that the most prevalent clinical feature was fever, observed in 70.6% of patients, followed by gradual weight loss in 53.3% of cases, while 18.0% of patients were asymptomatic.[17]

CSF samples (19.2 %) and oral swabs (18.26%) were the most frequently received samples in our study. The highest positive rates for fungal isolates were observed in oral swabs (66.10%), sputum (45.10%), and CSF (24.19%). In a study from New Delhi (2016), the most common sample was the oropharyngeal swab (100%), followed by induced sputum (32.5%), blood (31.8%), and CSF (26.2%). The highest rate of fungal isolation in that study was found in sputum samples (53.9%), followed by oropharyngeal swabs (49.3%), with only 9.6% of CSF samples testing positive for fungi.[5] Among the 200 individuals suspected of having an opportunistic fungal infection, 89 patients had confirmed fungal infections. In our study, 71% of individuals with confirmed fungal infection had a CD4 count of less than 200 cells/mm^3, indicating a correlation between low CD4 counts and OFIs.[6,18] Most fungal isolates (i.e., *Candida* species) were obtained from oral swabs, which are commonly associated with oropharyngeal candidiasis, the most prevalent opportunistic fungal infection. According to several other studies, oropharyngeal candidiasis is the most common opportunistic fungal infection.[1,18-22]

Although *Candida* species are part of the normal flora in the oral cavity, we categorized them as opportunistic fungal pathogens because patients experienced oral ulcers with burning sensations during eating or swallowing. Oral candidiasis was found to be more prevalent in our study, likely due to patients having irregular access to ART center sessions during the COVID-19 era. Poor oral hygiene and a lack of awareness about opportunistic infections among HIV-seropositive patients may also contribute to the incidence of oral candidiasis. In our study, *Candida albicans* was the most frequently isolated fungal species from oral swabs (97.43%) and sputum samples (78%).

There were two isolates of *Candida auris*, one from urine, for which subsequent surveillance measures were initiated, and another isolated from an axilla/groin swab of the same patient, hence infection control measures for *Candida auris* were reinforced.

In our study, among the 62 CSF samples, 15 (24.19%) tested positive for fungal isolates, with the sole fungal species identified being *Cryptococcus neoformans*. However, several other studies have reported significantly lower isolation rates of 9.6%, 6.7%, 2.9%, 4%, and 3.7% for cryptococcal meningitis than the isolation rate observed in our study.[5,18,19,23,24] The higher isolation rate observed in our study may be attributed to the study period coinciding with the COVID-19 era, during which most patients visited the hospital only when their condition worsened, experiencing seizures and altered sensorium that necessitated emergency medical monitoring. Given that cryptococcosis is the most common systemic fungal infection among AIDS patients, its prevalence is directly related to the rapid spread of the disease.[18,25,26]

In sputum samples, *Candida* species predominated at 82.6%, followed by *Aspergillus* species at 17.4%.

Upon further categorization, the percentage of *Candida albicans* was 78%, while non-*albicans Candida* accounted for 4.3%. Among the *Aspergillus* species, *Aspergillus niger*, *Aspergillus fumigatus*, and *Aspergillus flavus* were identified at 8.7 %,4.3%, and 4.3 %, respectively. These findings closely align with a study by Bharathi M. and Rani AU. (2011), which reported that 57% of isolates were *Candida* spp. Including 27% *albicans* and 30% non-*albicans Candida*, followed by 13.5% *Aspergillus* spp. as the major groups.[27] In another study by Chandwani *et al.*, (2016), *Candida albicans* was the most common isolate (31.7%), followed by *Aspergillus niger* (17.7%) and *Aspergillus flavus* (10%).[6] In sputum samples, *Candida* species are typically commensals, while *Aspergillus* species are considered contaminants. However, both can act as opportunistic pathogens in immunocompromised individuals. In our study, the same fungal isolate was found in three consecutive sputum samples, and patients presented with symptoms of fever, cough, and chest pain, prompting us to report these isolates as fungal pathogens.

Candida species (75.28%), *Cryptococcus neoformans* (17.97%), *Aspergillus* species (4.48%), *Alterneria species* (1.12%), and *Trichophyton mentagrophyte* (1.12%) were the most frequently isolated fungal species in our study. These results are comparable to a previous study by Parmar *et al.*, (2012), which reported *Candida* species (55%) as the most

Table 3: Prevalence of various fungal isolates from HIV/AIDS patients

Reference	*Candida spp.*	*Cryptococcus spp.*	*Aspergillus spp.*	Others
Our study	75.28%	17.97%	4.49%	2.24%
Kaur *et al.*[5] (2016)	86.5%	3.3%	6.5%	3.7%
Gandham *et al.*[31] (2013)	71.7%	1.2%	14%	13.1%
Parmar *et al.*[2] (2012)	83.3%	6.0%	4.7%	6.0%
Bharathi and Usha[27] (2011)	57%	5.2%	13.5%	24.3%
Jahromi and Khaksar[28] (2005)	69.4%	4.2%	13.9%	12.5%

HIV: Human immunodeficiency virus, AIDS: Acquired immunodeficiency syndrome

common fungal isolate, followed by *Cryptococcus* species (4%) and *Aspergillus* species (3%).[2]

Similarly, R. Kaur *et al.*, (2016) from New Delhi found *Candida* species (86.5%) to be the most prevalent fungal isolate, followed by *Aspergillus* species (6.5%), *Cryptococcus* species (3.3%), *Penicillium* species (1.9%). *Alterneria* and *Rhodutorula* species were reported at 0.9% each[5] [Table 3].

In another study from Iran by Jahromi SB and Khaksar AA (2005), *Candida* species accounted for 69.4%, followed by *Aspergillus* species (13.9%) and *Cryptococcus* species (4.2%).[28] A study by Pagano *et al.*, (2006) from Italy showed *Aspergillus* species as the most frequently isolated fungal species (57.6%), followed by *Candida* species (32.5%) and *Cryptococcus* species (1.4%).[29] Additionally, a study by Kashyap *et al.*, (2012) reported *Candida* species (18.3%) as the predominant fungal isolate, followed by *Aspergillus* species (6.9%) and *Cryptococcus* species (0.6%).[30] The most isolated fungal species in the study by Gandham *et al.*, (2013) was *Candida* species (71.7%), *Aspergillus* species (14%), *Penicillium* species (1.5%), *Cryptococcus* species (1.2%), and *Rhodutorula* species (0.9%).[31]

The isolation rate of *Cryptococcus* species in our study was 17.97%, which is significantly higher compared to the rates reported in other studies, which were 4%, 3.3%, 4.2%, 1.4%, 0.6%, and 1.2%.[2,5,28-31] [Table 3].

Among the 67 *Candida* species isolated in our study, *Candida albicans* was predominant (88.05%), followed by *Candida tropicalis* (5.97%), *Candida parasilosis* (2.98%), and *Candida auris* (2.98%). Similarly, a study from New Delhi, India, found *Candida albicans* (75.8%) to be the most prevalent among *Candida* isolates, followed by *Candida tropicalis* (9.7%), *Candida krusei* (6.5%), *Candida glabrata* (4.3%), *Candida parapsilosis* (2.7%), and *Candida kefyr* (1.1%).[5] Another study by Gandham *et al.*, (2013) reported similar results, with *Candida albicans* at 51.4%.[31] However, in contrast, Picardi *et al.*, (2012) from the USA found non-albicans *Candida* to be the most prevalent isolate in neutropenic patients.[32] Among *Aspergillus* species, *Aspergillus niger* was the most prominent at 50%, followed by *Aspergillus flavus* and *Aspergillus fumigatus* at 25% each. Another study from India also reported *Aspergillus niger* (50%) as the primary species, followed by *Aspergillus fumigatus* (35.7%) and *Aspergillus flavus* (14.3%).[5] Meanwhile, Gandham *et al.*, (2013) reported *Aspergillus fumigatus* (53.2%), followed by *Aspergillus niger* (25.5%) and *Aspergillus flavus* (14.9%).[31] In our study, only *Cryptococcus neoformans* was isolated among *Cryptococcus* species(100%), which is comparable the findings of Gandham *et al.* (2013).[31] However, Kaur *et al.*, (2016), from New Delhi, India, reported both *Cryptococcus neoformans* (71.4%) and *Cryptococcus gattii* (28.6%) among *Cryptococcus* species (14.9%).[5]

In our study, one isolate of *Alterneria* species (1.12%) was obtained from a nail sample. In contrast, a study from New Delhi reported an isolation rate of 0.9% for *Alternaria alternata* from sputum samples. However, a study by Warthe N *et al.* (2015) found that 5.6% of cancer/HIV patients from central India had *Alternaria alternata* isolated from their blood.[33] However, we did not find any case of *Alternaria* fungemia in HIV-seropositive patients.

CONCLUSION

Oropharyngeal candidiasis followed by cryptococcal meningitis are the most common opportunistic fungal infection in HIV-positive patients, particularly those with low CD4 counts. A detailed comparative study of CD4 cell counts, viral load, and OFIs could establish CD4 count as an indicator of opportunistic mycoses in HIV/AIDS patients. Such research would aid clinicians in t diagnosing and initiating early treatment for these infections, ultimately helping to prevent their severe consequences in developing countries like India.

Authors' contributions: SM, NK: Concept and design; NK, SM, AKC, NC, NKB: Acquisition, analysis, or interpretation of data; NK, SM, AKC: Drafting of the manuscript; SM, NKB: Critical revision of the manuscript for important intellectual content; NC, AKC: Technical and material support; SM, NKB: Supervision.

Ethical approval: The research/study is approved by the Institutional Ethics Committee at Atal Bihari Vajpayee Institute of Medical Sciences and Dr Ram Manohar Lohia Hospital, number TP (MD/MS) 34/2019/IEC/ABVIMS/RMLH 698/19, dated 22nd October 2019.
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Original Article

Assessment of radiation exposure: An in-depth analysis of dose evaluation in contrast-enhanced computed tomography abdomen imaging

Babina Aryal[1], Mohsin Rasool Bhat[2], Adil Ahmad Wani[2], Junaid Ul Islam[3]

[1]Department of School of Allied Health Sciences, Noida International University, Greater Noida, Uttar Pradesh, [2]Department of Allied Health Sciences, Brainware University, Kolkata, West Bengal, [3]Department of School of Sciences, Maulana Azad National Urdu University, Hyderabad, Telangana, India

ABSTRACT

Objectives: The advancement of diagnostic imaging highlights the critical role of computed tomography (CT) scans in disease diagnosis. contrast-enhanced computed tomography (CECT) abdomen is widely utilized for detailed visualization of abdominal structures. However, it entails exposure to ionizing radiation, raising concerns, particularly regarding cancer risk. The radiation dose from CECT varies based on scan parameters, patient size, and imaging protocols. Medical professionals aim to optimize scanning parameters to minimize radiation exposure while preserving diagnostic quality. The objective of this study was to assess the variance in estimated doses received during CECT abdomen scans.

Material and Methods: Data from patients undergoing CECT abdomen from March 2023 to March 2024, including volumetric CT dose index (CTDIvol) and dose length product (DLP), were analyzed by a medical physicist and Radiation Safety Officer. Mean and cumulative doses were calculated using CTDIvol and DLP, with the effective dose determined using total DLP and a k-factor of 0.015 for the abdomen.

Results: This study comprised 296 patients (211 males and 85 females), primarily presenting with abdominal symptoms, with an age range of 18–85 years. Mean CTDIvol varied from 5 mGy to 26.42 mGy in males and from 4.96 mGy to 21.9 mGy in females, with similar trends observed in DLP values and effective doses. Statistical analysis indicated no significant difference in radiation dose by sex, though variations in effective dose were noted, possibly due to differences in exposure parameters and patient demographics.

Conclusion: While CECT scans effectively diagnose abdominal conditions, they do pose radiation risks. Radiology departments should monitor doses, standardized protocols, refine imaging techniques, and collaborate to ensure safety. Diagnostic reference levels are crucial for balancing the need for diagnostic information with the necessity to minimize patient exposure to radiation.

Keywords: Contrast enhanced computed tomography, Computed tomography dose index, Dose-Length product, Dose, Effective dose

INTRODUCTION

Contrast-enhanced computed tomography (CECT) of the abdomen is a technique for accurately visualizing anatomy and achieving precise diagnosis by the use of radiopaque dye. Despite having invaluable diagnostic information it offers, the consideration of radiation exposure becomes essential, requiring careful management. Conversely to conventional X-rays computed tomography (CT), CT scans utilize highly energetic ionizing radiation to generate detailed images, which presents inherent risks, including the potential for long-term adverse effects such as radiation-induced cancer. In the complex field of abdominal imaging, the concept of "differential dose" emerges as a crucial factor to be taken into account. Differential dosing in CECT abdomen cases involves customizing the administration of contrast agents and radiation dosage according to individual patient characteristics and diagnostic needs. This refined strategy enables healthcare providers to refine imaging protocols, guaranteeing both diagnostic precision and patient well-being. While exploring the domain of differential dosing in CECT abdomen cases, it reveals a complex terrain that includes clinical indications and imaging objectives. Effective comprehension and application of these dosing strategies empower healthcare providers to refine diagnostic accuracy, reduce radiation exposure, and ultimately enhance patient outcomes. It is crucial to consider the associated radiation

***Corresponding author:** Junaid Ul Islam, Assistant Professor Medical Imaging and Technology, School of Sciences, Maulana Azad National Urdu University, Hyderabad, Telangana, India. peerjunaid9@gmail.com

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dose when conducting these examinations to ensure patient safety and optimize imaging protocols. When considering CT imaging, especially for younger female patients, it's essential to weigh the advantages against the potential risks posed by radiation exposure.[1] Due to the use of high-density contrast agents, the dose received in the CECT is much higher (30%) than the noncontrast scans.[2] Significant apprehensions have arisen due to the possible escalation in long-term radiation-induced cancer, leading some researchers to assert that the diagnostic application of CT scans could contribute to a notable number of fatalities annually. Based on the figures, 1 in every 250 CECT examinations may result in the development of cancer.[3] The advantages of CT scans outweigh the negative impacts of radiation exposure in patients, and the rising radiation doses across the population make a strong argument for lowering exposure from CT scans. Photon counting detector-CT facilitates oncologic abdominal CT scans with a substantially lower dose, maintaining image quality comparable to that of a -second-generation Dual Slice CT scanner.[4] In abdominal pelvic CT scans, direct radiation exposure affects the prostate and uterus, potentially posing health hazards to patients. A research investigation illustrated a notable linear dose-response relationship concerning prostate cancer, indicating an estimated excess relative risk per Gy of 0.57. This study's findings led to the conclusion that "the observed dose-response reinforces the evidence suggesting a radiation impact on the likelihood of prostate cancer incidence among atomic bomb survivors."[5] There is no distinction in diagnostic efficacy between hepatic venous phase (HVP)-CT alone and multiphasic CT for identifying the causes of abdominal pain in patients admitted to the emergency department without preexisting chronic conditions or neoplasms.[6] It is possible to maintain the amplitude of signal and contrast to noise ratios while achieving a balance between the radiation and contrast dose.[7] In routine contrast-enhanced CT scans of the abdomen and pelvis, an extra delayed phase is included that is of minimal importance, especially when dependable follow-up imaging is accessible to provide further clarification of ambiguous findings.[8] Obtaining a low-dose scan necessitates collaborative efforts, involving customizing the scan to suit the patient and medical inquiry, alongside ongoing quality improvement to incorporate evolving strategies for optimizing dose.[9] Due to multiple scans in CT, the radiation increases subsequently, unlike X-rays, producing higher absorbed doses; hence, radiologists need to ensure that the patient's benefit is much greater than the risk produced by the exposures, which may depend on the patient.[10] The radiation should be kept lower than the diagnostic reference levels (DRLs) to increase patient safety and maintain image quality resulting in precise diagnosis.[11] DRL is an existing standard for specific imaging procedures designed to optimize radiation exposure levels and ensure they remain within a safe and acceptable range. The relationship between DRL and computed tomography dose index (CTDI) is that DRL serves as a reference point to evaluate CTDI values, ensuring that they remain within acceptable limits and that radiation exposure is optimized and safe.

Aim and Objectives: This study is aimed to assess radiation exposure levels associated with CECT scans of the abdomen, and also to estimate DRL for CECT abdomen studies. The primary objective of this study was to measure levels of radiation exposure related to CECT abdomen and to compare radiation dose among the genders.

MATERIAL AND METHODS

Patient selection

This retrospective study was approved by our institutional review board. A total of 296 patients with clinical/laboratory/ultrasonography diagnosis of different abdominal findings who were referred for multiphasic CECT abdomen from March 2023 to March 2024 were included in this study. Patients who had recently undergone abdominal surgery, individuals with renal failure, patients who were allergic to contrast media, pregnant patients, and patients lacking proper radiation dose reports were excluded. The minimum age of the patient was 18 years and maximum was 86 years.

CT technique

For a contrast study, SmartPrep technique was activated in general electric Revolution Evo 128 Slice CT scanner to chase the uniform flow of contrast to the region of interest. On the whole, the contrast study of the abdomen consisted of three phases, namely the arterial phase, which was acquired after 18s, the venous phase after the 60s, and delayed phase after 5–7 minutes. Finally, the patient was instructed to drink plenty of water for the washout of the administered contrast. Retrospectively, image data of the patients who have undergone CECT abdomen for different clinical indications were assessed to evaluate the radiation dose.

Radiation dose analysis

Dose information was available in the CT unit. The details of the dose report, including volumetric CT dose index (CTDIvol) and dose length product (DLP) for all patients, were recorded for each phase. Radiation doses were analyzed by a medical physicist and radiation safety officer. The data was obtained from the digital imaging and communications in medicine server and radiology information system using a filtered data form (age, sex, diagnosis on CT, CTDIvol [mGy]),

dose length product (DLP [mGy.Cm]). CTDI is a dose descriptor that provides a measurement of the radiation dose due to the primary and scatter radiation per slice of tissue and is expressed as mGy. DLP, another CT dose descriptorprovides a measurement of the total amount of dose to the entire scan coverage and in mGy.Cm. CTDIvol and DLP were used to calculate the average and mean patient dose and compared with each other throughout the study. Effective dose, a dose descriptor reflecting the biological sensitivity of irradiated regions of interest, was calculated by taking the product of total DLP and the k-factor (the proportionality constant between the effective dose and the DLP). The k-factor for the abdomen is 0.015.

Statistical analysis

The statistical analysis of radiation dose involved examining various parameters such as mean, maximum/minimum dose values, and effective doses, which were calculated for all patients. The data has been analyzed using the Microsoft Excel 2016 calculation software. Descriptive statistics, including bar graphs and pie charts, have been employed to visualize the distribution of radiation doses.

RESULTS

This study revolves around two sections, including the sociodemographic characteristics of the participants as well as parameters associated with radiation exposure and dose evaluation comprising 296 patients (211 males and 85 females). Males comprised an age range of 18–83 years while females of 20–86 years; the average age of males was 47.8 years, and 51.2 years for females. A majority of the patients had a history of abdominal pain (n = 162), constipation (n = 65), recurrent vomiting (n = 37), and follow-up of different diagnosis (n = 17) and others (n = 15), respectively [Table 1].

Table 1: Table showing demographic details of the patients

Gender	Age	Total number of patients	Symptoms
Males	Mean: 47.8	211	Abdominal pain: 117
	Min: 18		Constipation: 55
	Max: 83		Vomiting: 23
			Follow-up cases: 7
			Others: 9
Females	Mean: 51.2	85	Abdominal pain: 45
	Min: 20		Constipation: 10
	Max: 86		Vomiting: 14
			Follow-up cases: 10
			Others: 6

Tube voltages ranged from 80 kVp to 140 kVp, pitch of 1 mm, tube current-time ranged from 150 mAs to 280 mAs, slice thickness of 5 mm, contrast amount of 1.2 mL per kg of body weight with a flow rate of 3–4 mL per second. These factors of radiation exposure, including current and potential of tube, thickness of slices, slice number, and pitch, were taken into account [Table 2].

The minimum and maximum CTDIvol for abdominal CT were found to be 5 mGy and 26.42 mGy in males and 4.96 mGy and 21.9 mGy in females, with a mean of 11.54 and 12.77 mGy in males and females, correspondingly. The minimum and maximum DLP for CECT abdomen was 1004.62 mGy.cm and 6484.2 for males and 1040 mGy.cm and 4964.1 mGy.cm for females, respectively, with a mean of 2734.56 mGy.cm. and 2842.61 mGy.cm. The minimum and maximum effective dose was determined to be 15.06 mSv and 97.2 mSv for males and 15.6 mSv and 74.4 mSv for females, respectively, with a mean of 40.93 mSv for males and 42.63 mSv for females [Table 3].

The DRLs for CTDIvol and DLP values were established for this study; DRLs for CTDIvol: 34 mGy, 45.9 mGy, and 56.4 mGy for the 25th, 50th, and 75th percentile, respectively, and the proposed DRLs for DLP are 2018.7 mGy.cm, 2679.4 mGy.cm, and 3363.125 mGy.cm for 25th, 50th, and 75th percentile, respectively. The established local DRL for CECT abdomen is shown in Table 4.

Table 2: Image acquisition parameters according to different genders

Gender	Tube voltage (kVp)	Tube current (mA/mAs)	Pitch	Slice thickness (mm)
Male	Mean: 110	Mean: 215	1	5
	Min: 80	Min: 150		
	Max: 140	Max:280		
Female	Mean: 110	Mean: 215	1	5
	Min: 80	Min:150		
	Max: 140	Max: 280		

Table 3: Dose data of CECT abdomen examinations

Gender	Computed tomography dose Index (CTDI) (mGy)	Dose length product (DLP) (mGy*cm)	Effective dose (mSv)
Male	Mean: 11.54	Mean: 2734.56	Mean: 40.93
	Min: 5	Min: 1004.62	Min: 15.06
	Max: 26.42	Max: 6484.22	Max: 97.26
Female	Mean: 12.77	Mean: 2842.61	Mean: 42.63
	Min: 4.96	Min: 1040	Min: 15.6
	Max: 21.9	Max: 4964.1	Max: 74.46

CECT: Contrast-enhanced computed tomography

Table 4: DRL for CECT abdomen

Percentile	25th	50th	75th
CTDI (mGy)	34	45.9	56.4
DLP (mGy.cm)	2018.725	2679.4	3363.125

DRL: Diagnostic reference levels, CECT: Contrast-enhanced computed tomography, CTDI: Computed tomography dose index, DLP: Dose length product

An independent sample t-test was done to check if there was any statistically significant difference between the radiation dose with sex, but it was not statistically significant. There was a difference in the calculated mean values of the effective dose that could have possibly occurred due to the different exposure settings and patient aspects.

DISCUSSION

Ever since its introduction into clinical practice, CT scanning has been acknowledged as a diagnostic imaging technique associated with higher radiation doses compared to other modalities. As scanner technology has evolved and its utilization has become increasingly widespread, concerns regarding patient radiation doses from CT scans have escalated.[12] Switching from conventional X-rays to CT results in a very sharp increase in the effective doses received by the patient. A study done by Yadav *et al*. (2023) examined 92 adult patients undergoing abdominal CT scans at a Nepalese medical imaging department from August 2018 to January 2019 using a 16-slice CT scanner. Radiation doses were assessed using CTDIvol, DLP, and effective dose and analyzed with SPSS version 20, which were 7.31 mGy, 421.46 mGy.cm, and 6.31 mSv, representing a lower value than the standards established by European guidelines and International Atomic Energy Agency. A direct relation was found between the dose and body mass indexof individuals in multiple scan types.[13] Choudhary *et al*. (2019) used a 16-slice scanner and evaluated radiation exposure in the head, thorax, abdomen, and pelvis. The CTDI results were adjusted for patient size using the size-specific dose estimate (SSDE) technique. The CTDIvol readings of 26.76 mGy, 16.27 mGy, 14.74 mGy, and 29.81 mGy were observed, respectively. A 4–8% variance from American Association of Physicists in Medicine-reported CTDI values were indicated by SSDE-calculated median doses, which raised concerns about depending exclusively on CTDI for accurate patient dose determination during CT operations.[14] The CTDI and SSDEs among the 75 patients in El Mansouri *et al*.'s (2022) study were also determined using an algorithm that showed the values for CTDI varied from 4.8 mGy to 12.2 mGy and for SSDE from 8.01 mGy to 14.15 mGy.[15]

The variation in mA and scan volume DLP value variations were calculated in this study. In the majority of cases, the radiation dose and mA were linear. As a result, lowering the tube current value lowered the radiation dose to the patient. Table 2 provides details of mean and range values for CTDIvol (mGy), DLP (mGy*cm), and effective (mSv). For males and females, the mean effective dose was around 40.93 mSv and 42.63 mSv, respectively. Women's effective dose was slightly greater (42.63 mSv) than men (40.93 mSv). Compared to 32- and 64-slice CT scanners, 16-slice CT scanners gave patients the least amount of radiation and produced images good enough for diagnosis.[16] This study investigated the sociodemographic characteristics and parameters related to radiation exposure and dose evaluation in 296 patients undergoing abdominal CT scans. The patients presented with symptoms such as abdominal pain, constipation, and recurrent vomiting. Factors including tube voltage, tube current, slice thickness, and contrast amount were considered in assessing radiation exposure. Analysis revealed a range of CTDIvol, DLP, and effective dose values, with slight variations between males and females. While statistical analysis did not show a significant difference in radiation dose by sex, differences in effective dose may be attributed to varying exposure parameters and patient body. The findings highlight the need for dose optimization techniques to reduce exposure while maintaining diagnostic accuracy. Establishing DRLs for CT scans is an essential tool for optimizing and ensuring safe radiation exposure for patients. This study has established DRLs for CTDIvol and DLP values, which are crucial for evaluating patient radiation doses during CT examinations. The proposed CTDIvol DRLs are 34 mGy, 45.9 mGy, and 56.4 mGy for the 25th, 50th, and 75th percentiles, respectively, comparable to those in similar studies, indicating our CT scanner's compliance with acceptable dose limits. These values help radiologists and radiographers optimize scanning protocols and minimize patient radiation exposure. The proposed DRLs for DLP are 2018.7 mGy.cm, 2679.4 mGy.cm, and 3363.125 mGy. cm for the 25th, 50th, and 75th percentiles, respectively, suggesting our scanner delivers acceptable doses. DLP values provide a comprehensive assessment of radiation exposure by considering scan length. These DRLs significantly impact radiation safety in our imaging department, guiding protocol optimization, reducing patient exposure, and improving care quality. They also serve as benchmarks for other departments, promoting radiation safety and dose optimization.

CONCLUSION

CECT scans are vital for diagnosing abdominal conditions, yet their high radiation doses pose risks to sensitive organs. Significant dose variation was observed throughout the study and this variation may have been due to differences in the scan protocol and parameters associated with the scanners and patient demographics. Radiology departments must monitor

doses and follow standardized protocols to optimize radiation levels across facilities. Refining imaging protocols is crucial to reducing patient exposure without compromising diagnostic accuracy. Collaboration among radiologists, physicists, and technologists is essential for ongoing improvement. Establishing national DRLs for CT examinations is recommended to ensure consistency in dose optimization efforts. DRLs in CT imaging serve as benchmark radiation dose levels for standard procedures, aiding in optimizing patient safety. This practice helps standardizing radiation doses across different institutions, promoting consistent and safe imaging practices. Implementing these measures enhances patient safety and mitigates risks associated with radiation exposure during CECT abdomen imaging.

Authors' contributions: BA: Concept and design; JUI: Data analysis and interpretation; MRB: Manuscript preparation; AAW: Manuscript preparation.

Ethical approval: The ethical committee waved off the ethical clearance for the study as the study only focused on the technical aspects which included dose factors of the scans. There was no patient involvement in the study.

Declaration of patient consent: Patient's consent not required as patients identity is not disclosed or compromised.

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Original Article

The link between serum vitamin D levels and bronchial asthma: A case control study

Pavan N Kumar[1], Amirullah Amirullah[1], Deepak Kumar R[1]

[1]Department of Respiratory Medicine Kempegowda Institute of Medical Sciences and Research Centre, VV Puram, Bengaluru, Karnataka, India

ABSTRACT

Objectives: Asthma is a common long-term respiratory condition that considerably increases morbidity worldwide. Because of its immunomodulatory properties, vitamin D may have an impact on the severity of asthma. This case control study explores the relationship between serum vitamin D levels and bronchial asthma.

Material and Methods: There were 70 participants in all, 35 of whom were matched controls and 35 of whom were asthma patients. Measurements of IgE and serum vitamin D were made to look for associations with asthma.

Results: Patients with asthma had higher IgE levels, suggesting heightened allergic reaction and substantially less vitamin D in their blood (13.83 ± 9.34 ng/mL) than control (27.34 ± 8.19 ng/mL) ($p < 0.001$).

Conclusion: This study highlights that individuals with bronchial asthma tend to have lower serum vitamin D levels and higher IgE levels, suggesting a link between vitamin D deficiency and asthma severity. Addressing vitamin D deficiency may offer a supportive role in asthma management, though further studies are needed to confirm these findings.

Keywords: Bronchial Asthma, IgE levels, Vitamin D levels

INTRODUCTION

Millions of people worldwide have bronchial asthma, a chronic condition marked by symptoms like dyspnea, tightness in the chest, wheezing, and fluctuating airflow blockage.[1,2] With more than 300 million individuals impacted globally and over 30 million in India alone, it is especially pervasive.[3,4] Variables like hypercapnia and hypoxia frequently signal the severity of asthma. A positive atopic status, allergen exposure, and a family history of allergy disorders are risk factors. In addition to being necessary for the regulation of calcium and phosphate, vitamin D is important for immunological modulation or cell differentiation.[5,6] An increasing amount of data points to a global epidemic of vitamin D deficiency, which has been linked to the exacerbation of asthma symptoms. Poor nutrition, insufficient sun exposure, prolonged breastfeeding sans supplementation, or maternal deficiency are some of the factors that contribute to this deficiency.[7] The purpose of this study was to investigate the potential link between vitamin D levels in the serum on asthma, specifically looking at how a deficiency may exacerbate the condition.

MATERIAL AND METHODS

We enrolled 35 patients having bronchial asthma and 35 sex-, age-, and BMI-matched control subjects, ranging in age from 20 to 67, in our first case-control research. Participants were drawn from the medicine ambulatory department; those in the control group were people who were there for unrelated, minor medical conditions but did not exhibit symptoms of asthma. Asthma patients were confirmed based on eosinophilia in blood smears, where control participants were evaluated through clinical examination to rule out asthma. Type 1 diabetes, malnutrition based on protein-energy intake, or recent consumption of drugs or supplements influencing vitamin D levels were among the exclusion criteria. Furthermore, the study excluded those with long-term liver, kidney, lung, and neurological conditions.

***Corresponding author:** Dr. Pavan N Kumar, Department of Respiratory Medicine, Kempegowda Institute of Medical Sciences and Research Centre VV Puram, Bangalore, India. pkreddy24297@gmail.com

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Venous blood samples of about 5 mL were taken from the patients and the controls. As soon as the nonfasting serum samples were collected, routine biochemical parameters were examined for both groups. In addition, aliquots of all the samples were kept at −20°C in order to test for IgE or 25-hydroxyvitamin D levels.

To assess the levels of IgE or 25-hydroxyvitamin D, commercial immunoassay enzyme linked immunosorbent assay kits were used. Student's *t*-test was used to do statistical analysis on the various biochemical parameters. The standard deviation, or mean ± SD, was used to express the results. The Mann–Whitney U test was used to assess nonparametric data, while the Student's unattached two-tailed *t*-test was used to compare means of two distributed sample groups. With SPSS software, every statistical test was carried out. It was deemed significant when $p<0.05$.

RESULTS

Our study compares the metabolic profiles and participant characteristics in the bronchial asthma unit (n = 35) with the control group (n = 35). There were 15 men and 20 women in the placebo group and 17 men and 18 women in the asthma group, respectively, according to sex distribution. The control group had an average age of 39.64 ± 13.1 years, while the asthma group had an average age of 38.94 ± 12.69 years. The asthma group had an upper body mass index (BMI) of 24.96 ± 2.29 kg/m², which was marginally higher than the control group's BMI of 23.27 ± 1.46 kg/m² [Table 1].

The asthma group had significantly greater serum IgE levels (665.2 ± 245.3 IU/L) than the control sample (141.8 ± 71.06 IU/L), which is a measure of allergic reaction. Nonetheless, there was no noteworthy distinction in the random blood sugar readings between the asthma unit (80.7 ± 12.28 mg/dL) and the control group (85.13 ± 10.42 mg/dL). In patients with bronchial asthma, plasma 25-hydroxyvitamin D levels were considerably lower than in controls (13.83 ± 9.34 ng/mL vs. 27.34 ± 8.19 ng/mL; $p < 0.001$) [Figure 1].

Table 1: Characteristics and biochemical profile of the participants.

	Control (n=35) means ± SD	Bronchial Asthma (n=35) means ± SD
Sex		
Male	15	17
Female	20	18
Age (in years)	39.64 ± 13.1	38.94 ± 12.69
BMI (kg/m²)	23.27 ± 1.46	24.96 ± 2.29
Serum IgE (IU/L)	141.8 ± 71.06	665.2 ± 245.3*
RBS (mg/dl)	85.13 ± 10.42	80.7 ± 12.28

RBS: Random blood sugar. Age, BMI, and serum levels of biochemical parameters were expressed as the means ± SD. Statistically significant, *p<0.05 vs. Control. SD: Standard deviation, BMI: Body mass index.

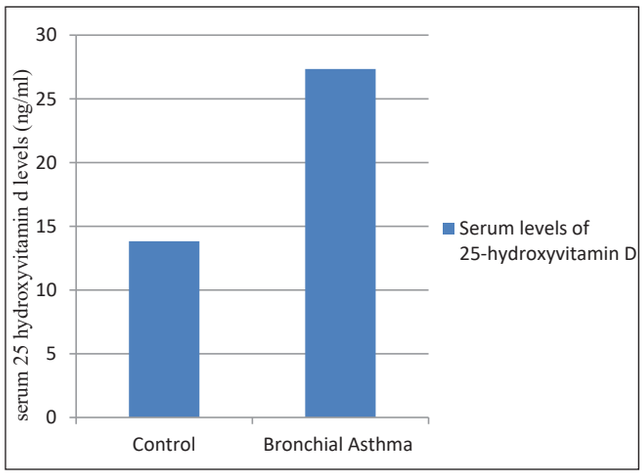

Figure 1: Serum 25-hydroxy vitamin D levels were significantly lower in bronchial asthma patients compared to controls ($p<0.001$).

These results show that blood IgE levels are higher in people with bronchial asthma than in nonasthmatics, suggesting that asthma patients have a more sensitive allergic reaction. While both groups' BMIs were within normal levels, the asthma group's BMI was marginally higher.

DISCUSSION

It is important to consider that seasonal variations affect vitamin D synthesis due to differing sunlight exposure across seasons, which may impact serum vitamin D levels and influence asthma outcomes. Future studies should account for these variations to provide a more accurate assessment.[8]

Vitamin D's role in asthma may be linked to its immunomodulatory effects. It can influence immune cells like monocytes, macrophages, and lymphocytes, potentially reducing airway inflammation and controlling immune responses in asthma. This immunomodulation may help alleviate asthma symptoms and improve patient outcomes.[9]

A number of causes, including increasing indoor activity, poor food, restricted sun exposure, sunscreen use, and biological characteristics like skin melanin content, that decrease the skin's capacity to synthesize vitamin D3, have contributed to the rise in vitamin D deficiency as a major global health concern. This shortage affects people of all ages in India.[10] A correlation has been shown in studies involving vitamin D deficiency or an increased risk of allergic reactions and asthma. Asthma and high blood IgE levels have even been linked to vitamin D insufficiency in some studies, and vitamin D deficiency in families may be a risk factor for asthma.[3]

In our investigation, we observed higher IgE levels and a significant decrease in the amount of serum vitamin D among individuals with bronchial asthma when compared with the control group. The significance of vitamin D in the development of asthma is explained by several theories. Vitamin D has the capacity to alter immune cell activity, such as that of monocytes, macrophages, lymphocytes, and even epithelial cells. This could exacerbate asthma symptoms. This shows that inadequate vitamin D may exacerbate immunological dysregulation and asthma-related inflammation or immune responses.[11]

Our results are consistent with a research by Li *et al*. (2011) that involved 435 adults with asthma (268 women and 167 men), and they showed lower levels of 25(OH)D.[12] Similar to our findings, Shaaban and Hashem's study involving 75 persons without asthma and 75 normal controls revealed vitamin D deficiency.[13] This correlation may be explained by decreased serum vitamin D levels increasing the expression of tumor necrosis factor-alpha (TNF-α), indicating that increased proinflammatory cytokine TNF-α may exacerbate asthma symptoms.[14]

A different study with 280 adult asthmatics found that people with bronchial asthma had reduced 25(OH)D concentrations. They came to the conclusion that there may be a hormonal influence on asthmatic inflammatory activity or vice versa given the substantial link between the severity of asthma and 25(OH)D concentrations. When respiratory infections occur, airway epithelia, which have large concentrations of the enzyme that changes circulating 25-OH-vitamin D3 into the active form of 1,25-OH-vitamin D3, may respond locally, thereby reducing inflammation.[15]

In addition, a study found a correlation among serum 25(OH) D levels as well as the likelihood of an asthma-related ER visit or hospital stay, indicating that vitamin D deficiency could be the most reliable predictor of asthma, surpassing even serum IgE levels and family history of asthma.[3]

Also, we discovered that people with bronchial asthma had higher blood IgE levels. Our findings align with Sandeep *et al*. (2010), who reported a correlation between total IgE levels and asthma, independent of allergen sensitization.[16]

According to these findings, bronchial asthma is linked to low vitamin D levels in both industrialized and developing nations. There is a correlation between the seriousness of bronchial asthma and the shortage of vitamin D. Vitamin d may help improve glucocorticoid responsiveness in severe asthmatics by upregulating CD4+ T cell production of the anti - inflammatory cytokine interleukin-10, regardless of total IgE levels, atopy type or corticosteroid use. Therefore, in bronchial asthma patients who are resistant to steroids, vitamin D may help regulatory T cells secrete interleukin-10 in response to these drugs.

Limitation

It is important to note that our study has certain limitations. Due to the small sample size and the use of topical corticosteroids and antihistamines by some patients, serum vitamin D levels may have been impacted.

CONCLUSION

This study indicates that individuals with bronchial asthma are more likely to have lower serum vitamin D levels and higher IgE levels, suggesting a potential role for vitamin D supplementation in asthma management. Treating vitamin D deficiency could be a beneficial strategy in improving asthma outcomes. Larger longitudinal studies are needed to validate these findings and further explore the mechanisms involved.

Authors' contributions: PNK: Study design, data collection, manuscript writing; AA: Statistical analysis, literature review, manuscript editing; DKR: Patient recruitment, manuscript review.

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Original Article

A five-year review of in-hospital neonatal mortality: Trends and implications for care

Priyanka Gupta[1], Divya Garg[1]

[1]Department of Pediatrics, ESIC Medical College and Hospital, Faridabad, Haryana, India

ABSTRACT

Objectives: The objectives of this study were to estimate the in-hospital mortality/survival outcomes at discharge and to determine the risk factors for in-hospital neonatal mortality.

Material and Methods: This study was a secondary data analysis (review) of the existing hospital records during the first five years of operationalization of the neonatal intensive care unit (NICU) in a tertiary care hospital at Haryana, India.

Results: There were 126 in-hospital mortality rates among a total of 2725 admissions (i.e., in-hospital neonatal mortality of 4.62 per 100). The in-hospital mortality among male and female neonates were comparable (4.52 vs 4.26%; P value 0.788). However, the in-hospital mortality among extramural births (5.52%) was significantly higher than the mortality among intramural births (4.26%; P = 0.010). Neonates with the lowest birth weight had the highest in-hospital mortality (P value < 0.00001). There was an exponential increase in the risk of in-hospital mortality among neonates with birth weight < 1500 g and < 1000 g, that is, 11.6% and 48.6%, respectively.

Conclusion: Information about in-hospital neonatal mortality and survival outcomes from NICU is an important indicator of quality of care. The in-hospital mortality in this study was comparable to other Indian studies, with poorer survival outcomes among neonates < 1500 g birth weight. Extramural births had higher mortality than intramural births, reminding us of the importance of in-utero fetus transfer among high-risk and preterm labor.

Key words: Birth weight, Extramural, Gender, Intramural, Neonatal mortality, Survival outcome

INTRODUCTION

Although there has been an overall improvement in the survival of very low birth weight (VLBW) and extremely low birth weight (ELBW) neonates in recent years, it varies significantly between countries and regions, depending on the facilities and quality of medical care. Low- and middle-income countries are disproportionately affected due to their lack of healthcare technology and shortage of trained health personnel. The mortality rates among overall admissions to the neonatal intensive care units (NICUs) have been noted to vary from 3% to 29%, figures varying from 20% to 46% among ELBW, and from 5% to 12% among VLBW neonates.[1] A recent systematic review and meta-analysis by Ramaswamy *et al.*[2] (2021) included 192 studies, enrolling 22,278 ELBW neonates. In this review, the survival of ELBW babies in low-income, lower-middle-income, and upper-middle-income countries was found to be 18% (11–28%), 28% (21–35%), and 39% (36–42%), respectively.

Information about individual in-hospital neonatal mortality and survival outcomes is an indicator of quality of care, which helps clinicians to counsel the families appropriately and also guides administrators in allocating limited NICU resources. In this study, we estimated the in-hospital mortality/neonatal survival rates (till discharge) in a recent operational NICU of a tertiary care hospital at Haryana, India; secondary objectives were to determine risk factors for in-hospital neonatal mortality with the limited records.

MATERIAL AND METHODS

This study was a secondary analysis of the existing hospital records (review) at the NICU of a tertiary care hospital in Haryana, India. The data from June 5, 2018, till June 4, 2023, that is, the initial five years of its inception and operationalization, were reviewed. This facility provides services to both intramural and extramural births covered under a social security scheme. An approval from the

***Corresponding author:** Dr. Priyanka Gupta, Department of Pediatrics, ESIC Medical College and Hospital, Faridabad, Haryana, India. drpriyankaguptakapil@gmail.com

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Institutional Ethics Committee was granted. This being a review of existing records, a waiver of consent from parents was provided by the Ethics Committee.

The data included all neonates admitted to the NICU irrespective of any other factor(s), as also both intramural and extramural NICU admissions > 23 weeks and > 400 g in birth weight. The in-hospital mortality rate was calculated as the number of deceased neonates divided by the total number of neonatal admissions multiplied by 100. Neonates with birth weight 1000–1499 g were defined as VLBW and < 1000 g as ELBW.

The anonymized data was analyzed with SPSS version 25.0. Frequencies and percentages were used to summarize categorical variables. Pearson Chi-square test was applied to study the association of in-hospital mortality with gender, mural status (intramural or extramural), and the birth weight category. P value < 0.05 was considered significant.

RESULTS

In total, 2725 neonates were admitted to the NICU during the five years of the study period. This included both intramural and extramural births. The calendar year-wise admissions and in-hospital mortality data are described in Table 1 and Table 2, respectively. There was a steady increase in the number of admissions per year, and the absolute number of in-hospital deaths also increased proportionately [Figure 1]. Overall, there were 126 in-hospital mortality rates among a total of 2725 admissions (i.e., in-hospital neonatal mortality rate of 4.62/100); this also seemed to increase every year which could be explained by many variables like the rising proportion of lower birth weight and extramural admissions [Tables 1–3].

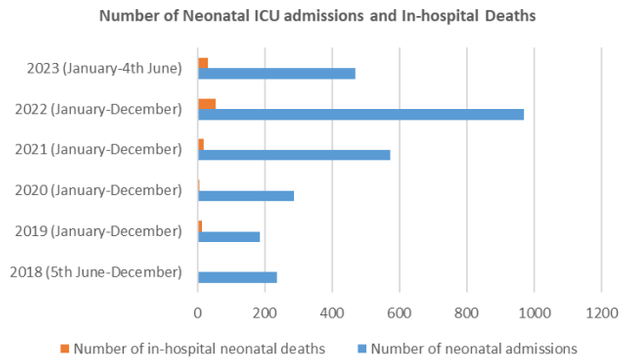

Figure 1: Number of admissions and in-hospital neonatal deaths.

Table 3 describes the in-hospital mortality rate separately for each gender, intramural and extramural births, and birth weight category. The in-hospital mortality rates among male and female neonates were comparable (4.52% vs 4.26%; P value 0.788; Chi-square test). However, the in-hospital mortality among extramural births (5.52%) was significantly higher than among intramural births (4.26%; P = 0.010). The risk of in-hospital mortality (per 100) among neonates with birth weight < 1000 g was 48.6 in contrast to this risk of 1.88 among neonates with birth weight ≥ 2500 g. Neonates with the lowest birth weight had the highest in-hospital mortality (P value < 0.00001) [Table 3]. Figure 2 depicts an exponential rise of in-hospital mortality among neonates with birth weight < 1500 g and < 1000 g [Figure 2].

Table 1: Characteristics of annual admissions to the neonatal intensive care unit

Calendar year/number of neonatal admissions	Total admissions (N = 2725)	Male N (%)	Female N (%)	Intramural births N (%)	Extramural births N (%)	Birth weight < 1000 g N (%)	Birth weight ≥ 1000–1500 g N (%)	Birth weight ≥ 1500–2000 g N (%)	Birth weight ≥ 2000–2500 g N (%)	Birth weight ≥ 2500 g N (%)
2018 (June 5 to December)	236	112 (47.46)	124 (52.54)	208 (88.14)	28 (11.86)	4 (1.69)	26 (11.02)	43 (18.22)	63 (26.69)	100 (42.37)
2019 (January to December)	186	104 (55.91)	82 (44.09)	137 (73.66)	49 (26.34)	5 (2.69)	27 (14.52)	33 (17.74)	40 (21.51)	81 (43.55)
2020 (January to December)	288	145 (50.35)	143 (49.65)	172 (59.72)	116 (40.28)	5 (1.74)	18 (6.25)	45 (15.63)	105 (30.46)	115 (39.93)
2021 (January to December)	574	295 (51.39)	279 (48.61)	411 (71.60)	163 (28.40)	8 (1.39)	51 (8.89)	107 (18.64)	164 (28.57)	244 (42.51)
2022 (January to December)	971	493 (50.77)	478 (49.23)	709 (73.02)	262 (26.98)	36 (3.71)	79 (8.14)	176 (18.13)	265 (27.29)	415 (42.74)
2023 (January to June 4)	470	267 (56.81)	203 (43.19)	309 (65.74)	161 (34.26)	16 (3.40)	57 (12.13)	75 (15.96)	108 (22.98)	214 (45.53)
Total admissions (N = 2725)	2725	1416 (51.96)	1309 (48.04)	1946 (71.41)	779 (28.59)	74 (2.71)	258 (9.47)	479 (17.58)	745 (27.34)	1169 (42.90)

Table 2: Characteristics of annual in-hospital deaths in a neonatal intensive care unit

Calendar year/ number of in-hospital neonatal deaths	Total deaths (N = 126)	Male N (%)	Female N (%)	Intramural births N (%)	Extramural births N (%)	Birth weight < 1000 g N (%)	Birth weight ≥ 1000–1500 g N (%)	Birth weight ≥ 1500–2000 g N (%)	Birth weight ≥ 2000–2500 g N (%)	Birth weight ≥ 2500 g N (%)
2018 (June 5 to December)	1	1 (100.00)	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)
2019 (January to December)	13	6 (46.15)	7 (53.85)	9 (69.23)	4 (30.77)	2 (15.38)	7 (53.85)	3 (23.08)	0 (0.00)	1 (7.69)
2020 (January to December)	7	4 (57.14)	3 (42.86)	5 (71.43)	2 (28.57)	1 (14.28)	1 (14.28)	1 (14.28)	2 (28.57)	2 (28.57)
2021 (January to December)	19	9 (47.37)	10 (52.63)	14 (73.68)	5 (26.32)	3 (15.79)	6 (31.58)	5 (26.32)	3 (15.79)	2 (10.53)
2022 (January to December)	54	26 (48.15)	28 (51.85)	32 (59.26)	22 (40.74)	20 (37.04)	9 (16.67)	5 (9.26)	11 (20.37)	9 (16.67)
2023 (January to June 4)	32	18 (56.25)	14 (43.75)	22 (68.75)	10 (31.25)	10 (31.25)	7 (21.87)	3 (9.37)	5 (15.62)	7 (21.87)
Total deaths (N = 126)	126	64 (50.79)	62 (49.21)	83 (65.87)	43 (34.13)	36 (28.57)	30 (23.81)	17 (13.49)	21 (16.67)	22 (17.46)

Table 3: In-hospital neonatal mortality (per 100) among various subgroups

Calendar year/ In-hospital mortality (per 100)	In-hospital mortality (per 100)	Males	Females	Intramural births	Extramural births	Birth weight < 1000 g	Birth weight ≥ 1000–1500 g	Birth weight ≥ 1500–2000 g	Birth weight ≥ 2000–2500 g	Birth weight ≥ 2500 g
2018 (June 5 to December)	0.42	0.89	0.00	0.48	0.00	0.00	0.00	0.00	0.00	0.00
2019 (January to December)	6.99	7.70	8.54	6.57	8.16	40.00	25.92	9.10	0.00	1.23
2020 (January to December)	2.43	2.76	2.10	2.91	1.72	20.00	5.55	2.22	1.90	1.73
2021 (January to December)	3.31	3.05	3.58	3.41	3.07	37.50	11.76	4.67	1.83	0.82
2022 (January to December)	5.56	5.27	5.86	4.51	8.40	55.55	11.40	2.84	4.15	2.17
2023 (January to June 4)	6.81	6.74	6.90	7.12	6.21	62.50	12.28	4.00	4.63	3.27
Overall, in-hospital mortality	4.62	4.52*	4.74*	4.26#	5.52#	48.65^	11.63^	3.55^	2.82^	1.88^

*P value 0.788: Chi-square test, #P value 0.010: Chi-square test, ^P value < 0.00001: Chi-square test

DISCUSSION

The overall in-hospital mortality rate has been reported to vary widely from 3.1% to 3.8% in South Africa during 2007–2008,[3] 4% in Canada during 1996–1997,[4] 5.7% in Portugal during 2004–2008,[5] 6.5% in Qatar during 2002–2006,[6] 8.1% in England during 2008–2010,[7] 9.2% in Australia during 1995–2006,[8] 14.2% in Nigeria during 2012–2013,[9] and 26–29% in Uganda in 2012.[10]

The association between LBW and poor survival outcomes is well established. Among VLBW neonates, the overall in-hospital mortality rate was reported to be 5% in New Zealand during 2009,[11] 6.5% in Korea during 2009,[12] and 12.9% in

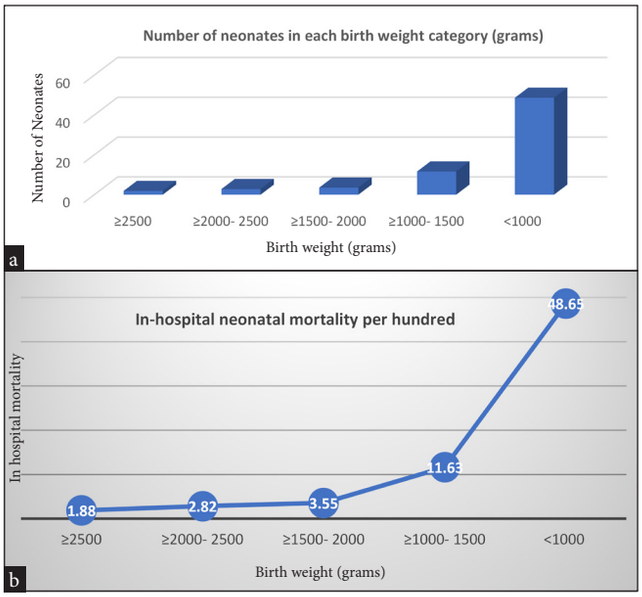

Figure 2: (a) Birth weight characteristics and (b) risk of in-hospital mortality per 100.

the United States during 2007–2008.[13] Neonatal mortality rates among ELBW were 34% in the United States during 2006–2009,[14] 46% in Australia during 2005–2010 ,[15] 30% in New Zealand during 2009,[11] 44.8% in Korea during 2009,[12] and 45.9% in India during 2006–2008.[16] This is also due to the variable study definitions of ELBW neonates. For instance, Alleman *et al.*[14] (2013) defined ELBW as 401–1,000 g and Keir *et al.*[15] (2014) defined ELBW as ≤ 500 g in their study.

National Neonatal-Perinatal Database report 2002–2003 recorded 55% mortality among ELBW neonates.[17] In a prospective study at the level III neonatal unit of a teaching hospital in Northern India during 2009–2011, only 78 out of 149 ELBW admissions (52%) were discharged alive.[18] Among other birth cohorts from India, VLBW mortality has been reported to vary from 14.8% to 40.9%.[19–21] A multicentric study by Murki *et al.*[20] (2015) evaluated the mortality of VLBW neonates (weighing 1500 g or less at birth) in 11 different neonatal units in India. Four centers admitted only intramural neonates and seven centers admitted both intra and extramural neonates. The study enrolled 1345 neonates, from which 199 (14.8%) died before discharge from the hospital.

Tripathy *et al.*[22] (2019), from Odissa, India, enrolled all 212 neonates < 1500 g born in a single hospital during 2011–2013. Mortality of ELBW babies was 61.11% and that of VLBW babies was 26.41%. The death rate in babies with a weight range of 500–749 g, 750–999 g, 1000–1249 g, and 1250–1499 g was 87.50%, 53.57%, 30.76%, and 20.97%, respectively. Another recent descriptive study at a level III NICU of a tertiary care teaching hospital in South India during January to December 2017 included 239 VLBW neonates. The mortality among VLBW and ELBW was 20.5% and 69.3%, respectively.[23]

CONCLUSION

Although this study had some limitations due to the use of historical data in which only limited variables could be studied for association with mortality, it still provides valuable local reference information. The in-hospital mortality rate and survival outcomes at discharge were comparable to other Indian studies. Neonates born elsewhere and transported to the study site for management had higher mortality than intramural births. This reminds us of the importance of timely in-utero fetus transfer among high-risk births. To keep improving neonatal care and outcomes, such audits should be done regularly to monitor progress and address any new challenges.

Authors' contributions: PG: developed the concept, design and disposition for the study; PG and DG: both were involved in collection of data and review of literature; PG prepared the initial draft of manuscript. The manuscript has been approved by both authors.

Ethical approval: The research/study approved by the Institutional Review Board at ESIC Medical College and Hospital, Faridabad, Haryana, number 134X/11/13/2023- IEC/DHR/118, dated 01st November 2023.

Declaration of patient consent: The study involved secondary analysis of anonytmized pre-existing hospital records and did not directly involve interaction with patients or their families. The requirement for obtaining informed consent was waived by the Institutional Review Board..

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Original Article

Safety and efficacy of TightRail mechanical sheath for transvenous lead extraction

Vijay Bohra[1], Naveen Aggarwal[2], G Keshavamurthy[3], Vivek Guleria[3], Balwinder Singh[1]

[1]Department of Cardiology, Command Hospital, Central Command, Lucknow Cantt, Lucknow, Uttar Pradesh, [2]Department of Cardiology, Paras Hospital, Panchkula, Haryana, [3]Department of Cardiology, Army Hospital Research and Referral, New Delhi, India

ABSTRACT

Objectives: This study aimed to evaluate the safety and efficacy of the bidirectional rotational mechanical sheath TightRail (Spectranetics Corp., Colorado Springs, CO, USA) for lead extraction in an Indian center.

Material and Methods: A prospective study of patients who underwent transvenous lead extractions (TLE) in whom manual extraction was ineffective during the period from March 2018 to March 2021.

Results: A total of 28 patients underwent lead extraction using TightRail. The mean age at the time of extraction was 62.4±18.07 years. The average duration between implantation and extraction was 8.8±4.6 years. The most common etiology was pocket site infection (78.6%), followed by lead endocarditis (7.1%), chronic pain (3.6%), and lead fracture (10.7%). In total, 53 lead extractions were attempted, with 51 procedures, resulting in a clinical success rate of 96.2%. Approximately 7.14% patients required blood transfusions, and 3.6% developed pericardial effusion. There was no incidents of cardiac avulsion, death or arrhythmias requiring cardioversion.

Conclusion: This extensive clinical study in India demonstrated that the use of TightRail provides high safety and efficacy for lead extractions across a wide range of lead age. The incidence of infectious etiology was found to be much higher in Indian patients compared to Western literature.

Keywords: Lead extraction, Pacemaker, TightRail

INTRODUCTION

In recent years there has been a surge in the use of cardiac implantation electronic devices (CIED). Concurrently, infections and lead malfunctions associated with these devices have led to a rise in transvenous lead extractions (TLE).[1] Despite advancements in technologies and techniques, TLE continues to be a challenging procedure, carrying the risk of potentially life-threatening complications.[2] Chronically implanted leads often develop fibrotic adhesions, which further complicate the TLE process. Byrd *et al.* (1999) reported that the likelihood of failure or partial removal doubles for every 3 years of implant duration.[3] Numerous studies have demonstrated the safety, efficiency, and high success rates of mechanical rotational TLE devices in extracting chronically implanted leads.[4,5] TightRail (Spectranetics Corp., Colorado Springs, CO, USA) is a bidirectional rotational mechanical sheath with a flexible shaft that ensures high coaxiality with the lead and a dilating blade that remains shielded until activated. However, there is a limited number of studies from India documenting the safety and effectiveness of mechanical TLE. This study aims to share our experience with the TightRail sheath for lead extractions in India.

MATERIAL AND METHODS

Study design and procedure

This prospective study included all patients who underwent TLE in whom manual traction was ineffective, and where the TightRail bidirectional rotational mechanical sheath was utilized, during the period from March-2018 to March 2021 in India.

A subclavian approach was adopted for all patients; if a patient was pacemaker (PM) dependent, a temporary PM was inserted via the femoral vein. The leads were carefully dissected from adhesions within the generator pocket and the fixation sutures were removed [Figure 1a]. Initially, simple

***Corresponding author:** Dr. Vijay Bohra, Department of Cardiology, Command Hospital, Central Command, Lucknow Cantt, Lucknow, Uttar Pradesh, India. aadivijay@gmail.com

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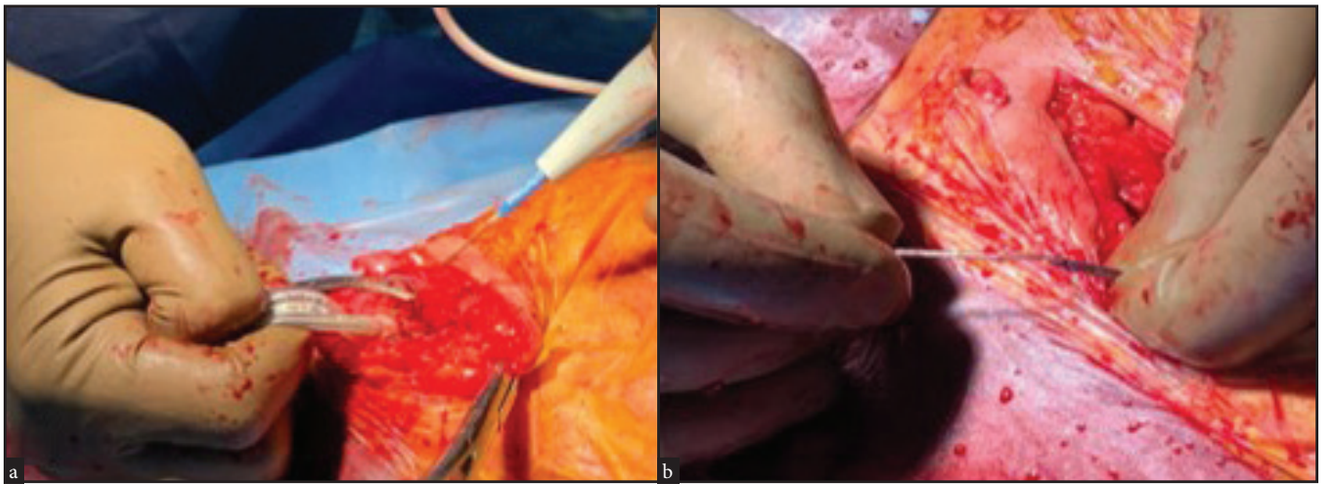

Figure 1: (a) Leads being dissected free from adhesions inside the generator pocket, (b) A lead locking stylet being introduced into the inner lumen of lead.

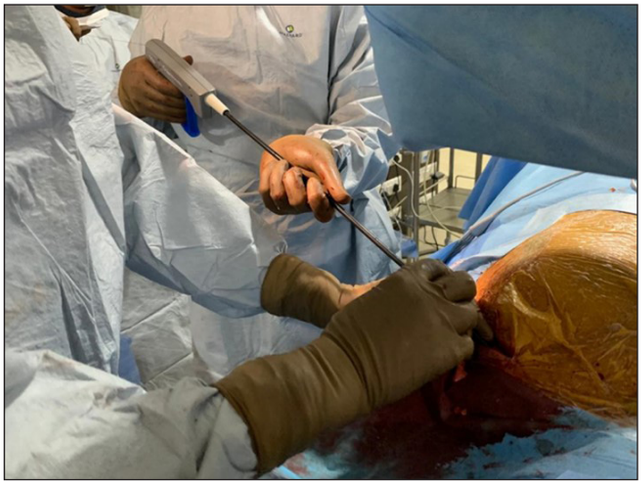

Figure 2: TightRail dilator sheath in use.

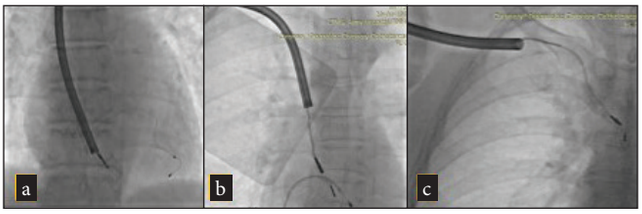

Figure 3: (a–c) Angiogram showing TightRail dilator sheath being used to extract a right ventricular lead (a) distal end of the lead, (b) SVC & RA junction, (c) at right subclavian vein.

traction was attempted in all cases. If this was unsuccessful, a locking stylet (Spectranics Corp., LLDTM lead locking device) was introduced into the inner lumen of the lead and deployed [Figure 1b]. If traction using the locking stylet did not work, the TightRail dilator sheath was then used [Figure 2]. Only cases that required this rotational dilator sheath were included in the study. The TightRail dilator sheath is composed of outer and inner shafts, with the inner shaft capable of rotating within the stationary outer shaft via a handled mechanism. The tip of the inner shaft has blades designed to cut and dilate the fibrous attachments to the leads, facilitating extraction [Figure 3].

Study endpoints

The primary endpoints of this study were to assess the rates of clinical success and complete procedural success. Clinical success was defined as the removal of all targeted leads and lead material from the vascular space, or retention of a small portion of the lead (fragment <4 cm) that did not impact the overall outcome of the procedure. Complete procedural success was defined as the removal of the targeted lead and all lead material from the vascular space, accompanied by the absence of permanently disabling complications or procedure-related mortality.[6] All procedure-related complications were noted.

Statistical analysis

Categorical variables are presented as frequencies and percentages, while continuous variables are presented as mean ± standard deviation (SD).

RESULTS

During the study period, a total of 28 patients underwent lead extraction using the TightRail bidirectional rotational mechanical extraction sheath. As shown in Table 1, there was a male preponderance, with 18 males (74%) and 10 females (36%) in the study population. The mean age at the time of extraction was 62.4±18.07 years. The average duration from

Table 1: Demography and risk factors among device extracted patients.

Variables	N = 28 patients
Age (Mean ± SD, years)	62.4±18.07
Males, n (%)	18 (64%)
Females, n (%)	10 (36%)
Diabetes mellitus, n (%)	17 (60%)
Coronary artery disease, n (%)	12 (45%)
Chronic obstructive pulmonary disease, n (%)	6 (20%)
Ejection fraction (Mean ± SD, %)	35 ± 16.3

SD: Standard deviation, N: Total number of patient in the study, n: Number of patients in the subgroups

the time of implantation to extraction was 8.8±4.6 years, with a maximum of 13.5 years and a minimum of 5 years. The indications for lead extraction in the study are presented in Table 2. Among the various etiologies, pocket site infection was the most common etiology for CIED extraction, accounting for 22 patients (78.6%).

Table 2: Indications of cardiac implantable electronic devices extraction

Etiology	N=28 patients
Pocket site infection, n (%)	22 (78.6%)
Lead endocarditis, n (%)	2 (7.1%)
Chronic pain, n (%)	1 (3.6%)
Lead fracture, n (%)	3 (10.7%)

Among the explanted CIED [Table 3], Dual chamber PM (DDDR) devices were the most common, accounting for 35.7% (10 patients). In total 53 lead extractions were attempted in this study, with 79.25% of the leads being of the screwing type. Of these attempts, 51 leads were successfully extracted, achieving a complete procedural success rate of 94.33% and a clinical success rate of 96.22%.

As shown in Table 4, the study included 20 right atrial, 28 right ventricular, and 3 left ventricular lead extractions. One patient underwent five lead extractions related to a cardiac resynchronization therapy-defibrillator (CRT-D)

Table 3: Type of extracted cardiac implantable electronic devices.

Type of CIED	Number of patients (%)	Pocket site infection	Lead endocarditis	Chronic pain	Lead fracture
DDDR	10 (35.7%)	8	1	1	-
AICD-D	7 (25%)	5	1	-	1
VVIR	6 (21.5%)	5	-	-	1
CRT-D	2 (7.14%)	2	-	-	-
CRT-P	1 (3.6%)	1	-	-	-
AICD-S	2 (7.14%)	1			1

AICD: Automated implantable cardioverter defibrillator, CIED: Cardiac implantable electronic devices, CRT-D: Cardiac resynchronization therapy – defibrillator, CRT-P: Cardiac resynchronization therapy – pacemaker, DDDR: Dual chamber pacemaker, VVIR: Single chamber pacemaker, S: Single chamber, D: Dual chamber.

Table 4: Procedural success and failure.

Type of CIED	Number of devices	Right atrial leads extracted	Right ventricular leads extracted	Left ventricular leads extracted	Total leads extracted	Leads couldn't be extracted	Leads partially extracted
DDDR	10	9	10	-	19	1	-
AICD-D	7	7	7	-	14	-	-
VVIR	6	-	5	-	5	1	-
CRT-D	2	3	3	2	8	-	-
CRT-P	1	1	1	1	3	-	1
AICD-S	2	-	2	-	2	-	-
TOTAL	28	20	28	3	51	2	1

AICD: Automated implantable cardioverter defibrillator, CIED: Cardiac implantable electronic devices, CRT-D: Cardiac resynchronization therapy – defibrillator, CRT-P: Cardiac resynchronization therapy – pacemaker, DDDR: Dual chamber pacemaker, VVIR: Single chamber pacemaker, S: Single chamber, D: Dual chamber.

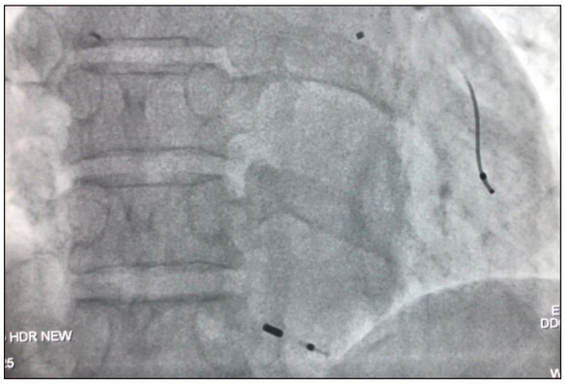

Figure 4: Partially extracted left and right ventricular leads.

Table 5: Adverse events.

Events	N (%)
Death	-
Bleeding requiring transfusion	2(7.14%)
Hematoma requiring drainage	-
Cardiac avulsion or tear requiring surgery	-
Pericardial effusion	1(3.6%)
Arrhythmias requiring cardioversion	-

upgrade from a dual-chamber automated implantable cardiac defibrillator (including 2 right ventricle, 2 right atrial, and 1 left ventricular). However, one right atrial lead from a DDDR PM implanted 11 years ago and a right ventricular lead from a V paced V sensed single chamber PM (VVVIR) PM implanted 12 years ago could not be extracted. Both the unextracted leads were of screwing type. Moreover, one patient had a cardiac resynchronization therapy-PM (CRT-P) right ventricular lead (screwing, less than 4 cm) and a left ventricular lead (more than 4 cm) that were partially extracted [Figure 4].

Two patients in this study required blood transfusion, and one patient developed moderate pericardial effusion, which was managed conservatively. There was no cases of cardiac avulsion, mortality, or arrhythmias requiring cardioversion [Table 5].

DISCUSSION

The term "lead extraction" refers to the use of specialized equipment to extract a lead that is at least one year old. In contrast, the term "lead explantation" is used for leads that are less than one year old and do not require special equipment.[2] The first documented case of lead extraction was reported in 1968. The procedure is complex, but the development of locking stylets has improved procedural success rates. The introduction of laser-assisted TLE devices has further improved these success rates.[7,8] These laser system utilize excimer lasers to break tissue bonds and vaporize the fibrotic bands surrounding the target leads. However, laser-assisted TLEs generally demonstrate lower clinical and procedural success rates compared to mechanical rotational sheaths.[9] Mechanical rotational sheaths, introduced in 2006, employ blades that effectively free chronically implanted leads. Numerous studies have shown that mechanical rotational TLE devices are efficient and have high success rates,[4,6] as well as reduced mortality risk compared to laser sheaths.

TLE has allowed us to achieve successful and safe extraction of leads in patients across a wide range of ages. The demographic profile of our study participants, including a mean age of 62.4 years and a preponderance of male patients, reflects a high prevalence of, diabetes mellitus (60%), and coronary artery disease (45%), which is consistent with findings from other TLE studies.[10]

The mean duration of lead implantation in our study was 8.8 ±4.6 years. Notably, pocket site infection and lead endocarditis constituted 85.7% of the extraction cases, which is much higher compared to other studies. In the 2010 LExICon study, infectious indications were reported in 56.9% of the extracted leads.8 Similarly, the authors of the ELECTRa study[11] (2017) and a large, multicentre Italian registry[4] (2018) reported infectious indications in 52.8% and 50.8% of lead extractions, respectively.

We achieved a complete procedural success rate of 94.33% and a clinical success rate of 96.22%. Compared with similar TLE studies, our research included patients with longer lead indwell times and reports better success rates. The rate of procedure-related major complications in the LExICon study was reported to be 0.9%.[8] Our study did not experience any major complications. Minor complications were observed in 10.74% patients, with 7.14% requiring blood transfusion due to localized bleeding and 3.6% experiencing moderate pericardial effusion. Data from the National Cardiovascular Data Registry, which included 11,304 ICD extractions, revealed that only 0.36% of patients required urgent cardiac surgery; however, these emergent procedures had a 34% mortality rate.[12] Our study is among the few in the literature documenting the use of Tightrail in Indian patients. Sawhney *et al.* (2016) reported successful TLE using TightRail in three patients.[13]

CONCLUSION

This study, the largest clinical investigation of Indian patients to date, demonstrates that the use of TightRail provides high safety and efficacy for lead extractions across a wide range of lead age. Infectious etiologies were found to be significantly more prevalent in Indian patients compared to Western literature.

Authors' contributions: VB: Conception, design, materials & method, analysis, writing literature review; NA: Critical review; GK: Supervision; VG: Material & method, analysis, writing, literature review; BS: Literature review.

Ethical approval: The research/study approved by the Institutional Review Board at Army Hospital (Research & Referral), New Delhi, number IEC-18/17, dated 23rd December 2017.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

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Task Force Report

NAMS task force report on breast cancer in India

Sudeep Gupta[1#], Atul Batra[2#], Shankar Prinja[3], Hemant Malhotra[4], T. Mohanapriya[5], Shaji Thomas[6], Sanjoy Chatterjee[7], Tanuja Shet[8], Sanjay Thulkar[9], Beela S Mathew[10]

[1]Department of Medical Oncology, Director, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, [2]Department of Medical Oncology, Dr. BR Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, [3]Department of Community Medicine and Public Health, Post Graduate Institute of Medical Education and Research, Chandigarh, [4]Sri Ram Cancer Centre (SRCC), Head of Medical Oncology, Mahatma Gandhi Medical College & Hospital (MGMCH), Jaipur, Rajasthan, [5]Professor of General Surgery, Sri Ramachandra Institute of Higher Education and Research, Chennai, [6]Department of Surgery, Lady Hardinge Medical College, New Delhi, [7]Department of Radiation Oncology, Tata Medical Center, Kolkata, [8]Department of Pathology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, [9]Department of Radiodiagnosis, Dr. BR Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, [10]Department of Radiation Oncology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India.*

[#]Both authors contributed equally to the manuscript.

EXECUTIVE SUMMARY

The National Academy of Medical Sciences (NAMS) has acknowledged the rising prevalence of breast cancer in India as a significant public health concern. In response, NAMS established a task force to prepare this report addressing this critical issue. Given that breast cancer is the most common malignancy among women and a leading cause of cancer-related deaths, there is an urgent need for a comprehensive approach to effectively manage the disease.

The task force conducted a comprehensive review of various aspects of breast cancer diagnosis and treatment across India. Highlighting the alarming rate of nearly 200,000 new cases each year,the group identified significant deficiencies in the healthcare system's ability to diagnose and treat breast cancer effectively in the country.

One of the most critical gaps identified was in diagnostic services. The availability of radiodiagnostic techniques and pathology services is concentrated in urban centers, resulting in delayed diagnosis in rural areas. The lack of modern imaging equipment and specialized pathology services in many parts of the country means that many patients do not receive the prompt and accurate diagnosis needed for effective treatment planning.

The task force observed a significant gap in the availability of treatment modalities, such as surgery, radiotherapy, and systemic treatments. While urban hospitals often have access to advanced treatment options, semi-urban and rural areas lack basic facilities and trained oncologists, severely hindering the provision of standard care. This disparity is further exacerbated by a general lack of awareness about breast cancer and its symptoms within the community, resulting in a higher proportion of patients presenting with advanced disease stages at the time of diagnosis.

To address these issues, the task force offers several recommendations. First, there is a critical need to enhance the infrastructure for diagnostics and treatment throughout India. This includes increasing the number of diagnostic mammography units and pathology laboratories equipped to diagnose cancer, as well as expanding training programs in oncology subspecialties.

Additionally, the task force emphasizes the importance of implementing nationwide screening programs focused on early detection. By increasing public awareness through comprehensive education campaigns and enhancing the accessibility of screening, the likelihood of detecting breast cancer at an earlier, more treatable stage could be significantly improved.

Furthermore, the task force advocates for a more robust integration of breast cancer care services across all levels of the healthcare system, from primary care to specialized oncology centers. This approach will ensure a continuum of care that is crucial for

Corresponding author: Dr. Sudeep Gupta, Professor, Department of Medical Oncology, Director, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India. sudeepgupta04@yahoo.com

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effective cancer management in the country. We recommend that policymakers prioritize breast cancer as a significant public health issue and support initiatives that facilitate research and development in oncology, improve healthcare access, and ensure the sustainability of cancer care programs.

The comprehensive roadmap provided by the task force outlines a coordinated effort among government agencies, healthcare providers, and community organizations to address breast cancer more effectively. With targeted policies and collaborative strategies, there is potential to significantly improve the outcomes for patients burdened by breast cancer in India through enhanced diagnostics, greater treatment accessibility, and effective public health strategies.

INTRODUCTION

According to the Global Cancer Observatory (GLOBOCAN) 2020 report, 19.3 million new cancer cases were diagnosed globally in 2020, and about 10.0 million deaths were estimated due to cancer.[1] Breast cancer emerged as the most common malignancy worldwide, surpassing lung cancer with approximately 2.3 million new cases annually, accounting for 11.7% of all cancer cases[1]. In India, about 200,000 new cases of breast cancer were reported in 2020, making it the most prevalent cancer among women in and representing nearly 13.5% of the country's cancer burden.[2] The National Cancer Registry 2020 indicates a steady and significant increase in age-adjusted incidence rates (AAR) of breast cancer across many population-based registries, and this trend is expected to continue.[2]

The diagnosis and treatment of breast cancer involve multidisciplinary teamwork, including specialists in radiodiagnosis, pathology, surgical, medical, and radiation oncology, nurses, counselors, physiotherapists, occupational therapists, and palliative care specialists. Patients suspected of having breast cancer typically present with a breast lump that is evaluated clinically. This is followed by mammography and/or ultrasound, and if findings are suspicious, a core needle biopsy is performed for pathological evaluation. Once a diagnosis is confirmed, most patients require a combination of treatments, including surgery, systemic therapies (chemotherapy, targeted therapy, immunotherapy, hormonal treatment), and radiotherapy. The choice and sequence of treatment modalities depend on the stage of breast cancer (I-IV), the pathological subtype (expression of estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor-2 [HER2]), and the patient's overall fitness to undergo these treatments. Based on the expression of these three markers, breast cancer is classified as hormone receptor (ER and/or PR) positive, HER2 positive, and triple-negative (ER, PR, and HER2).

Breast cancer is treatable and highly curable when diagnosed in its early stages. Significant advances in systemic treatment have improved survival rates for patients with metastatic breast cancer (stage IV); however, it remains an incurable disease. The 5-year overall survival rate are 95% for stage I, 92% for stage II, 70% for stage III, and only 21% for stage IV patients. In India, the survival rates for patients with breast cancer are lower compared to Western countries due to several factors, including the late stage presentation, delayed initiation of definitive management, and inadequate or fragmented treatment.

Therefore, there is an unmet need to improve outcomes for patients with breast cancer in India. This requires an integrated, multipronged approach that encompasses early diagnosis, timely referral, and affordable access to standardized multimodal treatment. This white paper, developed under the auspices of the National Academy of Medical Sciences, outlines several strategies to address these challenges.

BACKGROUND

Breast cancer poses a significant public health challenge in India, with its prevalence steadily rising over the years. Recognizing the urgent need for comprehensive strategies to address this issue, the National Academy of Medical Sciences (NAMS) has undertaken a proactive initiative. In alignment with its commitment to promoting health equity and advancing medical interventions, NAMS has constituted a task force to develop guidelines for stakeholders involved in combating breast cancer across the Indian population. The NAMS has establishment a task force on breast cancer which comprises experts from various medical fields, research institutions, and public health agencies. This task force is charged with the crucial mandate of drafting a white paper intended to serve as a comprehensive document that provides insights and recommendations for policymakers to enhance intervention activities related to breast cancer in India.

TERMS OF REFERENCE (TORS) FOR THE TASK FORCE

The main objectives of this task force include the following:

1. To identify the current status of breast cancer in the country.
2. Identify the deficiencies which need to be addressed.
3. To recommend measures for improving the interventions in the area of breast cancer.

METHODOLOGY

An initial online meeting of expert members was held on 08/02/2024, where the objectives and broad framework of the white paper were discussed and agreed upon by the members of the task force. The task force conducted a thorough examination of data and peer-reviewed publications relevant to their specialties for breast cancer. Through this process, consensus was reached on significant observations and recommendations, taking into account the diverse healthcare services and socio-cultural and economic contexts prevalent throughout the nation. The initial draft was compiled from inputs provided by several experts involved in the management of breast cancer, and consensus was achieved by circulating the draft among task force members for review and feedback. Subsequent modifications were made based on the suggestions received, and all members have approved the final version of the draft. This iterative process ensured that the document was comprehensive and reflective of the collective expertise and perspectives of the task force members.

OBSERVATIONS/CRITICAL REVIEW

Current situation in the country

Epidemiology

According to the GLOBOCAN 2020, 19.3 million new cancer cases were diagnosed globally in 2020, and about 10.0 million died.[1] These cancer cases (excluding non- melanomatous skin cancers) are estimated to rise to 26 million in 2040, according to the report. Current cancer incidence rates are three times higher in high-income countries (HIC) as compared to low- and middle-income countries (LMIC).[3] However, LMICs are expected to be largely responsible for the increase in cancer incidence worldwide over the next 50 years.[4] Sixty percent of the global population resides in Asia, which accounts for 50% of cancer cases and 58% of cancer-related deaths. Furthermore, India ranks third in accounting for cancer cases, following China and the United States of America.[5] The projected cancer burden in India is estimated to reach 2.08 million by 2040, representing a 57.5 % increase from 2020.

Breast cancer is the most common malignancy among women globally and in India. Approximately 200,000 new cases were reported in 2020, and it is expected that 232,832 cases will be diagnosed in 2025.[2] A higher incidence of breast cancer has been reported in urban population-based cancer registries (Hyderabad, Delhi, etc.) compared to rural registries (Barshi, Osmanabad, etc.). Among the data reported by hospital-based cancer registries, most diagnosed cases of breast cancer in females showed locoregional spread (57.0%), followed by localized disease (29.0%) and distant metastasis (10.3%).[2] A recent study from Mumbai (Tata Memorial Centre) and Pune analyzed 912 patients diagnosed with breast cancer. The median age at diagnosis was 47 years (range, 23 to 85 years); 63.2% had pathologically confirmed axillary lymph node involvement, and 54% of patients had ER-positive disease. Approximately one-quarter of patients had HER2 - positive disease and, triple-negative breast cancer (TNBC) was present in 266 (29.1%) patients.[6]

Diagnostics: Radiodiagnosis and pathology

Radiodiagnosis imaging has two main categories of indications: Screening the healthy population for early detection of breast cancer and diagnostic breast imaging. The latter involves evaluating of women with breast complaints to determine whether the findings are cancerous or non-cancerous. Imaging is also required for clinical staging, treatment planning for breast cancer, and monitoring individuals who have been treated for breast cancer.

Mammography: Mammography is the primary imaging modality for breast cancer. Other modalities, such as ultrasound, MRI, and positron emission tomography - computed tomography (PET-CT), serve as supplementary tools to mammography in specific contexts. Mammography screening has been extensively studied and is a time-tested method proven to reduce breast cancer-related deaths in certain age groups. However, it is a resource-intensive approach, predominantly available in a few developed countries worldwide.

Currently, there is no structured population-based mammography screening program in the country and it is unlikely to be feasible in the foreseeable future due to its resource-intensive nature and the large population. For example, the number of mammography machines in India is only about 5% of that in the USA, despite India having a population more than three times that of the USA. A negligible proportion of women population in India undergo self-volunteered and self-funded periodic mammography examinations as a part of regular health check- ups in private hospitals for early detection of breast cancer, known as opportunistic screening. However, the protocol and standard of these screening are highly variable, and no precise data on the number of examinations or their benefits are available. A few small-scale, sporadic mammography screening studies have been conducted in India, sometimes utilizing mobile machines. Some of these are single-round assessments that show prevalence rather than incidence of breast cancer, and others lack long-term follow-up or mortality data.

As population-based mammography screening is not feasible in our country, promoting awareness about breast cancer and its early symptoms is crucial. The benefits of seeking immediate medical attention and the importance of early-stage diagnosis should be emphasized. While self-breast examination and clinical breast examination have been studied in other countries, they have not proven effective in reducing breast cancer-specific mortality. However, a long-term population screening study conducted by Tata Memorial Hospital (TMH), which utilized clinical breast examination by trained healthcare workers, demonstrated that this approach can help downstage the disease at presentation and may reduce mortality to some extent in specific age groups.[7] This approach can be further explored on a large scale.

In India, breast imaging is primarily employed to evaluate women presenting with breast-related complaints, such as pain, lumps, and/or discharge, which is referred to as diagnostic breast imaging. This approach is useful for diagnosing breast diseases, cancer, or non-cancer. For women suspected of having breast cancer, imaging aids in confirming or ruling out breast cancer. If imaging indicates the presence of cancer, it is also used to obtain an image-guided biopsy for pathological confirmation. Once breast cancer is confirmed, imaging is used for staging, deciding on management, accessing the response to non-surgical management, and detecting recurrence in treated patients.

In pathology services, the following observations have been made:

Routine histopathology of breast cancer: The primary issue with pathology reporting of breast cancer in India is the lack of reporting essential features in histopathology reports and improper documentation of biomarkers. In a study conducted by the National Cancer Grid External Quality Assurance Scheme (NCGEQAS) at Tata Memorial Hospital in 2019, slides from a breast cancer excision were circulated for minimum data set reporting (unpublished observations). Overall, 89 out of 94 centers (95%) provided a concordant diagnosis, while five centers (05%) rendered a discordant diagnosis of invasive lobular carcinoma. The most significant challenges were observed in reporting lymph node status and margin assessments.

Biomarker reporting: The reported positivity rates for hormone receptors in breast cancer from India vary from 32% to 70%, indicating heterogeneity in testing practices across the country.[8] According to American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) recommendations, key reasons for the underestimation of hormone receptors include delayed transport of excised specimens, delayed fixation, and insufficient monitoring of cold ischemia time. Pathologists often hesitate to document delays in specimen transport due to concerns about potential of persecution by patients or surgeons. While poor fixation is the main issue for ER/PR testing, HER2 results are affected by the use of non- in vitro diagnostic (IVD) or non- Food and Drug Administration (FDA)-approved antibodies and the lack of automated platforms nationwide. The reported positivity for HER2 in breast cancer ranges from 16% to 30%.[9,10] In the most recent NCGEQAS run in 2024 for HER2 immunohistochemistry, only 63 out of 172 participating centers (36.6%) centers used the FDA-approved Ventana 4B5 antibody on the Ventana machine, indicating significant heterogeneity in the use of the FDA-approved tests in laboratories. (Unpublished observations). The NCGEQAS experience has recently been published highlighting the increasing use of FDA-approved HER2 testing in consistently participating centers, leading to improved laboratory performances.[11] Interpretative errors in the HER2 test are common in centers lacking molecular diagnostic facilities, resulting in pressure on these services to perform more HER2 tests than usual. For the programmed death-ligand 1 (PDL1) assay in triple-negative cancer, pembrozulimab is the recommended drug, with the companion test being the PDL22C3 antibody performed on a Dako link48 machine. Most laboratories in India have Ventana machine installed due to the availability of numerous FDA approved antibodies, making the use of PDL22C3 antibody on a Dako machine impractical. In a NCGEQAS exercise, only 25 out of 118 laboratories that perform immunohistochemistry volunteered for this cycle. All laboratories except one used the VENTANA SP263 for PDL1 testing, indicating a lack of capability to perform the other test. Only one laboratory utilized the Dako 22C3 for this purpose. Despite this, overall test performance was commendable, with only 3 out of 19 centers reporting discordant results. While this is encouraging, it suggests that most centers in India are not equipped to conduct PDL1.

Routine molecular testing in breast cancer for biomarkers: The primary biomarker regularly tested in breast cancer is HER2, using fluorescent in situ hybridization (FISH). However, this testing requires the establishment of molecular pathology services within Institutes and the presence of trained personnel. As HER2 testing has become mandatory, complex profiles are emerging. However, the practice of separating FISH from surgical pathology by sending samples to reference laboratories carries a risk of errors. Options and alternatives for FISH are discussed below.

Advanced molecular diagnostic and surrogates: In addition to ER, PR, and HER2, several other tests guide therapy decisions in breast cancer, including PI3k and ESR1 mutations in hormone-positive cancers, homologous recombination deficiency (HRD) in triple-negative breast cancers, and oncotype Dx for luminal cancers. Biomarkers that predict the need for chemotherapy in hormone-positive early breast cancer are essential; clinicians typically consider factors such as age, nodal status, Ki67, and gene expression profiling, with OncotypeDx being the standard choice recommended by most international guidelines. However, for economic reasons, many clinicians in India rely on alternate tests like Ki67 and CanAssist. There is insufficient evidence to confirm that high Ki-67 levels predict the efficacy of adjuvant chemotherapy or that patients with Ki-67-low breast cancer do not benefit from it.[12] Challenges associated with Ki67 include varying cut-off values, different counting methods, and significant effects from delayed fixation.[13] A study at our institute found a significant difference in Ki67 values between breast cancer samples fixed immediately and those fixed after 1 to 6 hours. Lin's concordance correlation coefficient (0.5350) indicated poor agreement between the two fixation times, highlighting the need for oncologists to be aware of how delayed fixation impacts Ki67 results. In a Delphi survey of oncologists in India, 84% preferred CanAssist, while 80% favored OncotypeDx for risk stratification.[14] CanAssist utilizes five immunohistochemistry biomarkers—CD44 (a stemness marker), N-Cadherin and pan-Cadherin (cell adhesion and invasion markers), and ABCC4 and ABCC11 (drug exporters)—which are not proliferation markers but have shown some ability to predict better outcomes compared to traditional factors.[15] While these tests provide better valuable information, it is essential to critically evaluate their scientific basis and the data behind them as these are often commercially driven. Looking towards IHC-4 translation and other gene-based options would be a more robust choice in India. HRD testing is available through several commercial platforms, including the gold standard Myriad myChoice CDx test for patients who can afford. However, HRD testing requires a NextSeq or HiSeq platform which is not feasible in many laboratories at present. Limited panel testing using MiSeq is the preferred method for Pi3K and BRCA mutation testing as an alternative to HRD tests in Indian patients. Most molecular tests are outsourced to commercial laboratories due to lack of resources and financial backing in institution-based laboratories. Consequently, effective marketing strategies from commercial laboratories have hindered the development of molecular diagnostics in even large cancer centers.

Treatment: Surgery, systemic treatment and radiotherapy

Surgery: The proportion of patients diagnosed with breast cancer at a younger age is notably higher in India compared to the high-income countries. In some studies, the median age of breast cancer presentation in India was found to be just 45 years; this is in sharp contrast to the USA, where the median age of presentation was 61 years.[16] Additionally, patients in India tend to present with later stage disease compared to the West. More than 60% of patients in India present at Stage 3 or 4, while around 60% of patients in the USA are diagnosed at in-situ or Stage 1.

Delay in seeking healthcare: More than 50% of patients in India experience a delay of over 3 months before seeking medical care.

Delayed definitive management/inadequate treatment: Regarding 5-year overall survival rates, studies report 95% for stage I, 92% for stage II, 70% for stage III, and only 21% for stage IV patients.[10,16] The survival rate for breast cancer patients in India is lower compared to Western countries due to factors such as earlier age at onset, late stage presentation, delayed initiation of definitive management, and inadequate or fragmented treatment.[17,18]

Limited Research Output: Despite the high burden of breast cancer in India, there is a lack of indigenous research contributing to global knowledge and innovation in breast cancer treatment. The high prevalence of poor-prognosis early-age breast cancer, despite the presence of low-risk hormonal profiles (early age at first childbirth, multiple pregnancies, prolonged breastfeeding, low prevalence of nulliparity, limited use of hormone replacement therapy, etc.), suggests the likely influence of as yet undetermined genetic, dietary, or environmental factors. However, due to the enormous patient load, specialists often lack time to dedicate to research.

Systemic therapy: Systemic therapy is a crucial component of modern breast cancer treatment, delivered by medical oncologists. It includes a range of drugs, such as chemotherapy, endocrine therapy, HER2 targeted therapy, other targeted therapies, and immunotherapy (primarily immune checkpoint inhibitors). Many generic, affordable versions of these drugs are available and are included in central and state health schemes in India. However, targeted therapies and immunotherapy are often expensive and not easily accessible due to financial constraints faced by the majority of breast cancer patients in the country. The following sections address some of the issues and potential solutions to enhance access to essential breast cancer drugs, as well as the infrastructure and expertise needed to administer them to eligible patients.

Radiotherapy: Radiotherapy of the remaining breast post-surgery is an integral part of the breast cancer treatment, delivered by radiation oncologists. It can result in up to 50% improvement in local control, which translates to saving approximately one life for every four local controls achieved.[19] In patients with node-positive cancer, post- mastectomy radiotherapy leads to a reduction of up to 69% in the relative risk of loco-regional recurrence, preventing one death for every 1.5 loco-regional recurrences avoided over 20 years.[19,20] The effectiveness of this treatment has been established across various tumor sizes and grades, regardless of the nodal burden. Additionally, regional nodal radiotherapy has been found to offer further benefits for patients with more advanced cancers. Notably, studies from India demonstrate comparable benefits of radiotherapy to those seen in stage-matched patients from Western data, confirming its effectiveness amongst Indian women.[21,22]

Hospital-Based Cancer Registry (HBCR) data revealed that 57% of patients presented with loco-regional disease, while 29% present with localized cancer.[2] Consequently, it is expected that over 85% of breast cancer patients will require radiotherapy during their lifetime, with the majority being potentially curable. However, many patients in India face a significant burden of locally advanced, incurable breast cancers requiring optimal symptomatic control.[16] For these patients, radiotherapy offers effective and durable symptom management, helping to maintain their quality of life while also improving objective response rates to the treated breast tumor.[23]

Current infrastructure, facilities, technologies, policies, programs, etc., in the country in the context of the problem/health issue

Human resource and healthcare system

The landscape of cancer care in India has seen significant advancements in treatment modalities and preventive measures. Human resources are crucial at various levels of healthcare delivery, as illustrated in Figure 1.

Through a multifaceted approach that includes awareness campaigns, wellness promotion, and targeted screenings-especially for women over 30 years of age at the community level, the initiative aims to reduce the cancer burden of cancer by identifying cases at earlier stages when treatment outcomes are more favorable.[24] Accredited Social Health Activists (ASHAs) play a pivotal role in this effort by gathering crucial information on breast cancer risk factors using community-based assessment checklists. This grassroots strategy helps identify individuals at higher risk, enabling timely interventions and referrals for further evaluation.

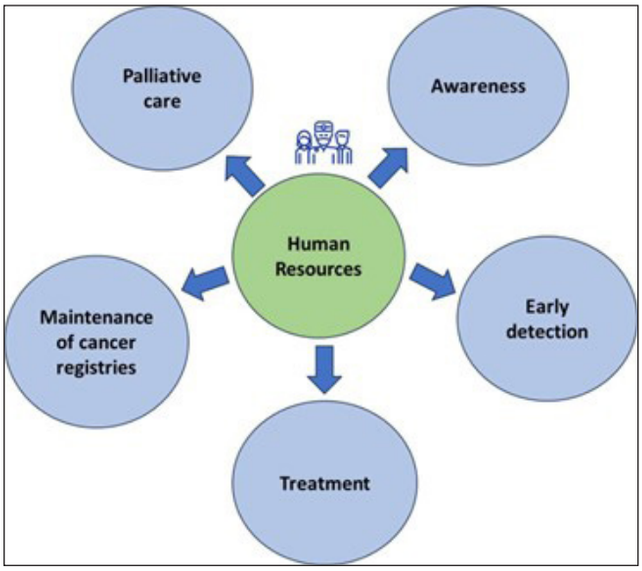

Figure 1: Human resources for cancer care.

At primary healthcare units, a diverse group of healthcare professionals, including community health officers, auxiliary nurse midwives, medical officers, and staff nurses, collaborate to conduct clinical breast examinations. Suspected cases are promptly referred for comprehensive evaluation, ensuring no potential malignancies are overlooked. Additionally, these frontline healthcare providers offer vital follow-up and palliative care services throughout patients' treatment journey, emphasizing holistic support and patient-centered care.[24]

The extensive reach of the Ayushman Arogya Mandir initiative is noteworthy, with over 1,63,402 operational centers by the end of 2023. Within these centers, primary healthcare teams have conducted a staggering 10.04 crore breast cancer screenings, underscoring the program's commitment to widespread outreach and accessibility.[25] Furthermore, the integration of yoga sessions highlights a holistic approach to wellness promotion and supportive care, addressing both physical and psychosocial needs.

In parallel, the establishment of non-communicable disease (NCD) clinics at community health centers (CHCs) and district hospitals under the national program for control of non-communicable diseases further strengthens the continuum of care. Nurses and doctors stationed at these facilities play a crucial role in facilitating early diagnosis, managing complicated cases, and coordinating follow-up chemotherapy at the district level.[26] The treatment of breast cancer is concentrated at tertiary-level health facilities and specialized cancer care centers staffed with oncologists. The staff provides comprehensive cancer care, conducts training of health personnel, maintains cancer registries,

and generates evidence through rigorous research activities. However, despite these significant strides, challenges persist in ensuring equitable access to breast cancer screening and treatment services across India.

A growing proportion of cancer cases is directly related to the increased demand for cancer care services. For instance, the number of patients estimated to need first- course chemotherapy in LMICs is projected to rise from 6·2 million to 10·0 million annually between 2018 and 2040, accounting for approximately 63%-67% of the global estimated patients requiring first-course chemotherapy[27] [Figures 2 and 3].

Similarly, the projected number of patients diagnosed with cancer requiring radiotherapy globally is expected to reach 12 million by 2035.[28] The estimated number of required radiotherapy fractions is projected to exceed 204 million worldwide by that same year, with India accounting for 18 million of those required fractions.

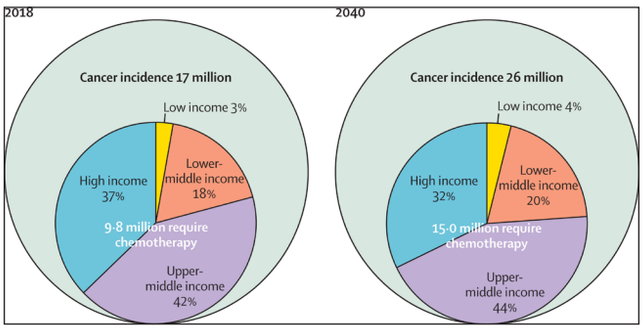

Figure 2: Growth in cancer incidence and chemotherapy demand between 2018 and 2040 stratified by income level. Source: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30163-9/abstract

The proportion of cancer patients receiving treatment for different types of cancer varies significantly worldwide and is lower in many LMICs.[27] These disparities may arise from issues related to access and availability of cancer care services. Inadequate service delivery results from a confluence of factors, including lack of resources for timely and accurate cancer diagnosis, poor infrastructure to support cancer care, a shortage of trained health personnel, and restricted access to medications due to high costs and supply-chain issues.[27] In India, cancer care is primarily concentrated in tertiary hospitals and major cancer centers in urban areas. However, among other factors, inadequate infrastructure and a lack of human resources make it challenging to provide high-quality cancer care.[29]

Existing health system framework for the provision of cancer care in India

To address the threat of cancer in India, the Government of India has established 599 NCD Clinics at the district level and 3,274 NCD Clinics at the community health center level under the NPCDCS. Additionally, the flagship national insurance program, Ayushman Bharat Pradhan Mantri Jan Aarogya Yojana (ABPM- JAY), was launched.

In 2018, India embarked on an ambitious path to enhance its health system and provide quality cancer care. At the population level, initiatives under the National Health Mission (NHM) were rolled out in over 215 districts to prevent, control, and screen for common NCDs (diabetes, hypertension, and common malignancies such as oral, breast, and cervical cancers). Screening for oral, breast, and cervical cancers is a critical component of service delivery under *Ayushman Arogya Mandirs* (formerly known as Health and Wellness Centers) implemented at the primary

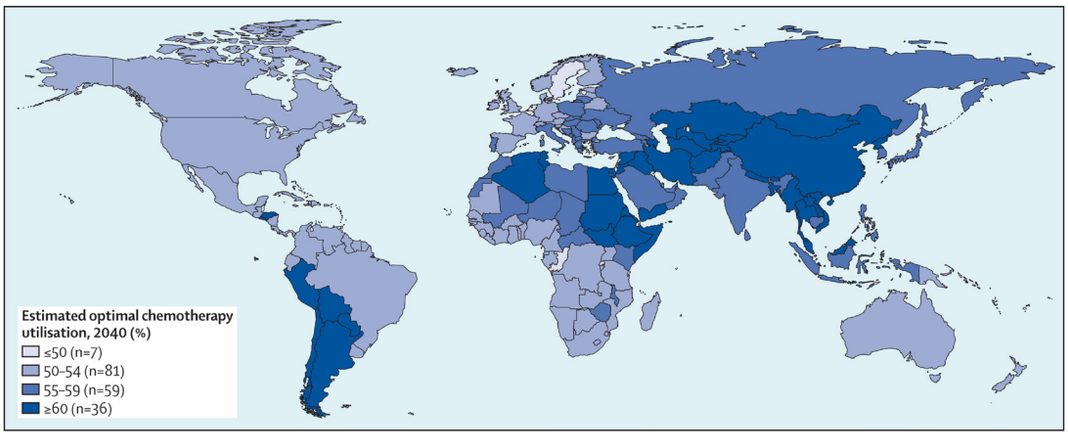

Figure 3: Estimated optimal chemotherapy in 2040 by country. Source: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30163-9/abstract

health care level [Figure 4]. Other initiatives, such as promoting healthy eating and regular physical activity, aim to encourage healthier lifestyles. The central government is also implementing the strengthening tertiary care for cancer scheme to improve cancer care facilities at the tertiary level. By 202, six State Cancer Institutes were operational, and the establishment of 19 additional State Cancer Institutes (SCIs) and 20 Tertiary Care Cancer Centers (TCCCs) has been approved.[30] Furthermore, oncology is a focus area for the new AIIMS facilities and many upgraded institutions under the Pradhan Mantri Swasthya Suraksha Yojana (PMSSY). In Indian cities like Bhopal, Patna, Bhubaneswar, Jodhpur, Raipur and Rishikesh the new All India Institute of Medical Sciences (AIIMS) are fully functional.[30]

Diagnostics: Radiodiagnosis and pathology

Radiodiagnosis: This includes both machines and manpower. Currently, there are approximately 3000 mammography units in India with almost all located in metro or tier 1 cities, primarily in private hospitals, diagnostic centers, or labs. Given that there are over 200,000 new cases of breast cancer each year in India, the current availability and accessibility of mammography facilities are highly inadequate for timely diagnosis and treatment. Additionally, significant variations in the quality, efficacy, and reliability of mammography machines further complicate the situation. Mammography is highly sensitive to quality control, and is the most regulated and legislated imaging modality in developed countries. In India, AERB oversees the radiation safety of these machines. However, there is no central regulatory authority or legislation to ensure quality assurance and clinical standards. Moreover, less than 10% of these machines are state-of- the-art full-field digital mammography machines that meet contemporary international standards, while the remainder are mostly suboptimal or outdated models.

Ultrasound: Ultrasound is the second most used breast imaging modality typically serving as a supplement to mammography, especially in younger women who often have mammographically dense breast tissue. In such cases, mammography is less sensitive for detecting breast cancer. However, breast ultrasound can be an effective primary modality of breast imaging in women under 35 years of age. It is also useful for diagnosing breast diseases, including cancer, in women presenting with symptoms when mammography is unavailable. Furthermore, ultrasound is the most commonly used modality for obtaining image-guided breast biopsy to establish or rule out the pathological presence of breast cancer. Limitations of ultrasound include higher operator dependence, less reproducibility, and comparatively lower sensitivity in detecting very small cancers. While it has not been extensively studied for population or community screening for breast cancer, ultrasound equipment and the expertise to use it are widely available across India, including in tier 2 and tier 3 cities, as well as in government and private centers, unlike the limited access to mammography. It has also been recognized that the average age of breast cancer onset in India is lower than that in Western countries. Given the established effectiveness of ultrasound in younger women and its widespread availability, it has significant potential to be used for early breast cancer detection. However, large studies are needed to generate data to support this hypothesis.

Breast MRI is the most sensitive breast imaging modality for diagnosing breast cancer, but it is also the most expensive and time-consuming. Consequently, it is used only in specific

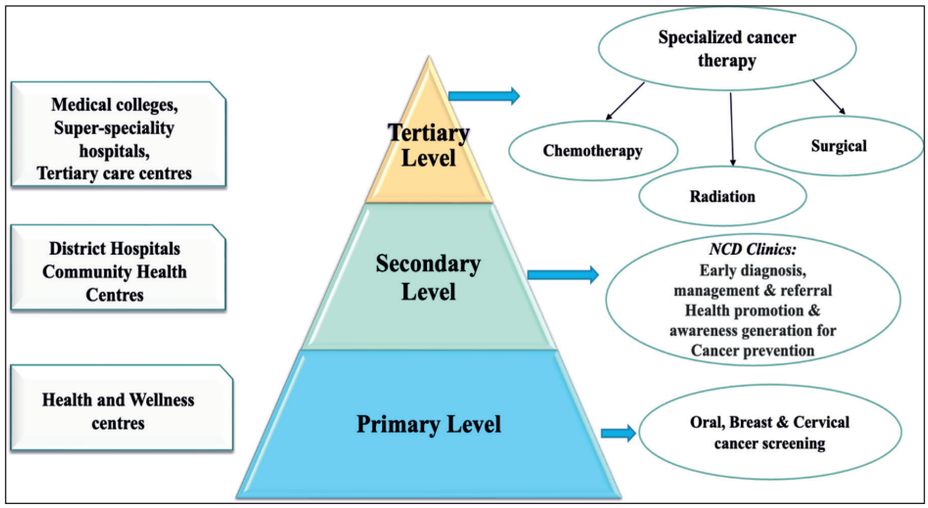

Figure 4: Indian health system framework – cancer care. NCD: Non-communicable disease

situations, such as for women with equivocal mammograms and women with a genetically high risk of breast cancer. It can also serve as a problem-solving imaging modality. Given its specialized indications, MRI are very specific and not widespread, and it may not be a priority in the context of public health. However, the necessary equipment and expertise are available in highly specialized tertiary care centers to meet its requirements.

Nuclear medicine techniques, such as radionuclide scans for breast scans or bone scans for the detection and staging breast cancer, have been commonly used in the past. However, with the advent of PET-CT and its growing availability in major cities, it has become the preferred modality as a single test for staging workup. It is also useful to monitor treatment responses in patients with metastatic breast cancer. Occasionally, PET-CT used in cases of small and early-stage cancer, even though most guidelines do not recommend it for those situations. Therefore, judicious use of this modality needs to be encouraged, as it is quite expensive.

Imaging-guided breast biopsy and other interventional procedures are essential components of breast cancer diagnosis and management. In majority of the cases, accurate diagnosis of breast cancer is mostly made on ultrasound-guided biopsy. In specific situations, mammography-guided stereotactic breast biopsy or MRI-guided breast biopsy is utilized. In addition to biopsies, pre-therapy tumor marker clip placement or pre-operative hook-wire localization of non-palpable breast cancers, performed by a team of specially trained radiologists and radiographers, are crucial procedures in modern breast cancer treatment protocols.

With the insufficient infrastructure for modern breast imaging facilities, which are primarily available only in large centers, it is crucial to optimize their use. Both under and over-utilization should be avoided. To achieve this, primary care doctors may be regularly updated on recent developments and best practices for using breast imaging techniques, including nuclear medicine. Ordering mammograms for very young women or too frequently should be avoided. Similarly, the overuse of MRI or PET-CT should be discouraged.

Manpower training for breast imaging: Mammography requires specially trained personnel, which includes radiologists and technologists (radiographers), who are well-versed in mammography. Mammography is included in the curriculum of post- graduate teaching courses, such as Doctor of medicine (MD) or Diplomate of National Board (DNB) in Radio-diagnosis across the country. However, state of the art mammography machines are available only in a few premier government and private medical colleges. Many medical colleges either have outdated or non-functional mammography machines, or they lack them entirely. Notably, some reputed government medical colleges in the national capital do not have functional digital mammography facilities. The situation makes it challenging to train and produce an adequate number of radiographers or radiologists specialized in mammography.

In the last decade, awareness of the need for specialist radiology manpower has increased. Specialty training for breast radiologists and radiographers is offered at a few tertiary care institutions like AIIMS, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, and other medical institutes of national importance, as well as at a few corporate hospitals that provide post-doctoral fellowship courses in breast imaging or women's imaging. While these institutions produce quality human resources the number generated every year remains highly inadequate. Given the limited expertise in modern breast imaging facilities, which are mostly concentrated in premier hospitals, encouraging short observer ships or basic training for radiologists from peripheral centers at nearby tertiary care centers may be beneficial.

Qualified breast radiologists who have been trained in premier Indian institutes, as well as those from international specialty centers practicing in India, came together to form the Breast Imaging Society of India about ten years ago. This professional society has actively conducted regular conferences and workshops to constantly update the knowledge and skills of breast imaging and interventions for radiologistsand radiographers across the country. These efforts have positively contributed to addressing the challenges in the field.

Pathology: Current infrastructure, facilities, technologies, policies, programs, etc., in the country concerning the health issue reveal that basic pathology services are still primarily concentrated in cancer institutes in India, but cancer surgeries are performed throughout the country, and the sample is transported to a "state-of-the-art" pathology center for diagnostics. However, the damage done by delayed fixation in formalin cannot be undone, and this is the root problem of many failed or discordant biomarkers in the country. Additionally, the FDA-approved antibodies are expensive, prompting laboratories that provide immunohistochemistry-based diagnostics to use non-IVD (in vitro diagnostic) antibodies, which can exhibit batch-to-batch variation. Automation in immunohistochemistry ensures uniformity due to locked protocols; however, these systems are complex and high maintenance and only available in centers with high workloads. Most international antibody companies are promoting the licensing of ready-to-use antibodies due to

the issue of dilution impacting test results. This, coupled with licensing norms introduced in the country for two years, has greatly reduced the quality of immunohistochemistry in the country.

Treatment, including surgery, systemic treatment, and radiotherapy

Surgery: Infrastructure and Facilities: India has been expanding its healthcare infrastructure, including cancer treatment facilities, across the country. Many hospitals now feature dedicated breast cancer clinics with state-of-the-art diagnostic and treatment capabilities.

Some notable cancer treatment centers in India include Tata Memorial Center in seven states in India including Mumbai, the AIIMS in New Delhi, and various regional cancer centers throughout the country.

Advanced breast cancer diagnosis and treatment technologies, such as digital mammography, ultrasound, MRI, PET-CT scans, and molecular profiling, are increasingly available in urban areas and major healthcare institutions.

Adopting telemedicine and teleconsultation services has also facilitated access to expert opinions for patients in remote areas.

The Indian government has initiated several policies aimed at improving cancer care, including breast cancer. For instance, the NPCDCS seeks to strengthen infrastructure, human resources, and screening programs for the early detection and management of cancer.

The government has also introduced various health insurance schemes to financially assist cancer patients with treatment expenses.

Various awareness and screening programs for breast cancer have been implemented at both national and regional levels. These programs aim to educate women about breast health, promote regular screenings, and facilitate early detection. NGOs and advocacy groups also play a crucial role in conducting awareness campaigns, providing patient support services, and advocating for policy changes to enhance breast cancer care.

Systemic treatment: Systemic treatment includes chemotherapy, targeted therapy, hormonal therapy, and immunotherapy, forming an integral part of multimodal treatment. The aim of administering systemic treatment is to control micrometastasis in early-stage diseases and prolong the survival of metastatic diseases. The following section discusses the absolute or relative benefit of administering such therapies.

Chemotherapy: In (neo)adjuvant settings, anthracyclines (doxorubicin or epirubicin) and taxanes (paclitaxel or docetaxel) form the backbone of chemotherapy. In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, the administration of an anthracycline-based chemotherapy regimen reduced the risk of recurrence from 47% to 39% (relative risk [RR], 0.73; 95% confidence interval [CI], 0.68-0.79), and the risk of breast cancer mortality decreased from 36% to 29% (RR, 0.79; 95% CI, 0.72-0.85) at ten years compared to no adjuvant treatment.[31] Furthermore, the addition of a taxane agent reduced the 10-year risk of recurrence from 39% to 36% (RR, 0.87; 95% CI 0.82-0.93) and the risk of breast cancer mortality from 28% to 24% (RR, 0.88; 95% CI, 0.82-0.95).[32] The benefits of additional taxane were independent of age, nodal status, tumor size, tumor grade, and estrogen receptor status.

In certain clinical scenarios, a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) is used, providing an advantage similar to that of four cycles of anthracycline-based chemotherapy.[31]

The addition of carboplatin in the TNBC subtype has been debated over the last few decades. However, a recently reported large randomized controlled trial from TMH, Mumbai, and a meta-analysis support the use of carboplatin in younger patients.[33] The benefit was limited to those patients aged ≤ 50 years, who showed an 11.2% increase in overall survival, with rates of 65.9% vs 77.1%, respectively (hazard ratio [HR] =0.611; P=0.003).[34] Additionally, the use of capecitabine in patients with stage I-III TNBC who have residual disease after receiving neoadjuvant chemotherapy improved disease-free survival to 69.8% in the capecitabine group compared to 56.1% in the control group (HR, 0.58; 95% CI, 0.39 to 0.87), and the overall survival rate to 78.8% versus 70.3% (HR, 0.52; 95% CI, 0.30 to 0.90).[35]

Endocrine therapy: Tamoxifen for five years is associated with a decreased risk of breast cancer recurrence (24.8% vs 37.7%; RR, 0.63; 95% CI, 0.58-0.68) and mortality due to breast cancer (23.9% vs 33.1%; RR, 0.70; 95% CI, 0.64-0.75).[36] Extending tamoxifen by another five years further reduced the recurrence by approximately 4% and breast cancer mortality by 3%.[37] Aromatase inhibitors (anastrozole, letrozole, exemestane): Aromatase inhibitors are preferred over tamoxifen for adjuvant hormonal therapy in postmenopausal women with hormone-receptor-positive breast cancer. In the comparisons of aromatase inhibitors versus tamoxifen, recurrence RRs significantly favored aromatase inhibitors during years 0-1 (RR, 0·64; 95% CI, 0·52-0·78) and 2-4 (RR 0·80, 0·68-0·93), though not significantly thereafter. The 10-year breast cancer mortality was lower with aromatase inhibitors than with

tamoxifen (12·1% versus 14·2%; RR, 0·85; 95% CI, 0·75-0·96).[38] Furthermore, no significant difference has been demonstrated among the various aromatase inhibitors.[39–41]

In premenopausal women at higher risk of breast cancer recurrence as assessed by tumor characteristics like nodal involvement, suppression of ovarian function is associated with a reduction in the 15-year risk of recurrence by 12·1% (28·9% vs. 41·0%; RR = 0·70, 0·63–0·78), 15-year breast cancer and all-cause mortality by 8·0% (20·9% vs 28·9%; RR 0·69, 0·60–0·80) and 7.2% (26·0% vs. 33·1%; RR = 0·73, 0·64–0·82), respectively.[42] GnRH agonists, including leuprolide and goserelin, are commonly used for ovarian function suppression for a duration of five years.

Bone-modifying agents, including zoledronic acid and denosumab, are often prescribed alongside hormonal treatment to reduce the risk of skeletal events (like fracture) associated with bone metastasis and osteoporosis caused by aromatase inhibitors.[43,44]

HER2-targeted therapy: Patients with HER2-positive breast cancer are typically treated with neoadjuvant chemotherapy and targeted therapy. Trastuzumab, an anti- HER2 antibody, when added to chemotherapy, has been shown to decrease the risk of recurrence of HER2-positive breast cancer by 9% (HR, 0.66, 95% CI 0.62-0.71) at ten years. The higher the tumor's risk, the greater the absolute reductions in five-year recurrence (e.g., 5.7% in N0 disease, 6.8% in N1 to N3 disease, and 10.7% in N4+ disease). Breast cancer mortality at ten years is reduced by 6.4% (HR 0.67, 95% CI 0.61-0.73).[45] The optimal duration of trastuzumab is 12 months; however, the most benefit is derived from the first six months of treatment, which may be considered essential.[46]

A newer HER2 antibody, pertuzumab, in addition to trastuzumab and chemotherapy backbone, showed a modest improvement in breast cancer recurrence and overall survival in the overall population. However, a preplanned subgroup analysis in patients with the node-positive disease showed that pertuzumab improved the six-year disease-free survival (88 versus 83 per cent; HR 0.72, 95% CI 0.59-0.87).[47]

An antibody-drug conjugate, trastuzumab emtansine (TDM-1), when administered in patients with HER2-positive breast cancer who have residual tumors after neoadjuvant systemic treatment, significantly improved disease-free survival (88% versus 77%; HR, 0.50; 95% CI, 0.39-0.64) and overall survival (89% versus 84% at seven years; HR, 0.66; 95% CI, 0.51-0.87).[48]

In metastatic settings, first-line treatment with trastuzumab and pertuzumab in addition to docetaxel was associated with a significant overall survival benefit compared to trastuzumab and docetaxel (57·1 vs 40·8 months; HR, 0·69; 95% CI, 0·58-0·82). In second line treatment, trastuzumab deruxtecan, demonstrated a significant improvement in progression-free survival compared to trastuzumab emtansine, (28.8 vs. 6.8 months; HR, 0.33; 95% CI, 0.26-0.43).[49] However, due to prohibitive cost, trastuzumab emtansine remains the most commonly used second-line agent, which also showed an improvement in overall survival compared to lapatinib and capecitabine (30.9 vs. 25.1 months; HR, 0.68; 95% CI, 0.55 to 0.85).[50]

Other targeted therapies: Olaparib: In patients with high-risk, HER2-negative early breast cancer and germline BReast CAncer1 (*BRCA1*) or BReast CAncer2 (BRCA2) pathogenic or likely pathogenic variants, adjuvant olaparib for one year after completing local treatment and neoadjuvant or adjuvant chemotherapy was associated with improved disease-free survival (85.9% versus 77.1%; HR, 0.58; 99.5% CI, 0.41 to 0.82) and overall survival (89.8% vs 86.4%).[51,52] In metastatic settings, olaparib was associated with an improvement in progression-free survival (7.0 vs. 4.2 months; HR, 0.58; 95% confidence interval, 0.43 to 0.80) compared to other chemotherapy agents.[53]

Abemaciclib is a CDK4/6 inhibitor that demonstrated an improvement in disease-free survival of 7.6% at five years in patients with high-risk hormone-receptor-positive breast cancer when treated after standard (neo)adjuvant chemotherapy and surgery. Treatment with two years of abemaciclib improved disease-free survival (DFS) (83.6% vs 76%; HR, 0.68; 95% CI, 0.60 to 0.77).[54] Other drugs in the same class include palbociclib, which did not show any benefit in a similar setting, while the data for ribociclib remains immature as of March 2024.[55–57] However, early data for ribociclib is promising (3-y DFS rates, 90.4% vs 87.1%; HR, 0.748; 95% CI, 0.618-0.906; P = 0.0014).[57]

In the metastatic setting, first-line treatment includes a combination of CDK4/6 inhibitor (palbociclib, abemaciclib, or ribociclib) and an aromatase inhibitor (anastrozole or letrozole), which has been shown to nearly double progression-free survival in various trials compared to an aromatase inhibitor alone.[58,59,60] The optimal second-line treatment is currently being investigated, with several options available, including fulvestrant, exemestane/everolimus, capivasertib/fulvestrant, elacestrant, alepelisib/fulvestrant, and conventional chemotherapeutic agents. In this setting, molecular alterations in certain genes (PI3K/PTEN/ESR1) can assist in choosing the most appropriate therapy (capivasertib

and elacestrant, respectively). However, neither of these drugs are currently available in India.

Immunotherapy: Pembrolizumab, an immune checkpoint inhibitor, inhibits PD-1 and has been shown to improve outcomes in patients with early TNBC and a subset of patients with metastatic TNBC. In the KEYNOTE-522 study, the addition of pembrolizumab to neoadjuvant chemotherapy and its continuation to complete one-year treatment improved disease-free survival to 84.5% compared to 76.8% in the placebo group (0.63; 95% CI, 0.48 to 0.82).[61] In the advanced setting, the KEYNOTE-355 trial, it demonstrated that pembrolizumab combined with to chemotherapy in a subset of patients with TNBC (combined positivity score of 10 or more), improved the median overall survival to 23.0 months compared to 16.1 months in the placebo– chemotherapy group (HR, 0.73; 95% CI, 0.55 to 0.95; P=0.0185).

Older frail patients: In older, frail patients with ER-positive breast cancer who cannot tolerate chemotherapy, aromatase inhibitors can be offered, and those with HER2-positive cancer are treated with targeted therapies (trastuzumab with/without pertuzumab). Triple-negative breast cancer in such a population is the most difficult to treat, and these patients are often offered low-dose oral metronomic therapy.[62]

Radiotherapy: The World Health Organization (WHO) recommends one linear accelerator (linac) per million population.[63] With an estimated total population of 1428.4 million in India in 2023,[64] according to the WHO standards, India requires 1428 linacs/RT units. As of September 2023, there are 607 radiotherapy centers licensed by the Atomic Energy Regulatory Board (AERB) in India.[65] In total, there are 954 RT machines (736 linear accelerators, 174 telecobalt units, 33 Tomotherapy units, and 11 Cyberknife units) [personal communication from AERB]. Most of these facilities are in the private sector and located in urban or semi-urban areas; making them inaccessible to those living in rural areas. Many publicly funded hospitals either lack machines or have limited numbers, which are mostly tele-cobalt units and are incapable of supporting advanced treatment techniques. As a result, there are long waiting lists for treatment, which leads to poor outcomes for patients due to logistic reasons. A simulation model estimated that increasing access to radiotherapy can potentially increase global 5-year breast cancer survival by 1.5% globally, of which LMICs such as India may benefit most possibly seeing gains of 5.8%.[66]

Most breast cancer patients receive RT using teletherapy (external beam radiotherapy) techniques. For effective breast cancer radiotherapy, minimal, albeit quality- assured infrastructure is essential. The bare minimum should include the availability of:

a) A written standard operating procedure (SOP) detailing the indications for radiotherapy, including communication with surgeons regarding a standard policy for applying tumor bed clips following conservation surgery and, preferably a multidisciplinary forum to discuss all patients requiring radiotherapy.
b) A detailed SOP for planning scan acquisition or a simulator- based radiotherapy field placement is needed.
c) A dose calculation and optimization protocol should be established, incorporating policies using 2-D and 3-D planning techniques. If a 3-D technique is utilized, compatible treatment planning software for the center's linear accelerator or telecobalt unit is necessary. A select few patients may require inverse planned treatment, and centers needing to commission inverse planned techniques must adhere to the as low as reasonably achievable (ALARA) principle of radiotherapy that the organs at risk doses (heart, lung, contralateral breast, brachial plexus) should be as close as possible to doses achieved using 3-d conformal techniques. Centers should collaborate to peer review the dose-volume constraints and aim for standards established in clinical trials before commissioning any intensity-modulated radiation therapy (IMRT) technique for service.
d) A peer review process of all plans and dose calculations should be encouraged within all treatment centers
e) Centers should be encouraged to participate in national and international studies or projects to facilitate external peer review of breast cancer plans. This is particularly important in the current era with ultra-hypofractionation techniques available for selected patients, where sub-optimal treatment plan leads to significant adverse effects, including breast pain, ultimately impacting patients' quality of life.[67] A major concern in our country is the heterogeneity of the treatment processes and the lack of uniform radiotherapy (RT) quality assurance standards. Quality assurance checks are necessary not only for the equipment but also for generating breast cancer RT plans and treatment delivery. Unacceptable long-term morbidity will affect the patients' quality of the life and their productivity in society.

Breast cancer RT involves daily sessions lasting from 3 to 6 weeks. This can be a deterrent for patients and caregivers due to the potential loss of income, as they must stay close to the hospital during that time, albeit temporarily. A three-week regimen for whole breast/post-mastectomy radiotherapy is now widely accepted as a standard of care. This has reduced

patient's out-of-pocket expenses for staying away from home. Ongoing research studies are testing the efficacy and safety of shorter (one-week) regimens.[68]

Skilled manpower is essential for the safe operation of any RT facility. radiation oncologists (ROs), medical physicists (MedPhys), and radiation therapy technologists (RTTs) form the trio that is essential for any radiotherapy center. No formal estimate was available for the number of ROs, Med Phys, or RTTs in the country. There are about 5000 qualified ROs for an approximate annual incidence of 1.4 million new cancer cases, and nearly 600 ROs graduate annually.[69] Daphtary *et al*. (2014) published a study on human resource requirements for cancer control in UP, India , estimating the number of ROs, MedPhys, and RTTs as 5, 4, and 12, respectively, for 1000 new cancer patients.[70] Corresponding numbers recommended by the International Atomic Energy Agency (IAEA) are 3-4, 2-3, and 6-7, respectively.[71] Most specialized personnel for radiotherapy are concentrated in urban areas where RT infrastructure is available. Unemployment and job saturation have led to qualified ROs moving to obtain Doctorate of Medicine (DM)/Doctorate of National Board (DrNB) Medical Oncology or taking up jobs in general medical service fields that do not treat cancer patients.

Current budget

The sources of funding include:

Government funding

The Indian government allocates funds for cancer prevention, diagnosis, treatment, and research through various national health programs and schemes. This includes the NPCDCS, which aims to strengthen cancer control efforts across the country. Funding is also channeled through government-run healthcare institutions, research organizations, and academic institutions involved in cancer research and treatment.

The Ayushman Bharat Pradhan Mantri Jan Arogya Yojana scheme initiated in 2018 provides funding and has transformed healthcare affordability for patients.[72] However, the penetration of the scheme among the underprivileged is less than optimum. This may be due to a lack of awareness and limited access to treatment.

Several State governments are also assisting with cancer treatment, including radiotherapy. The PMSSY scheme provides funding for enhancing/setting up oncology departments in all the AIIMSs and government Medical Colleges.

The government of India has allocated funds to improve facilities in tertiary cancer centers under the SCI and TCCC scheme. Various state governments also provide funding for the purchase of RT machines. The Assam Cancer Care Foundation, a joint venture by government of Assam and Tata Trusts to build 17 cancer hospitals in Assam, exemplifying private-public partnerships to enhance cancer care in the region. Additionally, various not-for-profit charitable hospitals are also available.

Private donations and philanthropy

NGOs, charitable foundations, and philanthropic individuals play a significant role in funding breast cancer awareness campaigns, screening programs, treatment facilities, and patient support services. Several NGOs and advocacy groups raise funds through donations, fundraising events, and corporate partnerships to support their initiatives in breast cancer education, early detection, and patient care.

International collaborations

International organizations, bilateral aid agencies, and global health initiatives collaborate with Indian counterparts to provide funding support for breast cancer control programs, research projects, and capacity-building activities; collaborations with international research institutions and universities often involve funding for collaborative research projects, clinical trials, and training programs for healthcare professionals.

Corporate social responsibility (CSR)

Many corporate entities in India allocate funds for breast cancer initiatives as part of their CSR activities. This includes sponsoring awareness campaigns, organizing screening camps, providing financial assistance to patients, and supporting research projects. Corporate partnerships with healthcare organizations and NGOs are crucial role for expanding access to breast cancer screening and treatment services, especially in underserved communities.

It is equally important to secure funding for radiotherapy research to ensure safer and optimized breast cancer treatment. Currently, there are very few funded options to allow ongoing peer review and quality assurance checks. Initiatives from the government and NGOs to promote peer review and benchmarking will enhance and sustain the quality of treatment delivery. Breast cancer ultra hypofractionation is likely to be adopted in the near future across cancer centers in India. It is essential that quality of treatment is ensured prior to such adaptation to prevent accidents.

Investment in high throughput pathology laboratories in the country is primarily commercially driven, and most cancer centers still struggle to maintain the standard of care.

Initiatives like the department of health research (DHR)-Indian Council of Medical Research (ICMR) advanced molecular oncology diagnostic services (DIAMOnDS) project have sought to improve the availability of molecular testing in cancer centers in India, but such a program does not exist for immunohistochemistry. Consequently, since most patients cannot afford their biomarkers, testing services often use cheaper alternatives, while the pathology of paying patients is sent to larger centers, resulting in variable out-of-pocket expenses for patients.

RECOMMENDATIONS

Key issues/gaps identified from public health perspective

Supply side barriers

There are several supply-side barriers to cancer care in India, including:

Skewed geographical distribution of cancer treatment facilities: There is a skewed distribution of cancer care facilities in India, with many areas facing a shortage of services. The number of cancer care facilities is higher in urban areas, especially in major metropolitan cities, whereas rural and remote areas have a limited number of cancer care facilities. This unequal distribution of cancer care facilities can be attributed to a range of factors, including inadequate infrastructure and resources, lack of awareness and education among the population, and insufficient funding and support from the government. In addition, the high cost of cancer treatment and lack of access to affordable healthcare services further exacerbate the problem of unequal distribution of cancer care facilities, particularly for people from economically disadvantaged backgrounds.

The existing evidence suggests that nearly 60% of specialist facilities are located in the southern and western regions of India.[29] However, over 50% of the population resides in the eastern and central regions, creating a distortion in service provision. For example, at least half of cancer patients will require radiotherapy at some point. However, data given by the Atomic Energy Regulation Board reveal that 26% of the population residing in India's eastern area has immediate access to only 11% of radiotherapy facilities [Figures 5 and 6].

Lack of treatment facilities: Radiotherapy is an essential component in the management of breast cancer patients and is used in conjunction with chemotherapy or surgery for both curative and palliative purposes. Modern-day cancer care increasingly requires a joint multimodality approach.[3] It is estimated that approximately 50% of all cancer patients are cured by surgery, 40% by radiotherapy alone (or combined with other surgery/chemotherapy), and 10% by chemotherapy alone (or combined with other surgery/chemotherapy).[3] The treatment of breast cancer requires a multimodal approach

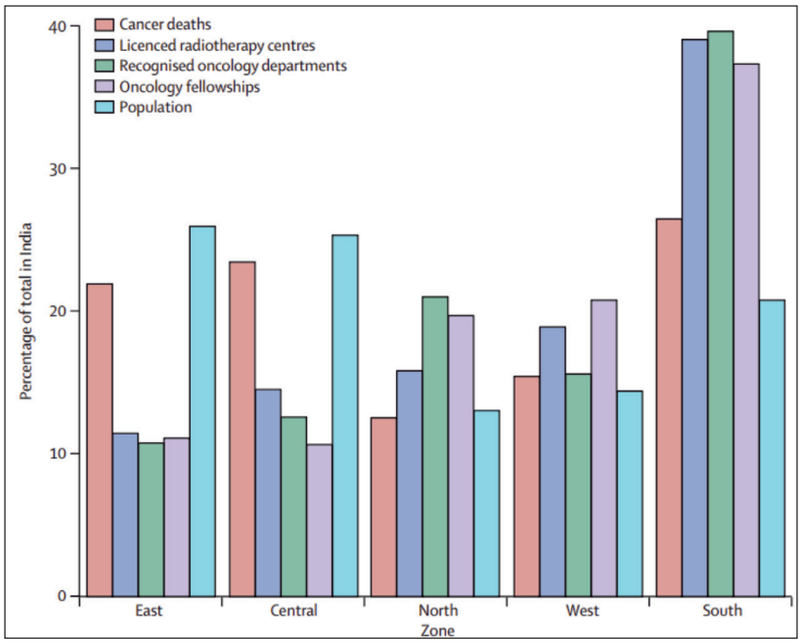

Figure 5: Population & cancer mortality against the corresponding proportion of cancer care facilities in India. Source: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)70115-9/abstract?version%253DprinterFriendly=

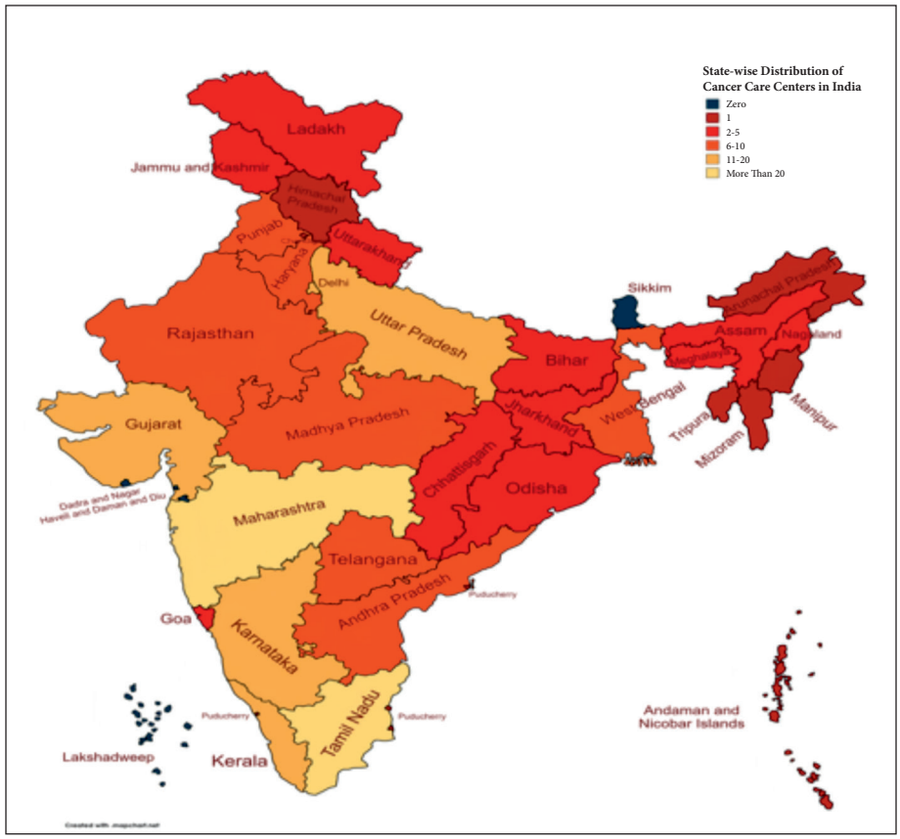

Figure 6: State-wise distribution of cancer care centres in India. Source: National Cancer Grid, https://www.ncgindia.org/hospitals-and-institutions/members

using all three modalities.

Present radiotherapy infrastructure in India: The radiotherapy centers in India have either teletherapy facilities alone or both teletherapy and brachytherapy facilities [Table 1]. The Directory of Radiotherapy Centers (DIRAC) 2012 from the IAEA has classified India alongside the poorest Sub-Saharan African countries, which have fewer than one radiotherapy machine per million people[73] [Figure 7]. Globally, India has the largest number of people living below the World Bank's poverty line of US$ 1.25 per day.[64] Currently, there are a total of 954 RT machines (736 linear accelerators, 174 telecobalt units, 33 Tomotherapy units, and 11 Cyberknife units) [personal communication from Atomic Energy Regulatory Board (AERB)].

Per capita radiotherapy statistics in India: In most high-income countries, there is at least one radiotherapy unit available for every 250,000 people,[5] which translates to an average of four radiotherapy machines per million population. Applying this factor to India indicates a total requirement of 5000 radiation therapy units in India now [Table 2]. Based on the current number of installed units in India, this reflects a shortfall of over >4500 machines. According to the WHO, there should be one teletherapy unit for every million people. There would still be a major shortage of teletherapy units in the country [Table 2]. While the number of teletherapy units has increased since this data was published; however, this is still lower than the optimal number.

Demand side challenges: To understand demand-side challenges or barriers, it is essential to understand them at individual and community levels. Most of the barriers have overlapping levels as these levels have their parts to play while attributing demand-side challenges [Figure 8].[74]

At individual level: Although tobacco use, lifestyle choices, and alcohol consumption have been proven to be causes of cancer, impediments related to treatment delays also significantly add to the cancer mortalities burden.[75] A systematic review identifying various delay stages in cancer diagnosis confirmed that there are identifiable stages between recognizing a symptom, first presenting to a health care professional, subsequent diagnosis, and initiation of

Table 1: Current status of radiotherapy facilities in India

Region	Population of each region (%)	Area of each region (%)	Simulator	Number of machines available in each region (%)					Cyber Knife	Gamma Knife
				CT-Sim	Telecobalt	Linacs	RAL Brachy	Tomo		
Central	8.10	13.6	1 (2.5)	2(4)	15 (8.3)	12 (3.3)	13 (5.2)	0(0)	0(0)	0(0)
East	22.33	12.8	4(10)	1 (2)	20 (11.1)	22 (6)	16 (6.4)	1 (12.5)	0(0)	0(0)
North	24.82	20.5	15 (37.5)	13 (26)	42 (23.3)	85 (23.3)	65 (26)	1 (12.5)	3 (42.9)	5 (71.4)
North-East	3.57	7.8	1 (2.5)	3(6)	10 (5.6)	6 (1.6)	6 (2.4)	0(0)	0(0)	0(0)
South	21.09	19.4	12 (30)	18 (36)	50 (27.8)	150 (41.1)	88 (35.2)	3 (37.5)	4 (57.1)	1 (14.3)
West	20.09	26.0	7 (17.5)	13 (26)	43 (23.9)	90 (24.7)	62 (24.8)	3 (37.5)	0(0)	1 (14.3)
Total	100	100	40 (100)	50 (100)	180 (100)	365 (100)	250 (100)	8 (100)	7 (100)	7 (100)

States included in each region: Central: Chhattisgarh, Madhya Pradesh, East: Bihar, Jharkhand, Orissa, West Bengal, North: Chandigarh. Delhi, Haryana, Himachal Pradesh. Jammu and Kashmir, Punjab, Uttar Pradesh. Uttarakhand, North-East: Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Tripura, South: Andhra Pradesh, Karnataka, Kerala, Puduchery, Tamilnadu. Telengana. West: Goa, Gujarat Maharashtra. Rajasthan. States not included: Andaman & Nicobar Islands. Sikkim. D & N Haveli. Daman & Diu. Lakshadweep; CT: Computed tomography, RAL: Remote after-loading

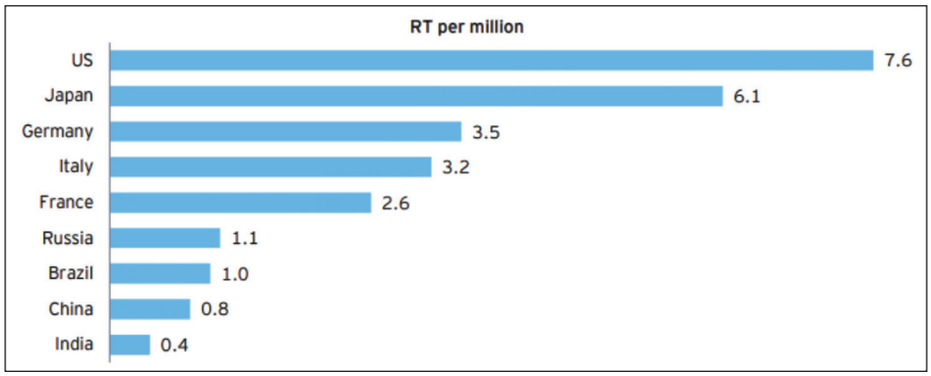

Figure 7: Availability of radiotherapy equipment across different countries. Source: "World population", worldpopulationreview.com "Directory of radiotherapy centres", Dirac.iaea.org. RT: Radiotherapy

Table 2: Shortfall of resources for radiotherapy in India

RT Equipment/Manpower	Recommendation in West (Per million people)	Required for whole country*	Existing, in the country	Shortfall
Teletherapy	4	5000	545	4550
Simulator	1	1250	90	1050
TPS	1	1250	500	750
Brachytherapy (remote)	1	1250	250	1000
Radiation oncologist	4	5000	1000	4000
Medical physicist	4	5000	1150	3850
Radiotherapy technologist	6	7500	2200	5300

*Assuming an Indian population of 1250 million. TPS: Treatment planning system

treatment.[75] The various reasons for the delay in treatment-seeking behavior at the individual level were:

Lack of awareness and perceived seriousness of signs and symptoms: For early diagnosis and the prompt initiation of therapy, it is crucial to recognize cancer signs and symptoms as soon as possible. A study conducted in Odisha found that most patients had never heard of cancer, and less than one-sixth were aware of carcinogenic factors.[74] Low levels of knowledge, educational status, and perception of the illness

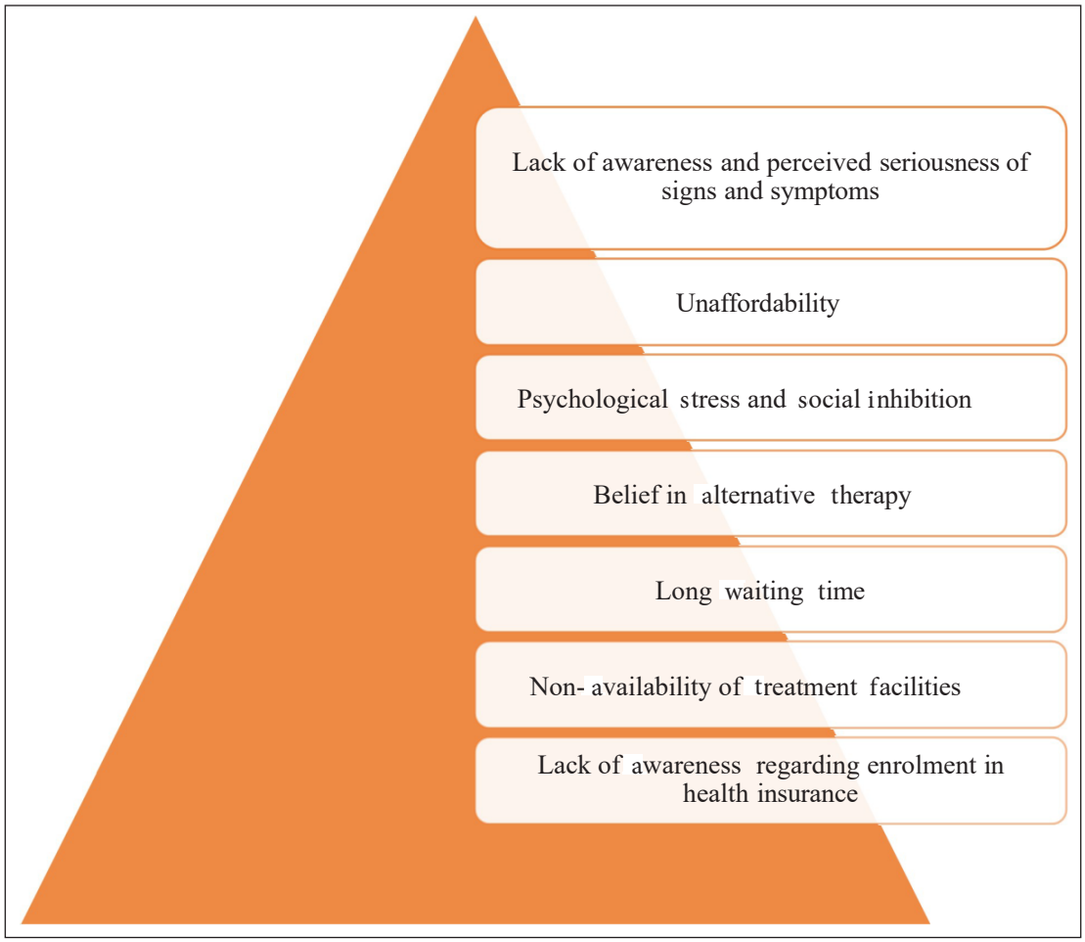

Figure 8: Demand side barriers in cancer treatment. Source: https://www.sciencedirect.com/science/article/abs/pii/S1877782113001641

severity are the leading causes of delay in getting cancer treatment.[76,77]

Given the lack of awareness and the fact that many cancer symptoms resemble those of other more prevalent benign conditions, it might be difficult for the patients to connect their symptoms to cancer.[78] One can argue that these factors could contribute to delayed consultation and prolonged watchful waiting[74] [Figure 9].

Financial constraints: Lower financial capabilities often lead individuals to adopt a more fatalistic and pessimistic when seeking healthcare.[79] Patients with low socioeconomic status (SES) tend to be diagnosed with more advanced cancers, receive less aggressive treatment, and face a higher risk of dying in the 5 years of diagnosis.[80,81] A study from India reported financial constraints as the major barrier to seeking treatment.[74] The analysis of the World Health Survey showed that low-household SES was significantly associated with cervical and breast screening rates in low-income countries.[80]

At the Individual and Community level

Psychological stress and social inhibition

Negative attitudes, stereotypes, and discrimination toward cancer patients are common in many societies.[82,83] Studies have found that cancer patients often experience social inhibition when speaking with community members about their symptoms.[73,74] Cancer-related stigma is not only associated with delayed treatment-seeking behavior but also with poor self-esteem, stress, anxiety, depression, and social isolation in different patient groups[84,85] [Figure 10].[86]

A meta-synthesis exploring barriers to health-seeking behavior among Malaysian breast cancer patients indicated that stress and a sense of denial were two prominent psychological factors linked to delays in seeking treatment.[87] This suggests that various social and psychological reasons hinder immediate treatment consultation or access to advanced care and surgery.

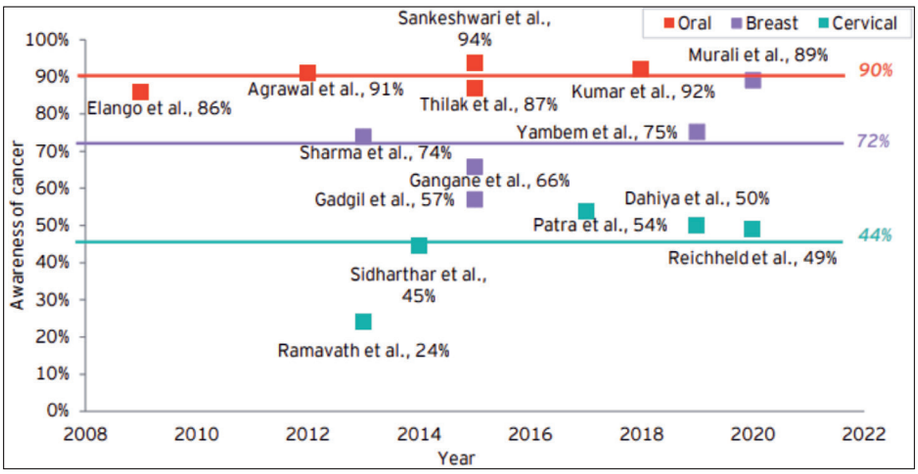

Figure 9: Awareness among the cancer patients in India. Source: Call for Action: Making quality cancer care more accessible and affordable in India, October 2022 - EY analysis report

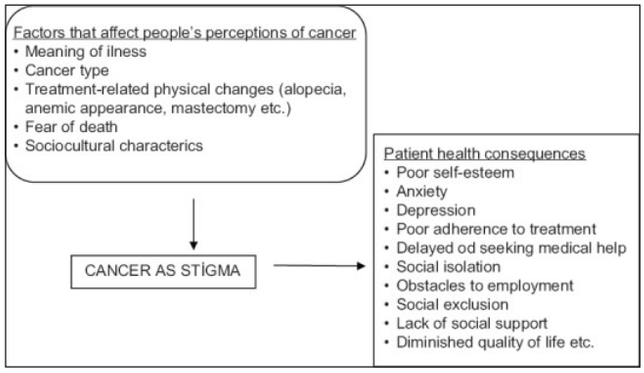

Figure 10: A conceptual framework of cancer stigma. Source: https://www.sciencedirect.com/science/article/pii/S2347562521001827

Belief in alternative therapy: According to estimates, cancer patients spend an average of an additional 139 days consulting various healthcare systems, including traditional healers and alternative medicine practices such as Ayurveda and homeopathy.[74] A cross-sectional study in Bangladesh demonstrated that the likelihood of alternative medicine delaying treatment-seeking behavior was four times higher among Bangladeshi Breast Cancer Patients.[88] In India, an exploratory study revealed that nearly half of the cancer patients reported being treated with complementary and alternative medicine (CAM).[89] Thus, belief in alternative therapies whether due to influenced or due to financial constraints has led to delays in availing conventional cancer treatment[90] [Figure 11].[74]

At the individual and health system level

Enrolment in health insurance schemes

In India, the launch of Ayushman Bharat PM-JAY in 2018 marked the introduction of the world's largest health assurance scheme in the world, making it crucial for the population to be aware of the insurance scheme. The scheme provides health cover of Rs. 5 lakhs per family per year for secondary and tertiary care hospitalization to over 10.74 crores of poor and vulnerable families, accounting for approximately 50 crore beneficiaries in the bottom 40% of the Indian population. However, a study conducted in one of the Indian states in 2021 assessed that awareness about the AB-PMJAY for treating disease, especially cancer care, was only about 50%).[91] The lack of awareness can be attributed to many factors, such as illiteracy, ignorance, improper knowledge about the scheme, and poor hospital connectivity. Even after enrolling in the scheme, the above factors lead to the inability to properly utilize the facilities.[92] While the government is emphasizing the need for increased awareness, recent studies have reported raising awareness levels among the population. Nonetheless, coverage and utilization of the scheme among the targeted groups remain minimal,[92] highlighting the need to enhance demand from the population..

Human resource barriers to access to breast cancer care

While human resources are essential for providing cancer care in India, several challenges impede their effectiveness, as outlined in Figure 12.

Shortage of skilled personnel: There is a shortage of healthcare professionals involved in oncology care at all levels of care, which limits the capacity to provide timely and comprehensive cancer care, particularly in rural and underserved areas. India exhibits a shortage of oncologists, with 2000 oncologists for 10 million patients, which is further skewed toward urban

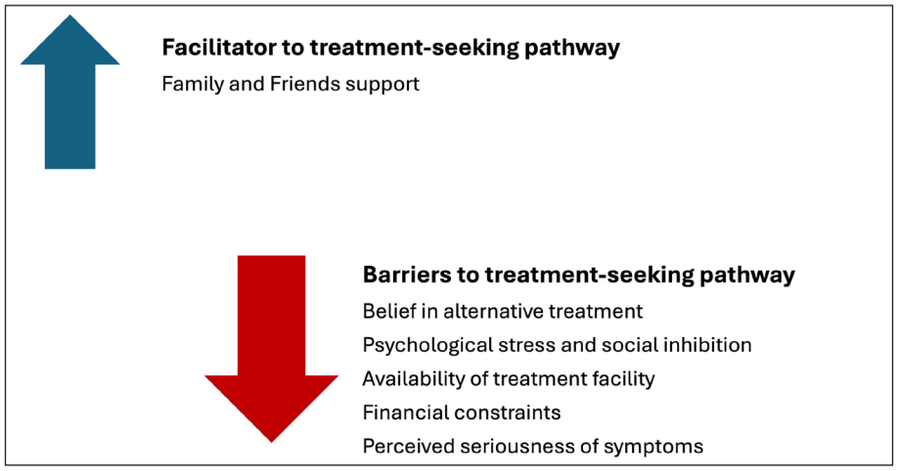

Figure 11: Qualitative qualifiers affecting the treatment-seeking pathways. Source: https://www.sciencedirect.com/science/article/abs/pii/S1877782113001641

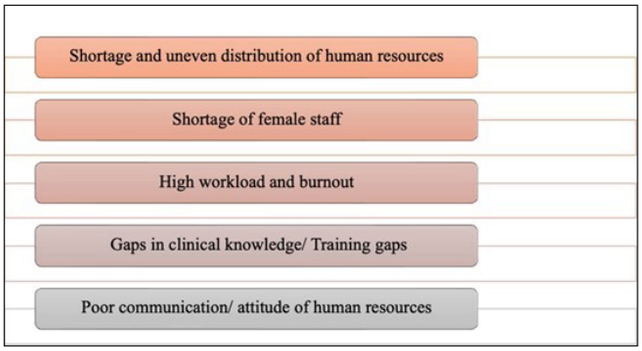

Figure 12: Human resources-related barriers to access to breast cancer care.

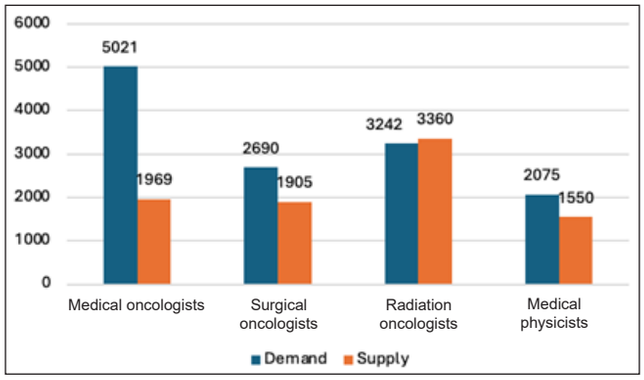

Figure 13: Difference in demand and supply of human resources.

areas.[16,29,93] Additionally, there is a notable north-south divide in availability, with about 60% of specialist facilities and the workforce located in southern and western India. Figure 13 depicts the shortage in demand and supply of treatment providers for cancer care.[93]

Furthermore, it has been noted that 27% of CHCs and 13% of district hospitals had not implemented the national program for control of non-communicable diseases in 2017-2018 due to a lack of workforce or equipment necessary for diagnosing cancers. This is in line with the general perception of primary care physicians on the limited utility of referrals to secondary-level health centers due to a shortage of specialists and equipment for confirmatory diagnosis and staging.

Shortage of female staff: The scarcity of female doctors, particularly in the context of breast cancer care, presents additional challenges to healthcare delivery in India. Several studies have reported the unavailability of female staff acts as a barrier to accessing breast cancer-related care due to cultural, religious, and social values.[94,95] The lack of female healthcare providers has been found to create barriers to open communication, leading to delays in seeking care, reluctance to undergo screenings, and decreased adherence to treatment recommendations.

High workload and burnout: The burden of cancer care in India is notably high, with each oncologist facing a staggering workload of 315 cases per practitioner, significantly surpassing the workload per oncologist in countries like China and the United States [Figure 14].[96] This overwhelming demand for medical and surgical oncologists exceeds the current availability by 2.6 and 1.4 times, respectively.[93] Consequently, skilled professionals experience immense pressure, impacting the quality of care, timely diagnosis, and patient attrition rates.

Research has elucidated various factors contributing to this strain on the healthcare system. For instance, studies have revealed that auxiliary nurse midwives (ANMs) in India, who play crucial roles in primary healthcare delivery, are often burdened with multiple responsibilities under national healthcare programs during scheduled work hours.[97] This situation results in the neglect of cancer care services, as

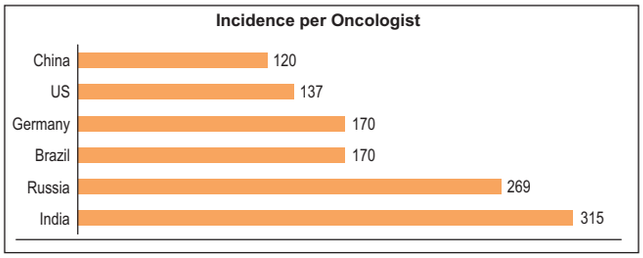

Figure 14: Comparison of incidence per clinical oncologist (radiation + medical). Source: https://ascopubs.org/doi/full/10.1200/JGO.17.00188

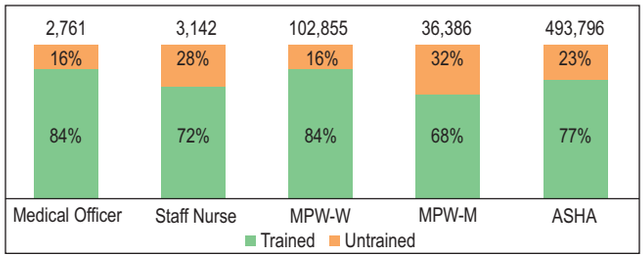

Figure 15: Percentage of trained health and wellness centre staff for prevention, screening, and management of NCDs, including cancer. Source: https://europepmc.org/article/nbk/nbk525285. NCDs: Non-communicable diseases, MPW-W: Multipurpose worker-women, MPW-M: Multipurpose worker-Men, ASHA: Accredited social health activist.

resources are diverted to address other pressing healthcare needs.

Furthermore, investigations into specialized cadres of medical oncologists from LMICs, including India, have underscored the alarming volume of work undertaken by these professionals.[98] The median number of annual consultations per medical oncologist in India stands at 475, significantly higher than the corresponding figure in other LMICs, which is around 350. Such high caseloads inevitably lead to burnout among healthcare staff, impacting their well-being and further straining the healthcare system's capacity to deliver quality cancer care.

Lack of adequate training in the workforce: Since breast cancer screening tests are dependent on observation, they have a high reliance on the skill set of the healthcare provider. Therefore, it is crucial to invest in the training of healthcare professionals to ensure effective screening. Of the current workforce deployed at HWCs nationwide, 26% still require training to perform screening tests. Among the ASHA workers, who form the backbone of the public health program in India, at least 23% need training for screening NCD patients, including those with malignancies. Additionally, nearly 16% of the 2,761 medical officers stationed in these facilities require training on the screening program and techniques [Figure 15].[99]

Gaps in training and continuing medical education: The failure of healthcare providers to recognize the signs and symptoms of breast cancer and to consider it as a potential diagnosis has emerged as a significant barrier to the timely detection and treatment of this disease. Studies investigating the knowledge, attitudes, and practices of healthcare providers across various cities have revealed low levels of awareness regarding breast cancer screening, available methods, and the practice of self-breast examination. For instance, research conducted in northern India uncovered a lack of awareness among 49% of healthcare workers regarding the risk factors and early detection methods associated with breast cancer.[100] These findings underscore the critical need for capacity-building initiatives and ongoing medical education to bridge these knowledge gaps.

Furthermore, studies have highlighted deficiencies in capacity-building efforts, with one-fourth of the staff at *Ayushman Arogya Mandirs*, healthcare facilities providing primary care services, lacking formal training. An Indian study reported the median time to diagnosis from the first contact with a provider as 30 [IQR 10-60] days, majorly due to a lack of awareness in identifying the cancer symptoms both among patients and primary care providers.[101] Thus, these gaps in training and education contribute to delays in the diagnosis of breast cancer, hindering efforts to identify and treat the disease at an early stage when outcomes are typically more favorable.

Poor doctor-patient communication: Effective communication between physicians and patients is crucial, as it has been consistently linked to positive health outcomes, including increased patient satisfaction, compliance with treatment plans, and overall improvement in health status. However, studies have revealed that patient-doctor communication in South Asia is often perceived as dissatisfying by patients, primarily due to a predominant pattern of one-way communication by healthcare providers.[94,95] The literature highlights that this deficiency in communication has significant implications for the accuracy and timeliness of diagnosis and treatment of breast cancer, highlighting the role of health system factors in shaping patient experiences and outcomes. While some studies have noted instances of comforting behavior exhibited by doctors, concerns have been raised regarding the attitude of paramedical staff and hospital administration.[102] Negative interactions with these healthcare professionals further exacerbate patients' dissatisfaction and impede their ability to navigate the complexities of breast cancer diagnosis and treatment.

Training of manpower remains an Achilles' heel in our ever-expanding cancer service strategy. More centers should be encouraged to establish in-house training for radiation oncologists, medical physicists, and radiotherapy technicians.

The current training in Radiation Oncology is short and quite generalized. Promoting site specialization in breast cancer oncology is essential for improving quality. Site-specific (e.g., breast cancer) Certificate courses or fellowships in high-throughput regional cancer centers must be encouraged and officially recognized. Additionally, international exposure should also be encouraged to understand the safeguards inherent to starting clinical practices. Hypofractionation and use of regional nodal irradiation remain topical issues, and mandatory seminars and certification should be encouraged to allow the same implementation.

Centers should be incentivized to start medical physics training and internship programs. Clinical site specialization of medical physicists during internship could be offered given the complex treatment processes. Radiotherapy quality assurance, junction dosimetry, as low as reasonably achievable (ALARA) principles, and its implementation in breast radiotherapy must be encouraged so that cardiac, lung, and brachial plexus doses do not compromise patient safety during breast radiotherapy.

Radiotherapy technicians must be well versed in the implementation of all treatment types and image guidance processes and also flag to clinicians any on-treatment adverse events. This, therefore, means that they are practically well-trained to ascertain when toxicities are more than envisaged. A career pathway for bright radiographers to be upgraded to dosimetrists after bridging courses are established could help address both skill upliftment issues and fulfill the need for more radiotherapy planning stuff by all departments.

Communication skills training is important across staff categories, and regular programs should organize regular programs to ensure that the benefits, risks, and both short- and long-term adverse events are communicated appropriately and in detail to patients.

Other barriers

Inadequate population coverage under cancer prevention and screening programs: There is a lack of cancer prevention and screening programs in India, which can lead to delayed diagnosis and treatment. This can result in poorer outcomes for cancer patients. The national cancer screening program in India has been in operation since November 2016. However, population coverage for cancer screening has been extremely low. Since 2018, when cancer screening was included in the National Health Mission's larger NCD screening program, India has made some progress. To date, 1.1% of the population has undergone cervical cancer screening, and less than 1% have received breast or oral cancer screening. Due to easy access to screening facilities, opportunistic screenings in private hospitals, and increased public awareness, screening coverage in urban regions is marginally better than that in rural ones. However, coverage for oral cancer screening among men in both urban and rural areas is low [Figure 16].

Due to inadequate screening systems and low awareness, late-stage disease identification exacerbates the problem of a high disease burden. Only 29% of breast cancers are detected at stages 1 and 2, respectively, India has a poor detection rate across major cancer sites, which is much lower than that in China, the UK, and the US [Figure 17]. This low rate of early diagnosis contributes to India's high mortality rate for malignancies, especially when compared to industrialized nations like the US and the UK, where early detection has been crucial in reducing mortality.

High cost of cancer treatment: The high and increasing cost of healthcare presents a major public health challenges in India. The amount of impoverishment and debt caused by high out-of-pocket expenses (OOPE) is growing as households continue to be the main source of funding for healthcare. Significantly, the OOPE for people with cancer is 2.5 times higher than for those with other disorders. The cost of cancer treatment can drive individuals and families into severe misery and even insolvency. Even Although the cost of treating cancer patients in hospitals is the highest among all NCDs, ineffective health financing systems and a heavy reliance on out-of-pocket medical expenses force many cancer patients to resort to desperate measures to afford their treatment.[103]

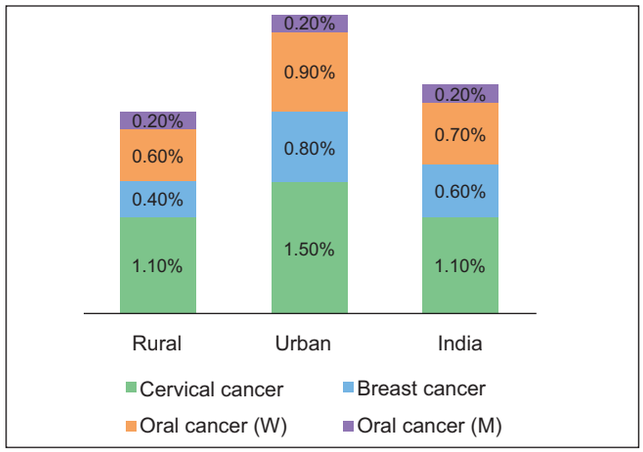

Figure 16: Screening coverage in India by percentage of population.

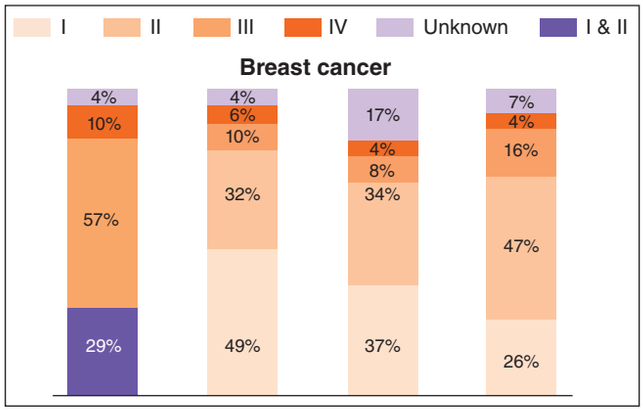

Figure 17: Percentage of cases diagnosed at various stages of breast cancer.

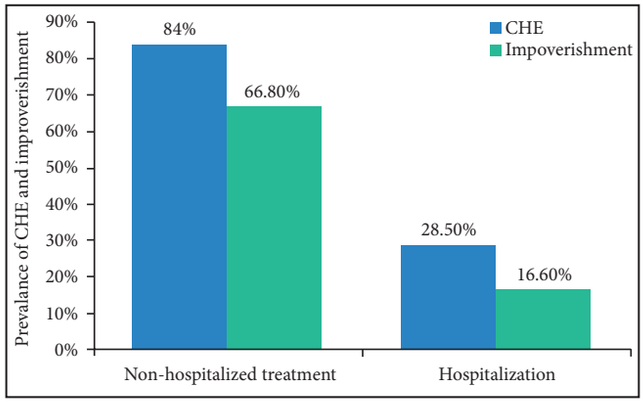

Figure 18: Financial toxicity due to cancer treatment in India. Source: https://www.frontiersin.org/journals/public-health/articles/10.3389/fpubh.2023.1065737/full, CHE: Catastrophic health expenditure.

One of the studies assessing the financial toxicity associated with cancer treatment reported that the prevalence of catastrophic health expenditure due to outpatient treatment was 80.4%, while the prevalence due to cancer-related hospitalization was 29.8%. The overall prevalence of impoverishment was 67% as a result of outpatient cancer treatment and 17.2% due to hospitalization [Figure 18].[104]

Inadequate health insurance coverage: Inadequate health insurance coverage can limit their ability to access cancer care services [Figure 19].[104]

Overall, these barriers to cancer care in India highlight the need for improved infrastructure, increased availability of healthcare professionals and cancer drugs, and expanded access to health insurance and cancer prevention and screening programs.

To implement the NPCDCS program under the auspices of universal primary health coverage, the government has included and prioritized screening for the three cancers as part of the program and is working to meet the goal of opening

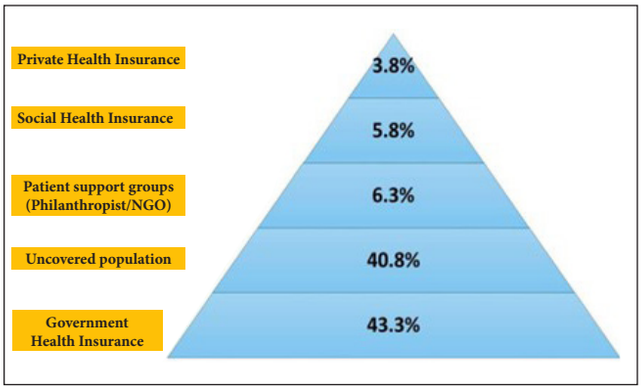

Figure 19: Coverage of health insurance in India. Source: https://www.frontiersin.org/journals/public-health/articles/10.3389/fpubh.2023.1065737/full, NGO: Non governmental organization.

1,50,000 health and wellness centers (HWCs) throughout India by December 2022. However, several challenges exist that are impacting the screening program from achieving its desired objectives [Table 3].

Recommendations made to bridge the critical gaps/ deficiencies in public health perspective

Recommendations to close the human resource gaps for cancer care

Closing the human resource gaps for cancer care requires a comprehensive and multi-dimensional approach that addresses workforce shortages, enhances training and education, and fosters professional development. We propose the following recommendations [Figure 20] to strengthen the health system building block of human resources to ensure access to quality cancer care:

Expansion of training programs in key areas of breast cancer care: The chronic shortage of staff for the provision of oncology care demands investment in expanding the capacity of medical schools, nursing programs, and allied health training institutions to produce more healthcare professionals specialized in key areas of cancer care, such as medical oncology, surgical oncology, radiation oncology, oncology nursing, palliative care, and supportive care.[93,105] This could involve increasing the number of training slots, establishing new training programs, or offering scholarships and incentives to attract students to oncology-related fields. Furthermore, such programs should focus on both clinical and non-clinical aspects of cancer care, including communication skills, patient-centered care, and interdisciplinary collaboration.

Capacity-building initiatives and continuing medical education: Structured capacity-building sessions based on comprehensive programs that cover various aspects of cancer

Table 3: Key challenges in the enforcement of the screening program

Indicator	Target	Status	Key points
Capacity - Physical infrastructure	1,50,000 HWCs with the necessary infrastructure required for screening of cancer within 30 minutes distance of the covered population by December 2022	As of March 2022, 1,17,000 HWCs set up	It is still difficult to find an appropriate number of HWCs nationwide. Moreover, some of the HWCs that are currently in operation lack a specialised area for cervical or breast examinations, considering privacy and infection control regulations.
Capacity - Workforce availability	According to IPHS guidelines, each sub-centre should be staffed with 1 CHO, 5 ASHAs, 2/3 multipurpose workers and PHC with 1 medical officer and other staff.	As of March 2021, there is shortage of 2.9% of female health worker/ ANM primarily due to shortfall in Himachal Pradesh, Rajasthan, Gujarat, Tripura, and Kerala. In comparison to those proposed at the PHC level, there is a shortfall of medical officers of around 4%, primarily in Orissa, Karnataka, and Chhattisgarh.	Having a skilled and sufficient workforce to cover the population for the HWC is as crucial to the physical infrastructure. Due to social and privacy concerns, a lack of female health professionals has a direct impact on the screening coverage for breast and cervical cancer screening. Any screening program's performance is further hampered by higher referral centres' insufficient staff, which delays confirmed diagnoses and, consequently, treatment, contradicting the purpose of early detection.
Capacity– Training	Every employee at HWCs has received cancer screening training.	There are currently 23% untrained employees working in these HWCs.	Conducting screening is quite difficult with an untrained team. A successful screening campaign is not always guaranteed by the simple availability of manpower.
Capacity- Referral network	Refer all cases 'at risk' to higher centres	Till 2017-18, NPCDCS had not been implemented in 27% of CHCs and 13% of DHs.	Triaging patients and sending them to the proper referral facilities is one of the key functions of health and wellness centres. The difficulty lies in these referral hospitals' readiness to take these patients. Less than 10% of the facilities at the district hospital where NPCDCS was implemented by the government had all the equipment for cancer screening.
Awareness	The objective is to raise awareness of cancer screening among all people through various information, education, and communication strategies.	According to several studies, healthcare professionals and the general public have little awareness about cancer screening.	Awareness, attitude, and knowledge, toward screening of cancer become important in a national screening program
Affordability and financing	At government centres, screening and treatment post diagnosis for the patients is free of cost.	About 55% patients with cancer are required to rely on private hospitals for management. Ayushman Bharat's and state healthcare programs had provided limited co verage, along with 10% to 12% of coverage by private insurance.	The financial condition of people affected with cancers is significantly impacted among all NCDs as cost of cancer treatment is highest.

HWC: Health and Wellness Centre; CHO: Community Health Officer; ASHA: Accredited Social Health Activist; ANM: Auxiliary Midwife Nurse; NPCDCS: National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases, and Stroke; DH: District hopital, NCDs: Non-communicable diseases

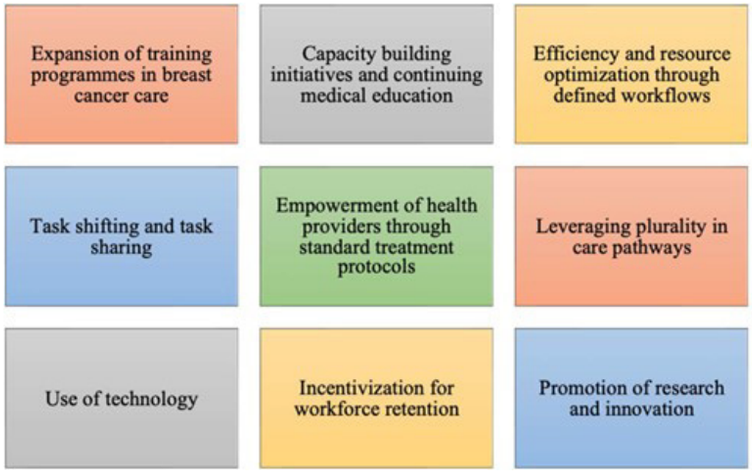

Figure 20: Recommendations to close the human resource gaps for cancer care.

care, including prevention, screening, diagnosis, treatment, and palliative care, should be organized for existing healthcare professionals to enhance their skills and knowledge in cancer care.[106]

Healthcare professionals should be provided with a variety of continuing education opportunities, including workshops, seminars, conferences, webinars, and online courses that focus on emerging trends, best practices, and evidence-based guidelines in cancer care. These activities should be accredited and provide healthcare professionals with continuing medical education (CME) credits.

Efficiency and resource optimization through defined workflows: Interdisciplinary teamwork plays a pivotal role in improving patient outcomes and ensuring holistic care for individuals affected by cancer. By fostering collaboration among healthcare professionals from diverse disciplines, including oncologists, surgeons, nurses, social workers, psychologists, rehabilitation specialists, and community health workers, healthcare systems can effectively address the complex needs of cancer patients across the continuum of care.[106,107] One key aspect of fostering interdisciplinary teamwork is the development of clear guidelines and algorithms for service delivery, particularly in the context of breast cancer care.

Task shifting and task sharing: India's structured workforce of primary care professionals and community health workers presents a valuable resource for expanding access to cancer care, particularly in resource-constrained settings. By leveraging the skills and capabilities of non-physician healthcare providers, such as nurse practitioners, physician assistants, community health workers, and peer educators, tasks and responsibilities can be delegated effectively under appropriate supervision and training. Task-shifting and task-sharing strategies can optimize healthcare delivery efficiency and improve access to cancer care services, especially in communities where access to specialized healthcare facilities is limited.

Drawing inspiration from successful models implemented in other countries, such as Peru, we can explore innovative approaches to community-based cancer care. For instance, Peru developed a model that trained community health promoters for outreach, professional midwives for clinical breast examinations, doctors for fine- needle aspiration biopsy sampling with ultrasound for triage, and patient navigators to ensure treatment adherence.[108] This holistic approach effectively addressed accessibility barriers and improved outcomes for the population.

Moreover, evidence from a 20-year prospective cluster-randomized trial conducted in Mumbai underscores the potential impact of task-shifting in cancer care. Primary health workers, with a minimum educational qualifications of matriculation, were trained to perform clinical breast examinations every 2 years. This intervention resulted in a reduction in the staging of breast cancer at diagnosis and a significant decrease in mortality among women aged 50 years and older.[109] This demonstrates the feasibility and effectiveness of training non-specialized healthcare workers to conduct essential cancer screening activities within a relatively short training period.

Empowerment of health providers through standard treatment protocols: Standard treatment protocols empower healthcare providers in decision-making while providing care to patients with breast cancer. Studies highlight that healthcare providers perceive the lack of standard treatment protocols as a hurdle in the provision of care for breast cancer in the communities. Therefore, it is essential to ensure access to defined protocols and necessary training covering all aspects of care, including

screening, diagnosis, staging, treatment modalities (such as surgery, chemotherapy, radiation therapy, and targeted therapy), follow-up care, and supportive care interventions.

Furthermore, standard treatment protocols should be regularly reviewed and updated based on emerging evidence and advancements in breast cancer research and treatment. Healthcare providers should be involved in the review process to provide feedback and insights from their clinical experiences, ensuring that the protocols remain relevant and effective in addressing evolving challenges in breast cancer care.

Leveraging plurality in care pathways: Studies have shown that a significant proportion of patients with breast cancer utilize traditional, complementary, and alternative medicine (TCAM) systems.[109,110] Therefore, the TCAM providers should be linked to the formal healthcare system to ensure standard, timely care to the patients. Adequate training should be ensured for the TCAM providers to ensure they have a comprehensive understanding of breast cancer, including its diagnosis, treatment modalities, and potential interactions with TCAM therapies. This training should emphasize evidence-based practices and promote safe and effective integration of TCAM with conventional cancer care. Additionally, structured pathways for integrative care that outline clear guidelines and protocols for collaboration between TCAM providers and formal healthcare professionals should be developed.

Use of technology: Leveraging telemedicine and tele-consultation platforms in cancer care can revolutionize access to specialized services, especially in remote and underserved areas of India. By connecting cancer patients with oncology specialists regardless of geographical location, these platforms address the shortage of oncologists and improve access to timely and quality care.[111,112]

In addition, the emergence of artificial intelligence (AI)-based technologies for breast cancer screening offers a promising solution to the challenges of early detection, particularly in regions with limited access to specialists and cultural barriers. Technologies such as iBreastExam, Mammoassist, Niramai, and Mammoalert use AI algorithms to detect abnormalities indicative of breast cancer.[112] Studies have shown that untrained healthcare workers can effectively use these AI-based devices with minimal training, achieving greater sensitivity than traditional clinical breast exam methods.

Incentivization for workforce retention: Policies and incentives should be implemented to attract and retain healthcare professionals in cancer care, including career advancement opportunities, workload management strategies, financial incentives, recognition, and support for work-life balance.

Promote research and innovation: It is essential to encourage research and innovation in cancer care workforce development, including studies on workforce needs, best practices in training and education, and novel models of care delivery. These studies can help inform workforce planning and resource allocation strategies to ensure that the healthcare system is equipped to meet the growing demands for cancer care services. Research efforts should focus on evaluating the effectiveness of existing training and education programs for healthcare professionals involved in cancer care. Studies should assess the impact of different training modalities, curriculum content, and teaching methods on knowledge acquisition, skill development, and clinical practice outcomes. By implementing these recommendations, healthcare systems can address human resource gaps in cancer care, strengthen the capacity of the workforce, and improve the quality and accessibility of cancer care services for individuals affected by cancer.

Recommendations for addressing the demand side barriers

The recommendations are classified as immediate-term, medium-term, and long-term to address this gap.

1. *Immediate-term (1-2 years)*

(i) *The integrative approach*: A multidisciplinary approach integrating traditional medical practices with modern medicine may be considered, where unequivocal evidence exists.[113] For example, a recent report summarized evidence and cost-effectiveness of diet and physical activity in primary prevention of breast cancer.[114] Such practices may be integrated in clinics.

(ii) *Empowering cancer awareness through the internet*: Regular education programs adopting the specific cultural contexts of local communities have led to an increased participation in screening programs.[114] Awareness about breast cancer in general population has to be increased substantially, and opportunistic education of relatives of patients is one of the effective measures. However, this may not always be possible at high-volume government centres in India. An alternative measure includes distribution of printed pamphlets that provide reliable and valuable information. With the increasing number of internet users, web content is increasingly being employed to disseminate health-related information.[115,116] Online search for information has become accessible to the population. However, this is a double-edged sword with a plethora of misinformation being readily available and therefore, Therefore, credible information sources, like 'Cancer India,' has been developed by the National Institute of Cancer Prevention and Research, that provides

authentic and comprehensive source to information.[117] The website has succeeded in providing the intended information to the target population.[118]

2. *Medium term (3-5 years)*

Digital breast tomosynthesis and newer biopsy techniques are available to diagnose breast cancer at an early stage.[16] These innovative health technologies can be evaluated through cost-effectiveness analysis to identify the best diagnostic and therapeutic interventions offering maximum value for money.

(i) *Affordability and financing*: Designing an intervention to provide financial risk protection against outpatient treatment: A recent study[104] reporting financial toxicity related to cancer indicated that the high economic burden of cancer treatment arises primarily from outpatient care rather than hospitalization . This finding significantly impacts existing publicly financed health insurance schemes which do not cover outpatient cancer care. An important recommendation of the study is to design interventions to provide financial risk protection against outpatient treatment.

(ii) *Strengthening the public sector*: Cancer care delivery in public sector hospitals is more cost-effective, and therefore, strengthening delivery in public sector is likely to prevent financial toxicity. Furthermore, publicly financed insurance is also more likely to provide protection against the financial risks. Such benefit packages should be rationally expanded to provide more cost effective treatments to a larger population, thus moving towards the goal of universal health coverage.

(iii) *Digital solutions for mitigating out-of-pocket expenditure on diagnostics*: An important determinant of OOPE for outpatient care is diagnostics accounting for 36.4%, as reported in a recent study by Prinja *et al.* (2023).[104] Digital technological solutions may play an important role here. The Government of India recently launched a digital voucher to provide social assistance on subsidy. This digital voucher, E-RUPI,[9] can be used to pay for expensive diagnostic and staging investigations once a patient has been confirmed to have cancer following histopathology.. A pilot program for this application of E-RUPI has been planned by the AB PM-JAY. Additionally, more laboratory and diagnostic centers are becoming part of the digital health ecosystem under the Ayushman Bharat Digital Mission (ABDM), enhancing the effectiveness of these initiatives.

Digital solutions for mitigating out-of-pocket expenditure on medicines: Expansion of E-RUPI can be used to pay for medicines in outpatient settings, which have been shown to constitute 27.8% of the total OOPE.[104,119]

The government should also nudge private insurance providers to include cancer screening in their plans.

(iv) *Infrastructure and capacity restraint*: The funds should be used not only to establish all 1,50,000 HWCs but also to ensure that these facilities employ adequately educated staff, including trained women, to inform the public about cancer screening and early warning indications.

A financial incentive system should be implemented at the local level to encourage Community Health Officer (CHO) and its teams to undertake successful screenings in their respective regions.

In order to effectively track and monitor the screening program, hospitals must use technology throughout the patient journey.

The use of mHealth and reliable data-gathering software or apps provides ASHAs, ANM, Medical Officer (MO), and experts with information about the patient. A clinical decision support tool for ASHAs can support ASHAs with standard screening criteria and patient triage based on risk level, advocating the best next steps. It can also help to ensure adequate data gathering.

To assist chief medical officers and radiologists across centers in addressing difficulties with workforce capacity, AI-based triaging and imaging solutions can be used. The use of software and IT systems to provide a seamless referral process should be encouraged. This would help in highlighting any dropouts or deviations from the pathway so that the proper actions can be taken.

3. *Long Term (> 5 years)*

(i) *Involvement of community health workers*: Government, healthcare system and community participation form the backbone of an effective cancer screening implementation strategy. Local volunteers can augment the breast cancer screening program in low-income settings, and thus, improve outcomes by early diagnosis.[120] Community health workers can assist by increasing breast cancer awareness, assisting clinical breast examinations, and navigation of patients through the referral system.

(ii) *Addressing financial toxicity due to cancer*: A national flagship insurance program -ABPM-JAY, has been functional in India to address certain out-of-pocket expenditure. Globally, it is the largest public health insurance system that covers expenditures upto Rs. 5 Lakhs (6814 USD) per family per year to over 10.74 crores of vulnerable families.[103] Further, outpatient financial risk mitigation strategies further need to be designed. digital voucher, E-RUPI,[119] launched to cover

expensive diagnostic and staging investigations, can also be expanded to pay for cancer medicines.

Furthermore, the Indian government's efforts to regulate the pricing of anti–HER2 drugs have improved access and outcomes. The launch of low-cost T-DM1 (the antibody-drug conjugate trastuzumab emtansine) and anti–HER2 therapy biosimilars is highly anticipated. The inclusion of newer treatment plans in health benefit packages should be based on empirical evidence (health-technology assessments).

The health information system needs to be linked with other databases including cancer registry, Ayushman Bharat, and death registrations. This will ensure better data capture in terms of cancer registration, follow-up and long-term outcomes.[121]

(iii) *Newer initiatives*: Health-tech start-ups are revolutionising different stages of cancer care. For example, Niramai® utilizes machine learning and big data analytics to develop low-cost breast cancer diagnostics.[122] Oncostem® assists in personalised treatment decisions using several prognostic biomarkers,[123] and UE Lifesciences® uses handheld screening devices that are contactless and radiation-free.[124] Panacea® and Mitra Biotech®[125] are companies that are developing precision therapies for cancer patients.

There are several patient assistance programs (PAPs) from companies like Roche®, Novartis®, etc., that support patients with cancer in reducing the cost of drugs and navigating patients through their cancer journies. Furthermore, patient navigation strategies are evolving. For example, 'Kevat' is the first initiative in India to facilitate patient's journey from entry to the hospital to subsequent follow-ups during cancer treatment.

In addition, the WHO introduced a Global Breast Cancer Initiative on March 9, 2021, with the goal of reducing global breast mortality by 2.5% by 2040. This initiative aims to reduce 2.5 million global deaths, particularly in low-income countries, where the progress in addressing the disease has been relatively slow. By providing technical support to implement effective strategies for breast cancer management, this evidence-based initiative holds promise for addressing disparities in breast cancer outcomes,[126] particularly in low-income countries.

In light of these advancements and initiatives, stakeholders in the field of oncology are encouraged to embrace and support these transformative approaches. Collaborative efforts among health-tech innovators, pharmaceutical companies, healthcare providers, and policymakers are essential for realizing the vision of improved breast cancer care outcomes and reducing the global burden of breast cancer.

Speciality-wise specific gaps and recommendations

Radiodiagnostics

The identified gaps and recommendations to address the gaps in the field of radiodiagnostics are listed in Table 4.

Pathology

Pathology is a critical specialty involved in the diagnosis of breast cancer. The management of breast cancer is dependent on the identification of subtypes of breast cancer. To address the gaps identified, the following recommendations are suggested.

Careful specimen transport: The specimen should ideally be sent immediately after removal to the histopathology laboratory. In instances where delayed transport is expected, the specimen should be sliced to ensure proper formalin penetration during transport, and this is especially crucial for a mastectomy specimen. Drawing inspiration from the UKNHS, a specimen transport van that carries the specimen in refrigerated boxes should be available at centers that plan to send the specimen out. Additionally, a network of specimen transport systems and sample tracking across the country should be set up at least at far-off places. Make surgeons more aware of the harmful effects of delayed fixation. Training should focus on making controlled single or cruciate incisions into the lesion, preserving the integrity of key margins while allowing for immediate penetration of fixatives.

Audit of biomarkers across each cancer center: European countries have established a system for auditing reported biomarkers in every hospital. This system ensures that any deviations are identified and investigated through root-cause analysis to address issues impacting test results.

Certification for quality pathology services and compulsory participation in an EQAS program: In spite of free NCGEQAS services, most government institutes do not participate to avoid the spotlight. Compulsory EQAS should be complemented with a cancer center's along with good pathology practice certification.

- Availability of FDA approved antibodies through a common portal like GEM after cost negotiation.
- Replacing FISH with D-DISH or validated chromogenic hybridization assays

In most developed nations, a HER2 score of 2+ is reflex tested with FISH. While a molecular laboratory may not be available at most centers, the D-DISH chromogenic in situ hybridization can be performed on the automated Ventana platform, though it requires some training. We have recently published data demonstrating high concordance between

Table 4: Gaps and recommendations for radiodiagnostics infrastructure in India

Observations	Short term recommendations	Long term recommendations
Low availability of mammography machines	Installation of digital mammography machines in all medical colleges, regional cancer centres and other tertiary care hospitals	Installation of digital mammography machines in all district hospitals
Inadequate number of manufacturers of state-of art digital mammography machines in India	Inclusion of digital mammography machines in the list of medical devices with make-in-India exemption to allow global tenders for procurement of machines for government hospitals	Investing in research and development for manufacturing of advanced digital mammography machines.
Wide availability of ultrasound machines	Encourage the use of ultrasound for diagnosis of breast diseases in symptomatic women, if mammography is not available	Pooling and analysis of data so generated across hospitals to determine the role of ultrasound in breast cancer diagnosis.
Limited availability and expensive nature of MRI and PET-CT facilities	Installation of MRI and PET- CT machines in all medical colleges, regional cancer centres and other tertiary care hospitals	Installation of MRI and PET- CT machines in all district hospitals
Optimal utilization of available infrastructure	Education of primary care doctors with recent updates and current concepts directed to prevent under or over use of breast imaging techniques.	Developing clinical guidelines specific to Indian population
Wide variations in quality and standard of breast imaging facilities	Defining minimum standards for breast imaging equipment, regular quality assurance tests and practice guidelines which are commensurate with existing infrastructure in the country. These may be optional but actively encouraged at the beginning. Breast Imaging Society of India has already developed and regularly updating such guidelines by expert from across the country. Collaboration with the Society for this purpose may be explored.	Practice guidelines of international standard should to developed. Apex licencing authority may be established for acceptance testing and periodic monitoring of quality of mammography machines, proficiency of manpower and renewal of licences. This may be made a mandatory requirement in future.
Training of breast radiographers	Structured mammography training in undergraduate courses of B.Sc. medical technology radiography programs wherever they are running.	Strating post graduate courses of MSc Breast imaging, after B.Sc. in medical technology radiography.
Training of radiologists	More emphasis on structured breast imaging and interventions in syllabus of post graduate medical courses of MD (Radio- diagnosis and DNB (Radio- diagnosis).	Recognizing Breast imaging as a distinct superspeciality stream by National Medical Commission and National Board of Examinations
Training of radiologists	Increase annual intake in post-doctoral fellowship in breast imaging programs in medical institutes of national importance, where it is already available	Starting of new post- doctoral fellowship in breast imaging programs in all medical institutes of national importance, where it is not already available
Continued medical breast education of radiologists and radiographers	Supporting Breast Imaging Society of India for conducting more CMEs and hand on workshops for skill developments in different parts of the country	Regular short term training or observer ships at regional premier centres for radiologists and radiographers working at peripheral government hospitals.
Research in breast imaging and interventions	Inviting research proposals and funding the same with specific emphasis on optimal utilization of existing infrastructure, use of AI to address inadequate trained manpower and product developments.	Centralized pooling of breast imaging data form across the country. This may be used to generate country specific data, recommendations and practice guidelines for breast imaging and interventions.
Research in screening for breast cancer	Large scale studies on population-based breast cancer screening with clinical breast examination by trained healthcare workers.	Pilot studies on opportunistic and self-volunteered mammographic and/or ultrasound screening in high-risk group women may be conducted to assess its utility.

MRI: Magnetic resonance imaging, PET-CT: Positron emission tomography - computed tomography, MD: Doctor of medicine, DNB: Diplomate of National Board, CME: Continuing medical education

D-DISH and FISH. Separate funding will be necessary to support such initiatives.

- Zonal oncopathology laboratory empowerment with molecular sequencers and know-how to generate patient population-specific panels.
- Development of gene-based predictive test akin to OncotypeDx in Indian population.

Surgery

To address critical gaps and deficiencies in human resources for breast cancer treatment in India, it's essential to implement targeted strategies across different timeframes. Here are recommendations classified based on their implementation timeframe.

1. *Immediate (1-2 years)*

(i) *Training programs*: Establish short-term training programs and workshops for healthcare professionals, including oncologists, surgeons, radiologists, pathologists, nurses, and allied health workers, to enhance their knowledge and skills in breast cancer diagnosis, treatment, and survivorship care.

(ii) *Capacity building*: Provide intensive training and certification courses for primary care physicians and nurses to improve their competency in clinical breast examination, early detection, and referral of breast cancer cases.

(iii) *Task shifting*: Explore the feasibility of task shifting by training allied health workers, such as community health workers and mid-level providers, to perform basic breast cancer screening, patient education, and supportive care services.

2. *Medium-term (3-5 years)*

(i) *Specialized fellowships*: Expand fellowship programs in breast oncology, surgical oncology, medical oncology, radiation oncology, and breast imaging to train a cadre of specialized healthcare professionals dedicated to breast cancer care.

(ii) *Interdisciplinary training*: Develop interdisciplinary training programs and tumor boards involving oncologists, surgeons, radiologists, pathologists, nurses, and psychologists to foster collaboration and improve care coordination for breast cancer patients.

(iii) *Workforce redistribution*: Implement policies to incentivize healthcare professionals to work in underserved areas by offering financial incentives, career development opportunities, and infrastructure support.

3. *Long-term (>5 years)*

(i) *Academic Partnerships*: Foster collaborations between medical institutions, academic universities, and research centers to establish comprehensive breast cancer training and research programs, including postgraduate courses and research fellowships.

(ii) *Subspecialty certification*: Work towards establishing subspecialty certification in breast oncology for healthcare professionals to recognize expertise and promote standardized care delivery in breast cancer treatment.

(iii) *Continuing education*: Develop continuous professional development programs, online courses, and tele-education platforms to facilitate ongoing learning and skill enhancement for healthcare professionals engaged in breast cancer care.

(iv) *Health workforce planning*: Conduct workforce needs assessments and long-term planning to anticipate future demand for breast cancer care services and ensure adequate human resources capacity to meet growing needs.

Collaboration among government agencies, professional associations, academic institutions, and healthcare providers is essential for the successful implementation of these programs.

Medical oncology

Access to drugs: With the evolution of systemic therapies for breast cancer, the cost of treatment has increased significantly. Access to newer therapies, when introduced in the Indian market, is extremely limited during the patent period; for example, when trastuzumab was introduced, less than 10% of patients in India could integrate it into their treatment despite significant benefits.[127] However, with the availability of Indian generic versions, usage increased to over 50% Additionally, integration into the PM-JAY program is expected to enable over 80% of patients to access trastuzumab in their treatment.[128] A shorter duration of trastuzumab has been advocated as a more effective strategy in India.[129] Similarly, there are several drugs, including but not limited to CDK4/6 inhibitors, immunotherapy (pembrolizumab), and newer anti-HER2 agents, that remain inaccessible to most patients.

Therefore, drugs used in the management of breast cancer have been categorized into essential and optimal classifications for non-metastatic and metastatic scenarios, respectively [Table 5]. The essential classification includes drugs that demonstrate significant efficacy in terms of disease-free survival or overall survival through randomized controlled trials and are currently accessible in India as of March 2024. Conversely, drugs are designated as optimal if there exists definitive evidence of enhanced disease-free

Table 5: List of essential and optimal drugs for breast cancer

	Early and locally advanced	Metastatic
Essential drugs	Doxorubicin Epirubicin Cyclophosphamide Paclitaxel Docetaxel Carboplatin Capecitabine 5-Fluorouracil Methotrexate Trastuzumab (A) Trastuzumab emtansine (A) (TDM-1) Leuprolide Goserelin Tamoxifen Anastrazole Letrozole Exemestane Olaparib (A) Zoledronate Denosumab	Doxorubicin Epirubicin Cyclophosphamide Paclitaxel Docetaxel Gemcitabine Nab-paclitaxel Carboplatin Capecitabine 5-Fluorouracil Methotrexate Trastuzumab Trastuzumab emtansine (4) (TDM-1) Tamoxifen Leuprolide Goserelin Anastrazole Letrozole Exemestane Zoledronate Denosumab Olaparib (4) Talazoparib (4) Vinorelbine Eribulin (2) Palbociclib (3/4) Ribociclib (4/5) Abemaciclib (3/4) Fulvestrant (2) Pertuzumab (4) Lapatinib (3/4) Everolimus (2)
Optimal	Pembrolizumab (A) Pertuzumab (A) Abemaciclib (A) Ribociclib	Trastuzumab deruxtecan (T- DXd) (4) Tucatinib (4) Sacituzumab govitecan (4) Alpelisib (2) Pembrolizumab (4)
Currently not available in India		Elacestrant (3) Capivasertib (3)

survival, notwithstanding the absence of overall survival data, or if the drugs remain largely inaccessible due to prohibitively high costs. Thus, access to all essential drugs is imperative for all patients diagnosed with breast cancer, with the additional aim of providing access to optimal drugs. Given the evolving landscape of evidence, periodic reevaluation and potential reclassification of drugs may be warranted in the future. Furthermore, ongoing clinical trials investigating novel drugs may lead to their integration into breast cancer treatment protocols, necessitating regular updates to the drug classification list.

The list also includes the European Society of Medical Oncology (ESMO) magnitude of clinical benefit scale (MCBS), which is designed to enhance decision-making concerning the value of anti-cancer treatments. Its aim is to ensure fair access and reduce disparities in cancer care.[130] The MCBS helps oncologists communicate treatment benefits to patients and assists health policymakers in prioritizing therapies for reimbursement. It is currently integrated into ESMO Clinical Practice Guidelines and utilized in Health Technology Assessment processes globally.

Briefly, the ESMO-MCBS grading system delineates treatments that substantially enhance patient survival or quality of life from those with more limited benefits based on outcomes from randomized clinical trials.[131,132] This evaluation encompasses factors, including overall survival, progression-

free survival, and quality of life, providing a comprehensive framework for assessing cancer medicines. Therapies that achieve higher ESMO-MCBS scores, particularly those falling into categories A and B for curative intent and scores 4 and 5 for non-curative setting, warrant expedited evaluation for value and cost-effectiveness.

Access to genetic testing: Approximately 18% of individuals diagnosed with breast cancer may have a pathogenic or likely pathogenic mutation within one of the genes associated with hereditary breast cancer predisposition.[132] Such genetic anomalies carry significant clinical ramifications, including the implementation of risk reduction strategies for the affected individual, such as intensified surveillance protocols or prophylactic surgeries. Additionally, these mutations may influence therapeutic decisions, with the emergence of PARP inhibitors such as olaparib as potential treatment options. Furthermore, there is a cascade effect necessitating genetic testing for at-risk family members. In the Indian context, a consensus document has been previously published outlining guidelines for genetic counseling, testing, and management of hereditary breast and ovarian cancer.[133] Therefore, ensuring access to germline testing for eligible breast cancer patients is paramount. Such testing should include a comprehensive multigene panel analysis using next-generation sequencing techniques, supplemented by reflex testing using multiplex ligation-dependent probe amplification assays (MLPA) to detect large genomic rearrangements.

Essential recommendations:

Access to a genetic counsellor

Access to germline testing with a multigene panel and reflex

Human resources for delivering systemic treatment: The systemic treatment of breast cancer has evolved significantly over the last decades. It is arguably the most complex part of treatment, where a trained medical oncologist is required to provide an optimal systemic treatment strategy. Moreover, systemic treatments are associated with unique side effects that require trained and experienced personnel to identify and treat such treatment-related complications. In a recent survey in 2022, it was estimated that India needs approximately 5,000 medical oncologists to address the rising burden of cancer, while there are only 2000 specialists available in the country.[134] This leads to a higher clinical burden on the existing Medical Oncologists in India, as well as poor access of patients with breast cancer to comprehensive multidisciplinary care.[97]

Therefore, we recommend that all medical colleges in India must have a department of Medical Oncology to ensure optimal management of patients with breast cancer. This department should ideally be staffed with trained medical oncologists who possess qualifications such as DM or DNB in medical oncology. However, in cases where a trained medical oncologist is not available, the responsibility for managing patients with breast cancer can temporarily fall under the Department of Internal Medicine.

Given that there are 706 National Medical Commission (NMC)-recognized Medical Colleges in India as of March 2024, each of these institutions must meet the requirement of having a Department of Medical Oncology or a suitable alternative arrangement in place for managing breast cancer patients. This requirement ensures that patients receive appropriate care and treatment for their condition.

Radiation oncology

Key issues/gaps in the human resource component

(i) *Immediate*: There is an urgent need to ensure an appropriate understanding of hypofractionated radiotherapy practices that are emerging in breast cancer. Clinicians and Medical Physicists must attend breast cancer site-specific workshops to understand the nuances of breast radiotherapy planning. National and International bodies should be approached immediately to ensure multiple courses on breast radiotherapy planning are available through various regional centers across the country.

It is imperative that, alongside the enhancement of infrastructure for radiotherapy across India, the shortage of skilled manpower in radiotherapy practices is addressed. Nodal centers must be encouraged to start training programs on Medical Physics and Radiotherapy technician courses.

A nationwide consortium is essential to ensure that patient-specific quality assurance practices are maintained across all treating centers. A national breast cancer radiotherapy treatment protocol is essential. This should encompass all aspects of breast radiotherapy treatment, be practical, and should address all issues needed for treatment in cobalt and linear accelerator-based centers. This protocol can be implemented in a phased manner, starting with regional centers agreeing on the processes, followed by smaller centers across the country.

Government and non-government institutions must be encouraged to allow external peer review of breast radiotherapy services and protocols.

Additionally, it must be essential for all clinical staff to attend communication skills programs across the country. This could include mandatory attendance of workshops and certification courses. The government must ensure repeated revision courses with a gap of 3-5 years to allow continued education.

Radiotherapy technicians must undergo image guidance training and should be certified for the same. Programs must be available nationally to do so.

Under-utilization of palliative breast radiotherapy for regional symptom control and improving patient quality of life remains a matter of concern. Various reasons, including referral bias and lack of coherent multidisciplinary team working, could be contributory factors. Enhancing knowledge and breast cancer, multidisciplinary team working is an area of need, and national policies to enroll multidisciplinary team (MDT) across the country and provide guidance for successful protocol-driven teamwork should be encouraged.

(ii) *Medium-term*: The Government of India plans to open one medical college in each district across the country. Radiotherapy departments must be made essential, at least within two adjacent districts, within the next five years.

New centers for training Medical Physicists and Radiotherapy technicians should be commissioned across the country.

A bridging course should be allowed to train radiotherapy technicians to allow them to plan radiotherapy treatments under supervision (dosimetrists). This will allow the technicians to have a career pathway and also help institutions safely address radiotherapy planning bottlenecks. The government should work with nodal bodies such as the Atomic Energy Regulatory Board to establish such courses.

Radiotherapy-specific nurses must be trained across the country to allow appropriate management of any and all adverse events and provide patients with information and support during therapy. ASHA workers should also be trained to counsel patients on their breast radiotherapy treatment and highlight any unaddressed adverse events.

(iii) *Long term*: Each center must have site-specific (breast cancer) radiation oncologists and radiotherapy planners.

Nodal centers should be identified, and leaders in the field must be encouraged to draw a breast cancer radiotherapy-specific audit and research plan.

(iv) *Key issues/gaps in the current infrastructure, facilities, technologies, policies, programs, etc.*: More centers that allow patients to get radiotherapy treatment near their homes must be encouraged. Such centers must have essential quality assurance systems, SOPs, and audit processes in place.

All centers treating breast cancer must be encouraged to provide cardiac-sparing radiotherapy strategies, at least using multi-leaf collimators. Given the strong relationship between heart dose and cardiac morbidity and mortality, it is important that hardware (multi-leaf collimators, gating cameras) and compatible software are available in all centers.

All centers, including smaller centers, should be included within a national program to establish clinical protocol-based treatment processes in breast radiotherapy. This would include internal audit processes.

All centers should participate in an external peer review process.

A national audit process must be in place that will allow analysis, collation, and publication of treatment-related near misses and accidents.

The audit process above should also ensure that site-specific outcomes of breast cancer radiotherapy planning are in place.

Recommendations

(i) *Immediate*: Create a state-wise map of available RT facilities and catchment areas to identify underserved regions.

Develop a national detailed radiotherapy planning SOP.

Develop a detailed quality assurance SOP for treatment planning and delivery. The SOP should include mandatory and optimal recommendations. It is preferred that a group of competent experts develop the same.

(ii) *Medium and long term*: Cancer therapy/radiation Oncology department may be made mandatory criteria for recognition of medical colleges. The departments can be set up with one Professor, one Associate Professor, and, one Assistant Professor, and senior residents for one unit (as mandated by NMC) initially to start the service run outpatient (OPs) and inpatient (IP) service. Radiotherapy machine (at least one linac) installation is to be performed within the next 3 years. Two medical physicists and four radiotherapy technicians should be the minimum number of paramedical staff members to run a linear accelerator.[135]

Identify a District/General/Taluk hospital where an RT machine could be installed to work on the hub and spoke (satellite radiotherapy center) model with a cancer center/medical college. Patients could travel to the hub center for simulation and RT planning (1-2 visits) and receive treatment at a peripheral unit closer to home. There should be internet connectivity between the centers for online transmission of RT plans. The peripheral unit could work on a single-shift basis with a minimum staff requirement as required by AERB. The peripheral unit could be under the administrative control of the parent center with regard to the RT program. (3-5 years and beyond five years, depending on the needs of the locality).

Identify major cancer centers in each state that can serve as facilitators - providing guidance on quality assurance standards and conducting QA audits. This initiative can be structured over different timeframes: 1-2 years for initial identification and planning 3-5 years for implementation and training, and beyond 5 years for ongoing support and assessment, depending on the availability of human resources and infrastructure.

(iii) *Key issues/gaps in the current funding scenario in the country*: Accessibility of radiotherapy can be improved with a plan for delivering radiotherapy near home, using the above-mentioned hub-spoke model. Infrastructure funding for the same is necessary.

Funding for enhancing quality in breast cancer therapy is required for appropriate national group functioning to deliver SOP, audit, and peer review, which is of utmost need.

Clinical trials specifically related to testing radiotherapy techniques and hypotheses in India must be prioritized. Radiotherapy, being one of the most cost-effective measures, allows such infrastructure funding to reap quick benefits with a reduction in patient care costs.

Training programs and workshops for doctors (radiation oncologists) on-site specializing in the safe use of modern techniques such as regional nodal radiotherapy, ultra hypofractionation, etc., should be funded. The medical physics team is to be upskilled for the same purposes.

A national audit database on core outcome parameters must be commissioned. This funded body must ensure the quality of uploaded data and should be allowed to peer review centers. Such audit should link to international endeavors on service enhancement and further enhance the quality of cancer care,

A program for developing training for communication skills is essential, and funding for workshops for the same is likely to directly improve patient care.

Workshops for training specialist breast care nurses and ASHA workers will need funding and support.

Recommendations

(i) *Immediate*: Seed funding from government agencies to initiate high-quality multicentric audits across Indian centers will soon affect the quality of care. This funding will promote transparency, and a peer review process will improve the standards of breast radiotherapy care. Such audits will facilitate the establishment of a national database of key outcomes, identify areas of need, enhance protocol-based working patterns, and highlight areas requiring research.

Bridging courses for competent radiation technicians to function as dosimetrists under the supervision of medical physics staff could be funded through the national skill development program. This will ease planning bottlenecks.

Certificate programs should be encouraged for all staff to upskill their breast radiotherapy practices.

Communication skills training programs should be made mandatory, and funded workshops should be encouraged.

(ii) *Medium and long term*: Setting up an RT facility requires intense capital outlay for the purchase of equipment, construction to conform to radiation safety standards, quality assurance, and personnel. Although the initial investment in setting up RT machines is high, modern linacs are versatile and run for 12-15 years without major breakdowns.

Encourage public-private participation in setting up RT facilities. (3-5 years).

Explore collaboration with organizations such as IAEA for funding for the RT unit. (3-5 years). The IAEA Rays of Hope initiative (RoH) is aimed at assisting member states in establishing/expanding capacities in radiotherapy and multimodality medical imaging. The initiative will support the designated RoH Anchor Centers, thereby strengthening and expanding their capacity to conduct critical work more effectively. RoH emphasizes equipment, training, research/innovation, and support for high-impact interventions for cancer patients, thereby contributing directly to the achievement of the United Nations Sustainable Development Goal.[136]

Collaboration with RT machine vendors for a bulk order of work-horse linacs with the capability of 3DCRT and IMRT with KV (2D) imaging for installation at multiple sites so that total cost may be reduced. (3-5 years)

Government subsidy or relaxation in statutory taxes for the infrastructure investment by the government/government autonomous and not-for-profit organizations must be encouraged. ((>5 years)

Explore the possibility of having the international vendors set up their manufacturing units in India. (>3 years)

The manufacture of high-quality indigenous linear accelerators is essential. These machines should deliver the same precision as imported models, be user-friendly, and provide timely, high-quality service. This initiative should be targeted for development over a timeframe of more than five years.

Patients can receive treatment through government insurance schemes. However, the loss of wages for the caregiver and other costs are a significant hurdle. Providing sustenance amounts for caregivers during the period of radiotherapy to compensate for the loss of wages (only for caregivers who are unemployed/not more than unskilled laborers and conditional on the patient completing the planned treatment). This support could serve as an incentive to complete treatment.

Key issues/gaps in the current policymaking.

(i) *Immediate*: Ensure a strong steering group is formed that drives a national breast cancer radiotherapy delivery program. This should include developing an SOP by consensus, driving QA processes, and developing an audit program.

Mandate setting up of Cancer Therapy/RO dept in all medical colleges - NMC notification

Consider subsidizing/incentivizing centers investing in cancer infrastructure in areas of need (at least for Govt & Govt grant-in-aid institutions).

Commission a multidisciplinary group that enhances breast cancer research, which examines India-specific solutions on breast cancer radiotherapy areas of need.

Strategize to work with regulatory authorities to provide bridging programs for radiotherapy technicians and nurses.

(ii) *Medium and long term*: Develop Private-Public relationships and commission more cancer centers delivering radiation therapy near patients' homes.

Work with regulatory bodies to train dosimetrists.

Incentivize training of medical physicists and radiation therapy technicians.

Key issues and gaps in research infrastructure, human resources, and output. Recommendations to bridge the research gaps

(i) *Immediate*: Develop customized bridging courses and certificate programs for enhancing breast radiotherapy skills for doctors, medical physicists, dosimetrists, and radiotherapy technologists.

Fund a national outcome audits database that documents and reviews key radiotherapy outcomes in breast cancer.

Funding for clinical research addressing efficacy and safety issues in RT is relevant to India and is expected to benefit most patients.

WAY FORWARD

Suggested policy activities and advocacy for policymakers

Equitable distribution of cancer care services

Inequitable distribution of cancer care services has been identified as one of the major barriers to providing comprehensive breast cancer care in the country. Focusing on underserved areas in the development of cancer care infrastructure can help overcome this barrier.

Manpower training

There is a significant shortage of human resources especially medical oncologists and medical physicists. With the development of infrastructure, trained manpower will be required for treating cancer patients. Many medical colleges associated with tertiary care centers currently lack these departments. Policymakers may consider establishing these departments in top medical colleges where adequate training can be provided in the future to overcome this barrier.

Expansion of infrastructure

In diagnostics, there is a critical need for digital mammography machines and radiotherapy services to treat patients with breast cancer in India.

Improved access to systemic treatment drugs

The cost of breast cancer treatment is increasing as newer and more effective drugs are incorporated into treatment. We have classified the drugs as essential and optimal [Table 5]. Access to essential drugs should be improved to increase the proportion of patients who can receive such treatment.

Access to genetic counseling and testing

Approximately 18% of women with breast cancer have a genetic mutation. Despite a significant decrease in the cost of testing, access to genetic testing remains limited for many patients. The inclusion of genetic counselor teleconsultation and genetic testing in PM-JAY may improve access for a significant number of beneficiaries.

Screening program for breast cancer

The incidence of breast cancer in urban India is steadily increasing. We need a two-pronged approach. A screening program with clinical breast examination and an augmentation of diagnostic mammography infrastructure may be cost-effective for the Indian scenario.

Awareness programs

A significant proportion of patients present with advanced breast cancer. Programs using mass media channels have the potential to increase public awareness of breast cancer.

Industry-academia partnership for research and development

Most innovation in breast cancer treatment originates from the West, resulting in the ever-increasing cost of newer cancer drugs. Industry-academia partnerships and funding for research and development are needed to bring innovation from the countryside and keep the cost of cancer care under control.

Recommendations for health/medical professionals

Early introduction of breast cancer in curriculum of medical education:

Every physician in the country should be familiar with common cancer presentations and diagnostic workups. There is a significant delay between the presentation of a patient and the appropriate referral to an oncology center. This can be reduced by including breast cancer early in medical education.

Training programs

Establish short-term educational programs and workshops for healthcare professionals, including oncologists, surgeons, radiologists, pathologists, nurses, and allied health professionals, to improve their knowledge and skills in breast cancer diagnosis, treatment, and survivorship care.

Interdisciplinary training

Develop interdisciplinary training programs and tumor boards involving oncologists, surgeons, radiologists, pathologists, nurses, and psychologists to foster collaboration and improve care coordination for breast cancer patients.

Suggestions to create awareness among the general public, NGOs, and community stakeholders

Patient advocacy

There is a significant unmet need for breast cancer patient advocates in India who can play a critical role in bridging the gap between policy makers and patients. NGOs and community stakeholders need to form such disease- specific patient advocacy groups.

Awareness campaigns

In addition to policy makers, NGOs and community stakeholders need to be involved in awareness campaigns. Key community stakeholders can be selected as ambassadors for such campaigns.

Philanthropic donations for access to treatment and research

Most research funding in India comes from government agencies. However, NGOs can play a critical role in channeling philanthropic donations to improve access to treatment and promote indigenous research.

Patient support groups

Patient support groups can help patients navigate their treatment and survivorship issues, and NGOs can help bring together patients and survivors from multiple oncology centers to address their needs..

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Task Force Report

NAMS task force report on antimicrobial resistance

Arunaloke Chakrabarti[1], V Balaji[2], Nitin Bansal[3], Ram Gopalakrishnan[4], Pratima Gupta[5], Amita Jain[6], Pratibha Kale[7], Arti Kapil[8], Kashi Nath Prasad[9], Pallab Ray[10], Camila Rodrigues[11], Kamini Walia[12]

[1]Chairperson, Task Force, Director, Doodhadhari Burfani Hospital and Research Institute, Haridwar, [2]Department of Microbiology, Christian Medical College and Hospital, Vellore, [3]Rajiv Gandhi Cancer Institute, Delhi, [4]Institute of Infectious Diseases, Apollo Hospital, Chennai, [5]Department of Microbiology, All India Institute of Medical Sciences, Deoghar, Jharkhand, [6]Department of Microbiology, King George's Medical University, Lucknow, Uttar Pradesh, [7]Department of Clinical Microbiology, Institute of Liver and Biliary Sciences, New Delhi, [8]Department of Microbiology, North DMC Medical College and Hindu Rao Hospital, New Delhi, [9]Department of Microbiology, Apollomedics Super Speciality Hospital, Lucknow, [10]Faculty, KIMS, Bhubaneswar and Department of Medical Microbiology, PGIMER, Chandigarh, [11]Department of Laboratory Medicine, Hinduja Hospital, Mumbai, [12]Division of Descriptive Studies, Indian Council of Medical Research, New Delhi, India.*

EXECUTIVE SUMMARY

Background

Antimicrobial resistance (AMR) has emerged as a public health concern, especially in light of the fact that newer antibiotic classes have been slow to develop and investments in novel antimicrobial drug classes have been receding. India is among the countries that contribute significantly to global AMR due to extensive antibiotic abuse, a prime driver of AMR. Widespread resistance increases the use of broad-spectrum empiric antibiotic therapy, narrowing treatment options and worsening patient outcomes. Over-the-counter use of antibiotics, lack of awareness, inadequate use of diagnostics, overcrowding, cross-infections, financial compensation of doctors by pharmaceuticals, and poor health infrastructure also amplify AMR problems in India. Referred to as the world's AMR capital, India is battling emergent superbugs with limited treatment options. In India, annually, more than 58,000 newborns die due to sepsis triggered by resistant bacteria, which is expected to rise to 2 million deaths by 2050.

Current antimicrobial resistance scenario in India

The available data indicates a rise in the AMR rates across multiple pathogens of clinical importance. An indicator of the rising tide of AMR in India is the rapidly increasing proportion of isolates that are resistant to extended-spectrum cephalosporins and carbapenems. Among Enterobacterales, >70% of *Escherichia coli* and at least 80% of *Klebsiella pneumoniae* were extended-spectrum beta-lactamase producers. A substantial level of carbapenem resistance has been reported in *K. pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. In the past 6 years, carbapenem resistance has substantially increased in hospital-acquired isolates of both *E. coli* (from 19% in 2017 to 34% in 2022) and *K. pneumoniae* (from 41% in 2017 to 58% in 2022). More than 30% of *P. aeruginosa* isolates and >90% of *A. baumannii* isolates are resistant to carbapenems. Carbapenem-resistant *A. baumannii* is the leading cause of ventilator-associated pneumonia in Indian intensive care units (ICUs).

In India, a sharp increase in carbapenem resistance in gram-negative pathogens leaves patients with limited treatment options and increases the risk of AMR-attributed mortality in patients. Emergence of resistance to colistin has already been documented in India, although current resistance rates are estimated to be less than 10%. In addition, emerging new resistance mechanisms such as PBP3 insert in *E. coli* and mutation in the siderophore iron transport channels contributing to the development of pan-drug resistance are of great concern. As India has been witnessing a dominance of New Delhi metallo-β-lactamase (NDM) among Enterobacterales, clinicians are desperately looking for safer and effective substitutes for polymyxins that are currently considered as salvage therapies. Among gram-positive pathogens, there is an incremental increase in the trend of Methicillin

Corresponding author: Prof. Arunaloke Chakrabarti, MD, Department of Infectious Disease, Doodhadhari Burfani Hospital and Research Institute, Bhupatwala, Haridwar, India. arunaloke@hotmail.com

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resistant staphylococcus aureus (MRSA), 33% in 2017 to 44.5% in 2023. Similarly, there is a noticeable increase in the proportion of vancomycin resistance in *Enterococcus* sp., which is five times higher in *E. faecium* than *E. faecalis*.

The Indian Council of Medical Research (ICMR) has established a national network on surveillance of AMR in laboratories based at academic centers, targeting medically important index microbes that have been identified by the World Health Organization (WHO). The Antimicrobial Resistance Surveillance Research Network (AMRSN) established by the ICMR has six reference laboratories for six pathogenic groups that are located in four tertiary care medical institutions. The AMRSN also incorporates an in-depth understanding of the clonality of drug-resistant pathogens and the transmission dynamics to enable a better understanding of AMR in the Indian context and devise suitable interventions. However, more proactive steps are warranted. The burden of AMR in community, livestock, and food animals has been poorly documented in India. Apart from sporadic, small, localized studies, evidence that can be extrapolated to the national level is lacking. The AMRSN, although currently limited to human health, plans to scale up on a national level and expand its ambit to include samples from a wider spectrum of sources, including animal, environmental, and food samples, to reflect the One Health approach to surveillance. Apart from the absence of a One Health approach to surveillance, another weakness of the existing surveillance systems for AMR in India is that it does not account for antibiotic use.

The existence of a surveillance system that can establish the relationship between antibiotic consumption patterns and the emergence of AMR is vital in producing evidence that may help in the designing and evaluation of effective interventions. In 2017, the Indian Ministry of Health and Family Welfare published the national action plan (NAP) for containing AMR. This 5-year NAP on AMR (2017–2021) outlines the priorities and implementation strategies for curbing AMR in India. NAP focuses equally on human, environment, and food–animal sectors to encompass a One Health approach. Priorities outlined in the NAP for antimicrobial resistance in India are as follows: i) improve awareness and understanding of AMR through effective communication, education, and training; ii) strengthen knowledge and evidence through surveillance; iii) reduce the incidence of infection through effective infection, prevention, and control; iv) optimize the use of antimicrobial agents in all sectors; v) promote investments for AMR activities, research, and innovations; and vi) strengthen India's leadership on AMR by means of collaborations on AMR at international, national, and subnational levels. However, implementation is slow and a big push is needed by all stakeholders. The lack of a separate financial allocation remains the greatest challenge for the implementation of NAPs in India.

Antifungal resistance was never a major concern till the emergence of multidrug-resistant *Candida auris*. This resistant fungus entered Indian ICUs in 2009 and has since been isolated in nearly all hospitals in India. This fungus behaves like a bacterium, develops resistance very quickly, is easily transmitted, causes outbreaks, contaminates the hospital environment, resists many disinfectants, and is not easily identified. Indian strains are classified under Clade I, which has resistance rates of 58–100% to fluconazole, 50% to voriconazole, 30% to amphotericin B, and 10% to at least one echinocandin. At present, *C. auris* is the most common yeast fungus isolated from blood in many Indian ICUs. Besides *C. auris,* fluconazole resistance is increasing in the commonly isolated species such as *C. tropicalis* and *C. parapsilosis* in many centers of this country. Among mycelial fungi, though azole resistance is not very high in *Aspergillus fumigatus* in India, the comparatively more resistant *A. flavus* is isolated as often as *A. fumigatus* from patients with invasive aspergillosis.

Management of dermatophytosis was never considered difficult until the emergence of *Trichophyton indotineae,* a new species of the *T. mentagrophytes* complex, which is resistant to multiple antifungal agents, especially allylamines, across India.

Gaps in addressing antimicrobial resistance

Unnecessary or irrational use of antibiotics in humans, animals, and agro-industries and inadequate diagnostic facilities are among the leading causes of AMR. There is a lack of national-level data on the overuse or misuse of antibiotics in the community, animals, environment, and agriculture. The inappropriate use of colistin in animals as a growth promoter and in agriculture has led to colistin resistance in India. Given that there are few regulations against the use of antibiotics for non-therapeutic purposes in India, with no stringent implementation protocols even when there are regulations, the emergence of AMR from antibiotic overuse in the animal sector is likely to be an unmeasured burden in India.

Lack of trained manpower and inadequate laboratory facilities to support clinicians with the microbial culture test and suggesting an appropriate antibiotic may result in inappropriate antibiotic use. Moreover, India lacks diagnostic facilities to identify resistant pathogens' susceptibility to antibiotics. Respiratory tract infections are common, and improved diagnostics could substantially reduce antibiotic overuse.

Rapid diagnostic tests are quick, easy to perform, highly sensitive, and specific in point-of-care settings, thereby facilitating timely definitive therapy and reducing length of stay, cost, morbidity, and mortality. This is further compounded by the inadequacy of healthcare facilities lack of monitoring systems to control antibiotic prescription and dispensing practice by health system (to stop the sales of over-the-counter antibiotics).

India is also known for poor antibiotic stewardship practices that are reflected in the high antibiotic resistance rate. Inadequate training on antimicrobial prescription combined with the lack of a functional policy on antimicrobial use has led to unchecked growth of AMR in Indian hospitals. AMSP program at the Indian healthcare level is still rudimentary and needs to gain momentum to develop proper disease surveillance infrastructure and initiate basic AMR research. Structured education and training on AMSP are inadequate in India. A survey found that 88% of postgraduate students did not receive any education and training at induction or during employment. The intervention of various stakeholders is essential for the sustainable design and implementation of hospital-based AMSP in India.

Inadequate infection prevention control practices, including hand hygiene promotes the transmission of AMR.

Increasing awareness and understanding of AMR through effective communication, education, and training is one of the main strategies to contain AMR. It has to leverage public communication programs to encourage behavior change in target populations, namely, stakeholders in human and animal health, and agriculture. There is also a need to increase awareness about the necessity to contain AMR at higher levels of policymaking, so that this aspect may emerge as a priority in the health policies of the nation. In addition, the exit of big pharma from antibiotic development and the lack of investment from venture capitalists to support the commercial viability of antibacterial agents have pushed AMR into a global health crisis. Without addressing gaps in the identified areas, sustained progress in AMR mitigation is unlikely.

Recommended intervention strategies

Tackling AMR requires a comprehensive set of interventions. Health workers across a spectrum of disciplines play an important role in ensuring the responsible use of antimicrobial agents to treat prevalent infectious diseases. Simple measures to prevent infections, such as vaccinations and promoting hand hygiene and better hygiene in healthcare facilities, more than halve the risk of death and decrease the health burden of AMR. Similarly, integrated delivery of policies that promote hospital hygiene, antimicrobial stewardship (AMS), and the use of diagnostic tests to differentiate bacterial versus viral infections and mass media campaigns could significantly reduce the burden of drug-resistant infections. WHO defines AMS as a coherent set of integrated actions that promote the responsible and appropriate use of antimicrobials to help improve patient outcomes across the continuum of care. Moreover, effective implementation of AMS activities in healthcare facilities require a comprehensive approach at national policy and program levels.

Responsible and appropriate use of antimicrobials include prescribing only when needed and selection of the optimal drug regimen, drug dosing, route of administration, and duration of treatment following proper and optimized diagnosis. Evidence shows that health workers and students want to improve their knowledge and level of competency through targeted, effective, and relevant education and training on AMR. The module of the curricula guide includes the following: i) build knowledge and awareness of AMR; ii) appropriate use of antimicrobial agents; iii) infection prevention and control; iv) diagnostic stewardship and surveillance; and v) ethics, leadership, communication, and governance. In addition, public engagement and education aim to empower and engage the public on the risk of exposure to antimicrobials. Moreover, strengthening AMR surveillance improve the understanding of AMR, and how resistant microorganisms spread across and between humans, animals, agriculture, and the environment.

Many organizations have been formed and policies framed to control infectious diseases, optimize antibiotic usage, and prevent AMR. Between 2009 and 2011, the Global Antibiotic Resistance Partnership (GARP), India working group was established to create a platform for developing practical policy proposals on AMR. In 2012, ICMR initiated an antimicrobial stewardship program (AMSP) in collaboration with many institutions. In 2014, the Central Drug Standard Control Organization (CDSCO) introduced Schedule H1, in which antibiotics could be dispensed only against a valid prescription, with records of antibiotic sales to be maintained for at least 3 years. In 2016, the National Center for Disease Control (NCDC) published the National Treatment Guidelines for antimicrobial use in infectious diseases. Further, in 2017, ICMR published guidelines on the optimization of antibiotics, which includes the new WHO method of antibiotic classification ("AWaRe") in the 20th Essential Medicine list to strengthen AMSPs in hospitals. The ICMR also instituted an evaluation of the AMSP through an in-depth facility survey in private and government healthcare institutions. It is observed that the stewardship programs in private institutions were better equipped to deal with emerging crises such as AMR or hospital-associated infection outbreaks, as compared to the

government facilities in the survey. It is suggested that the accreditation mandates, which certain private institutes adhere to on account of financial compulsions, may have a positive impact on the program. The purpose of the document is to provide core interventions to mitigate AMR. The proposed interventions are based on the strategies at the level of policymakers, regulatory, and healthcare facilities, including antimicrobial stewardship and prevention of infections, clinical microbiology laboratory for timely and accurate diagnosis, research and development of novel antibiotics, and rapid diagnostics and one health approach. Undoubtedly, mitigating AMR requires a coordinated approach across the human and animal health, agriculture, and the environment sectors. In the long term, effective multisectoral collaboration requires governments to take ownership of the NAP implementation process and ensure it is appropriately resourced and given sufficient visibility to keep it a national priority. The document could be helpful to other stakeholders, such as those responsible for healthcare quality improvement, patient safety, health facility accreditation or regulation, public health, infectious disease control and surveillance, water, sanitation and hygiene, occupational health, AMSP, clinical microbiology, and environmental health interventions.

CURRENT STATUS OF ANTIMICROBIAL RESISTANCE IN INDIA

(a) Antibacterial resistance

Antimicrobial resistance (AMR) has been identified as a serious threat to global health, with an estimated 4.95 million deaths associated with bacterial AMR.[1] The speed with which new resistance phenotypes and mechanisms has emerged and spread highlights that the development of new drugs alone is not sufficient to address the growing resistance problem. Two institutions within India's Ministry of Health, the Indian Council of Medical Research (ICMR) and the National Center for Disease Control (NCDC), have developed national networks of public and private hospitals to measure AMR trends, prevent healthcare-associated infections (HAIs), and enhance appropriate use of antibiotics.

Gram-negative pathogens

In the study of national AMR surveillance conducted by ICMR and NCDC, Enterobacterales and non-fermenting gram-negative bacilli (*P. aeruginosa* and *A. baumannii*) were reported as the most common gram-negative pathogens.[2,3] The AMR surveillance data for 2022, reported by ICMR and National Antimicrobial Surveillance network (NARS-Net) Net by NCDC, is given in Table 1. In *E. coli*, >70% of the isolates are phenotypically identified as Extended-spectrum beta-lactamase (ESBL)-producers; among them, CTXM-15 (34%) was the most common ESBL-encoding gene, followed by CTXM-1 (19%) and Temoniera extended spectrum beta-lactamase (TEM) (17%). An inhibitor-resistant penicillinase, OXA-1, was found in 28% of ESBL *E. coli* isolates. Among *K. pneumoniae*, at least 80% of the isolates were identified as ESBL producers, SHV (49%) was predominant, followed by CTXM-15 (34%) and CTXM-1 (23%). OXA-1 was identified in 22% of *K. pneumoniae* isolates. In the past 6 years, carbapenem resistance has substantially increased in both *E. coli* (from 19% in 2017 to 34% in 2022), and *K. pneumoniae* (from 41% in 2017 to 58% in 2022). Among carbapenem-resistant *E. coli*, NDM-1 was seen in >95% of the isolates.[4] In carbapenem-resistant *K. pneumoniae*, dual carriage of both New Delhi metallo-β-lactamase (NDM) and OXA-48-like carbapenemases was found in 60% of the isolates, while OXA-48-like carbapenemases alone was seen in 40% of the isolates.[5]

Susceptibility to amikacin was significantly different between carbapenem-resistant *E.* coli (52%) and *K. pneumoniae* (16%) isolates. Recently, in 2022, the Clinical and Laboratory Standards Institute (CLSI) guideline has lowered the susceptibility breakpoint of amikacin to ≤ 4 mg/L: applying this revised breakpoint further reduces the susceptibility to amikacin.[6] Further, the combination of aminoglycoside-modifying enzymes with 16SRMTases is observed in 48% of NDM-producing *E. coli* and 35% of OXA-48-like-producing *K. pneumoniae*.[7] Therefore, the increasing prevalence of 16SRMTases limits the clinical utility of aminoglycosides including the new agent plazomicin against carbapenem-resistant Enterobacterales. Fluroquinolones (>60% of isolates are resistant) showed limited activity against Enterobacterales.[2,3]

The acronym SPICE (*Serratia* spp, *Providencia* spp, indole-positive proteus, *Citrobacter* spp., and *Enterobacter* spp.) denotes organisms at risk for ampC production. Indole-positive *Proteus* spp. currently refers to organisms such as *P. vulgaris* and *P. penneri*, which generally do not contain chromosomal ampC genes. The emergence of clinically relevant ampC expression during antibiotic treatment has been most frequently described in *E. cloacae*, *K. aerogenes* (formerly *Enterobacter aerogenes*), and *C. freundii*.[8] Clinical reports suggest that the emergence of resistance after exposure to an agent like ceftriaxone may occur in approximately 8–40% of infections caused by these pathogens.[9] Therefore, when *E. cloacae*, *K. aerogenes*, or *C. freundii* are recovered in clinical cultures (other than those associated with uncomplicated cystitis), treatment with ceftriaxone or ceftazidime is not recommended, even if an isolate initially tests susceptible to these agents.[9] In contrast, other organisms historically presumed to be at risk for the development of clinically significant ampC expression, such as *Serratia marcescens*, *Morganella morganii*, and *Providencia* species, express clinically significant ampC production in less than 5% of isolates, and antibiotics can be selected according to susceptibility testing results.[8]

Enterobacter spp. and *Citrobacter spp.* are the most common pathogens, and the remaining are seen in ≤ 1% of the clinical cultures.[2,3] Carbapenem resistance rates are lesser than 30% in the SPICE pathogens (27% in *E. cloacae*, 29% in *C. freundii*, 22% in *C. koseri*, and 23% in *S. marcescens*). In the past 6 years, susceptibility to piperacillin/tazobactam has been steadily decreased in *Enterobacter* spp. (62% in 2017 to 38% in 2022) and *Citrobacter spp.* (58% in 2017 to 43% in 2022), perhaps due to the revised piperacillin or tazobactam susceptibility breakpoint published in 2022. No significant change in the trend of carbapenem susceptibility has been noticed in these pathogens.[2,3]

In *P. aeruginosa*, nearly 41–44% of the isolates are found to be cephalosporin resistant.[2,3] The presence of *Pseudomonas*-derived cephalosporinase (PDC) variants can confer resistance to cephalosporins, some variants (PDC-10, PDC-11) can hydrolyze penicillin and first-generation cephalosporins, and some can hydrolyze up to third-generation cephalosporins (PDC-2, PDC-3). In *P. aeruginosa*, Vietnamese extended-spectrum beta-lactamase (VEB) is identified as the most common ESBL gene, followed by TEM. More than 30% of *P. aeruginosa* isolates are resistant to carbapenems, and among them, NDM (41%) is predominant, followed by Verona Integron-encoded Metallo-beta-lactamase (VIM) (9%).[2] Interestingly, dual carbapenemase producers of NDM with VIM or Imipenemase (IMP) is also noticed among carbapenemase-producing *P. aeruginosa* isolates. In the last 3 years, there has been a significant shift from VIM to IMP producers in different geographic regions of India.[2,10] This change has led to NDM being the predominant carbapenemase in >95% of *P. aeruginosa* isolates in many hospital settings. Nearly half of the *P. aeruginosa* isolates are susceptible to fluroquinolones. The CLSI guideline recommends amikacin's susceptibility breakpoints only for urinary isolates, suggesting that amikacin monotherapy may not be appropriate for treating systemic infections.[11]

The high carbapenem resistance rate of >80% in *A. baumannii* makes it challenging to treat.[2,3] Nearly 55% of the isolates are susceptible to minocycline though, in the last 6 years of surveillance, there has been a drop in the susceptibility rate from 67% in 2017 to 59% in 2022.[2] Among carbapenem-resistant *A. baumannii*, 40% of the isolates have an OXA-23-like gene and dual carbapenemase production of OXA- 23-like and NDM are identified in 60% of the isolates.[2]

Over 50% of infections in most ICUs in tertiary care centers in India are caused by difficult-to-treat (DTR) gram-negative pathogens. It is important to note that both ICMR and NARS-Net surveillance studies have documented dramatically higher resistance rates in isolates from the ICUs to all antibiotics in comparison to wards or outpatient clinics. In India, a sharp increase in carbapenem resistance in gram-negative pathogens is seen [Table 1], which leaves patients with limited treatment options and increases the risk of AMR-attributed mortality in patients. Further, the declining effectiveness of antibiotics imposes potentially large health and economic burdens.

Polymyxins- or tigecycline-based combinations are most often deployed as first-line therapy for treating DTR gram-negative infections. The emergence of resistance to polymyxin has already been documented in India, however, the resistance rate seems to be <10%.[12] For *Acinetobacter* spp., neither CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) has defined the susceptibility breakpoints for tigecycline. Against carbapenem-resistant *A. baumannii*, the MIC90 of tigecycline is 8 mg/L; this elevated MIC could be due to the presence of multidrug-resistant efflux pumps.[13] Minocycline retains its activity against 57% of carbapenem-

Table 1: Carbapenem resistance rates reported by the national AMR surveillance studies for the year 2022, from India

	% of cephalosporin-resistant gram negative pathogens			
	E. coli	***K. pneumoniae***	***P. aeruginosa***	***A. baumannii***
ICMR	81	81	41	91
NARS-Net	76	83	44	73
	% of carbapenem resistance in gram negative pathogens			
	E. coli	***K. pneumoniae***	***P. aeruginosa***	***A. baumannii***
ICMR	30	56	36	86
NARS-Net	35	47	27	59
	% of colistin resistance in gram negative pathogens			
	E. coli	***K. pneumoniae***	***P. aeruginosa***	***A. baumannii***
ICMR	3	6	3	5
NARS-Net	0	< 1 (0.4)	< 1 (0.1)	< 1 (0.4)

AMR: Antimicrobial resistance, ICMR: Indian Council of Medical Research, NARS: National Antimicrobial Resistance Surveillance Network (NARS-Net India)

resistant *A. baumannii* with a MIC90 of 16 mg/L.[13] Despite active treatment, carbapenem-resistant *A. baumannii* has been reported to be associated with 40% mortality.[14]

Among the recent Food and Drug Administration-approved beta-lactam OR beta-lactamase inhibitors, only ceftazidime/avibactam has been approved for clinical use in India. Ceftazidime/avibactam offers broad spectrum of coverage against ESBL, ampCs, and carbapenemases such as OXA-48-like and KPCs, but lacks activity against metallo-beta-lactamase producers, including NDM.[15] In Indian scenario, almost all the NDM-producing *E. coli* (>95%) and dual NDM/OXA-48-like-producing *K. pneumoniae* isolates (at least 60%) are completely resistant to ceftazidime/avibactam.[16] This suggests that ceftazidime/avibactam is a reasonable alternative to standard therapy only for the treatment of infections caused exclusively by OXA-48-like-producing Enterobacterales.

The only NDM-active β-lactam treatment option available in India is the combination of ceftazidime/avibactam plus aztreonam and is viewed as a "rescue therapy" for serious NDM infections.[17,18] This triple combination evades the activity of NDM enzymes as well as several other β-lactamase enzymes commonly co-produced with NDMs. More specifically, aztreonam is able to withstand hydrolysis from NDM enzymes. The β-lactamase inhibitor avibactam inactivates co-produced serine β-lactamases, enabling aztreonam to bypass hydrolysis from these enzymes and to safely reach its site of activity, penicillin-binding protein 3 (PBP3). However, susceptibility estimates of NDM-producing Enterobacterales to the combination of ceftazidime/avibactam with aztreonam are unclear, given the heterogeneity of susceptibility testing methods used for testing this combination.[17] Recently, there have been reports showing the presence of novel four-amino-acid inserts (YRIN/YRIK) in *E. coli* PBP3, which is a worrisome phenomenon.[19] PBP3 is a primary target for many beta-lactams, these four amino acid inserts reduce the affinity of PBP3 against beta-lactams such as aztreonam, ceftazidime, ceftolozane, and piperacillin.[19] Moreover, PBP3 mutants in conjunction with NDM in *E. coli* can confer resistance to ceftazidime/avibactam with aztreonam combination.[16] It is expected that in the future, cefiderocol, aztreonam/avibactam, and cefepime/taniborbactam will be available in India as NDM-targeted treatment options. Cefiderocol is a siderophore-conjugated cephalosporin with activity against NDM-producing Enterobacterales. PBP3 is also a site of action of cefiderocol, and therefore PBP3 inserts in *E.* coli have the ability to compromise the activity of cefiderocol. Analysis of PBP3 for the presence of 4-amino-acid insertions among *E. coli* isolates revealed an overwhelming proportion of isolates (97%) harbored the inserts. Cefiderocol showed limited activity against *E. coli* isolates cocarrying NDM with PBP3 inserts, with only 39.3% being susceptible (Dr Balaji V unpublished data). Compared to *E. coli*, cefiderocol exhibited an improved activity against NDM and/or OXA-48-like-producing *K. pneumoniae*, and 80% were susceptible (Dr Balaji V unpublished data). The activity of cefiderocol against the NDM producers was lower compared to KPC and OXA-48-like producers. The vulnerability of cefiderocol to NDM producers was likely due to a combination of the resistance mechanisms, namely, i) PBP3 insert, ii) truncated iron-binding protein, *cir* A, and iii) a CMY gene.[20]

Resistance to aztreonam/avibactam is increasingly being reported in *E. coli* isolates co-harboring PBP3 inserts with NDM.[19] It seems that the combination of two resistance mechanisms, NDM and PBP3 inserts in *E. coli*, leads to a significant compromise in the activity of aztreonam/avibactam through an incremental increase in their MICs in nearly 33% of the isolates.[16] Finally, the presence of the CMY-42 variant in the background of resistance mechanisms such as NDM and PBP3 inserts has been linked to elevated MICs and confers frank resistance to aztreonam/avibactam.[21] This is plausible as alterations in PBP3 reduce the amount of aztreonam reaching its target, making it vulnerable to hydrolysis from CMY enzymes. Among NDM-producing *K. pneumoniae*, almost all isolates are highly susceptible to aztreonam/avibactam, as PBP3 insert has not been reported in *K. pneumoniae*.[16]

In the series of beta-lactamase inhibitors, taniborbactam is shown to inhibit all four Ambler class A, B, C, and D enzymes (except IMP), and its combination with cefepime has recently completed a registrational Phase 3 trial. Analysis of cefepime/taniborbactam activity based on MICs revealed excellent activity against isolates expressing OXA-48-like producers and suboptimal activity for isolates producing NDM alone or NDM with OXA-48-like. Against NDM-producing *E. coli* isolates, susceptibility to cefepime/taniborbactam is only 12.3%.[16] On the other hand, improved activity of cefepime/taniborbactam against NDM-producing *K. pneumoniae* with 74.5% inhibition is observed.[16] The presence of NDM with four amino-acid inserts in PBP3 of *E. coli* leads to a significant compromise in cefepime/taniborbactam activity.[16] In *K. pneumoniae*, it is believed that the poor activity of cefepime/taniborbactam against such isolates could be linked with impermeability.

Cefepime/zidebactam is a beta-lactam/beta-lactam enhancer combination in Phase III clinical development. Cefepime (binds with PBP1a, 1b and PBP3) and zidebactam (binds with PBP2) have been reported to concurrently inactivate multiple PBPs, thereby triggering synergistic and pleiotropic bactericidal action that is independent of beta-lactamase inhibition. Cefepime/zidebactam potently inhibited all NDM-producing *E. coli* at MIC of ≤ 2 mg/L and NDM-producing *K. pneumoniae* at ≤8 mg/L.[16] Importantly, cefepime/zidebactam readily overcomes the challenge of NDM plus PBP3 amino acid inserts in *E. coli*, which is attributed to zidebactam's PBP2-binding-mediated beta-lactam-enhancer action.

Preexisting resistance mechanisms to cefiderocol, aztreonam/avibactam, and cefepime/taniborbactam even before their approval for clinical use in India are of great concern. As India has been witnessing a dominance of NDM among Enterobacterales, clinicians are desperately looking for safer and more effective substitutes for polymyxins that are currently considered salvage therapies. The aforementioned evidence indicates that cefiderocol, aztreonam/avibactam, and cefepime/taniborbactam may not be able to comprehensively address the challenge of NDMs, and there is a continued need for novel options to ensure coverage of NDM-producing Enterobacterales.

Gram-positive pathogens

In *Staphylococcus aureus*, > 40% of isolates are identified as MRSA [Table 2]. The incidence of MRSA is higher in ICUs (50%), compared to wards (47%) and OPD clinics (40%). There is an incremental increase in the trend of MRSA from 33% in 2017 to 44.5% in 2022.[2] Erythromycin (24% vs 51%) and clindamycin (64% vs 83%) were substantially less active against MRSA than against MSSA isolates.[2,3] Inducible clindamycin resistance is conferred through the acquisition of either *erm*A or *erm*C gene. In Indian *S. aureus* isolates, *erm*C (67%) was predominant while *erm*A (33%) was also found.[22] Fluroquinolones had no activity against both MSSA and MRSA isolates. The heteroresistant vancomycin intermediate *S. aureus* has been reported in 12% of MRSA isolates causing bloodstream infections.[23,24] Genome sequencing of hVISA isolates revealed multiple mutations in the two component systems in *vra*SR, *gra*SR, and *tca*RAB. [23] Vancomycin or daptomycin insusceptible *S. aureus* has not yet been reported in India. However, phenotypic resistance to linezolid is documented in both MRSA (2%) and MSSA (<1%) isolates, though these isolates are not studied further for the molecular resistance mechanism.[2]

Among *Enterococcus spp*., *E. faecium* (52%) is more common than *E. faecalis* (48%).[2,3] Resistance to ampicillin (85% vs %24) and high-level gentamicin (64% vs 42%) is generally higher in *E. faecium* compared to *E. faecalis*.[2] Similarly, resistance to vancomycin is five times higher in *E. faecium* (27%) than *E. faecalis* (5%) [Table 2]. Vancomycin resistance–encoding gene, *van*A, is identified in >99% of Vancomycin resistant enterococci (VRE) isolates. In the past 6 years, the proportion of *E. faecium* and *E. faecalis* isolates resistant to vancomycin has substantially increased. In addition, resistance to linezolid is identified in 6% of *E. faecium* and 2% of *E. faecalis* isolates.[2,3]

Interestingly, Tn1546-like element carrying *van*A gene on a novel linear plasmid has been reported.[25] These linear plasmids are smaller in size compared to the circular plasmids, which facilitate rapid dissemination of vancomycin resistance in *Enterococcus* spp. The dual resistance mechanism of G2592T mutation in the 23S rRNA and acquisition of plasmid-meditated *optr*A conferring linezolid resistance have been reported in *E. faecium*.[26] The novel plasmid (pVB3025_2) co-carrying vancomycin and linezolid-resistance determinants highlight the threat for potential dissemination.

Table 2: Prevalence of MRSA and VRE reported by ICMR and NARS-Net

Resistant pathogens	% reported by ICMR	% reported by NARS-Net
MRSA	44.5	59%
Vancomycin resistant *E. faecium*	27%	-
Vancomycin resistant *E. faecalis*	5%	-
VRE	-	13%

MRSA: Methicillin resistant staphylococcus aureus; VRE: Vancomycin resistant enterococci; NARS: National Antimicrobial Resistance Surveillance Network (NARS-Net India), ICMR: Indian Council of Medical Research.

(b) Antifungal resistance in India

Antifungal resistance is steadily increasing in India, as is being observed worldwide. Of all fungal infections, Indian ICUs report an overall incidence of invasive candidiasis at 6.51 cases/1000 ICU admissions.[27,28] Among different *Candida* species, azole and multidrug resistance are reported in 11.8 and 1.9% isolates, respectively, with significantly higher prevalence of resistant bugs such as *C. auris* and *C. rugosa* in public sector hospitals.[27,28] Resistance rates of *C. auris* across Indian ICUs are 58.1% against fluconazole, 13.5% against amphotericin B, and 9.5% against caspofungin, the drug of choice for this species.[29] In North India, this multidrug-resistant yeast has even become the commonest species of *Candida,* causing candidemia in ICU settings.[30] Indian studies have shown resistance in *Candida* species to fluconazole (3.3–64%), amphotericin B (2.1–9%), voriconazole (2.4–44%), itraconazole (1.2–69%), and echinocandins (1.7–6.2%).[31] These are mostly reported in *C. parapsilosis* (fluconazole 32%); *C. krusei* (voriconazole 1.9%); *C. glabrata*, *C. guilliermondii*, *C. tropicalis, and C. krusei* (amphotericin B, up to 4.9%); and *C. tropicalis, C. albicans*, *C. glabrata*, and *C. krusei* (echinocandin, 6.2%).[31,32]

Among the mold infections, dermatophytes are notorious for the emergence of antifungal drug resistance in India. Resistance to terbinafine, the drug of choice for dermatophytosis, has become epidemic with development of atypical, widespread lesions and recalcitrant disease.[33–36] Recurrent dermatophytosis ranges from 9–60% of the cases, with predominance of infection by *T. interdigitale* (66.1%) and *T. rubrum* (26.3%).[36,37] Higher terbinafine resistance

(18–61%) is noted in *T. interdigitale* (17–76%) and *T. rubrum* (17.3%).[37–39] Various mutations responsible for terbinafine resistance are reported from Indian isolates, Phe397Leu, Ser395Pro/Ala448Thr, Leu335Phe/ Ala448Thr, Ser443Pro, Leu393Ser, and His440Tyr.[39] Fluconazole resistance is noted at nearly 35–39.5%.[37,38] No response to griseofulvin has also been noted with higher MICs to the drug.[37,40] This is attributed to the rampant use of over-the-counter topical creams having steroids in addition to antifungals and antibiotics. Moreover, this has probably led to the emergence of a virulent species, *T. indotineae* in India, where animal reservoirs of this agent and lack of infection control are considered as challenges, which require One Health approach to tackle the situation. Higher MICs of *T. mentagrophytes* as compared to *T. rubrum* have been noticed in various Indian studies.[36] The correlation between clinical resistance and higher MICs has also been noted in *T. rubrum* isolates.[41]

Invasive mold infections are reported at an incidence of 9.5 cases/1000 ICU admissions, with invasive aspergillosis and invasive mucormycosis being predominant infections.[42] Azole resistance in *A. fumigatus*, which is quite high in Europe (>20%), is low in India (1.5–2%).[43] This could possibly be due to under reporting or lower use of long-term azole therapy or non-azole fungicides. However, molecular-based study directly from respiratory samples detected azole-resistant mutations in 59% patients with chronic pulmonary aspergillosis (CPA) and 43% allergic bronchopulmonary aspergillosis (ABPA).[44] Similar mutations have been reported in 7% of environmental samples in India.[44] A country-wide analysis is required to determine the exact prevalence of azole resistance in *Aspergillus*.

GAPS AND CHALLENGES IN ADDRESSING ANTIMICROBIAL RESISTANCE

Antimicrobial resistance has established itself as one of the major global public health threats and in particular is at a grim scenario in India. In 2019, AMR was found to be directly responsible for 1.27 million global deaths and 4.95 million associated deaths. Various stakeholders have addressed AMR, however several gaps and challenges persist, which are as follows:

Overuse and misuse of antibiotics

Widespread overuse and misuse of antibiotics in human health, agriculture, and veterinary practices (driven by lack of awareness or negligence) contribute to the acceleration of AMR. In many regions, antibiotics are easily accessible without a prescription, leading to inappropriate usage.

Inadequate infection prevention and control

Weak infection prevention and control measures in healthcare facilities (due to inadequate training, infrastructure and implementation) facilitate the spread of antibiotic-resistant pathogens. Poor hygiene practices, inadequate sanitation, and insufficient access to clean water exacerbate the problem.

Limited new drug development and alternative therapies

There is a scarcity of new antimicrobial drugs in the pipeline. Pharmaceutical companies often find it economically unviable to invest in research and development for new antibiotics due to low profitability compared to chronic disease medications. The world faces an antibiotics pipeline crisis. There is inadequate research to generate a robust antibiotic pipeline in the face of rising levels of resistance, and there is also an urgent need for additional measures to ensure equitable access to new and existing vaccines, diagnostics, and medicines.

Lack of real-time and high-quality surveillance data

Many existing surveillance systems suffer from delays in data reporting and analysis, leading to a lag in identifying emerging resistance trends and implementing timely interventions. This issue is particularly pronounced in low- and middle-income countries, where robust surveillance infrastructure, standard protocols, and data-sharing capabilities are lacking.

Global coordination

AMR is a transnational issue requiring global cooperation, however, coordination among countries is often lacking. Fragmentation in policies, regulations, and standards hinders collective action against AMR. The Global Antimicrobial Resistance Surveillance System (GLASS) study aimed to standardize data collection, analysis, and monitoring of AMR on a global scale. However, it highlighted the stark scarcity of data from resource-limited settings. Constraints such as limited laboratory capacity, inadequate infrastructure, and funding shortages severely hamper their ability to effectively collect, analyze, and report AMR data. Furthermore, funds to fight AMR are not available proportionate to the severity of AMR problem.

Lack of public awareness

Low awareness among the general public, healthcare providers, and policymakers about the seriousness of AMR and the actions needed to mitigate it remains a challenge. Effective communication strategies are needed to increase awareness and promote responsible antimicrobial use. More importantly, AMR has not found its due weightage in political discussions.

Lack of trained manpower

The shortage of skilled personnel undermines the effectiveness of surveillance efforts and hampers the ability to detect, monitor, and respond to emerging threats of antimicrobial

resistance. Insufficient access to training programs and continuing education opportunities for healthcare professionals in resource-limited settings limits their capacity to conduct AMR surveillance activities. Without adequately trained professionals, there is a risk of inaccurate data collection, suboptimal laboratory testing, and inadequate analysis and interpretation of surveillance data.

Lack of well-equipped laboratories

Many lower and middle income countries (LMICs) lack well-equipped laboratories with trained personnel capable of conducting accurate and comprehensive AMR testing. This leads to incomplete or unreliable data on AMR patterns and trends, hindering the ability to effectively monitor and respond to antimicrobial resistance.

Lack of preparedness for outbreaks

Inadequate planning and resources devoted to AMR surveillance limit the ability to detect and respond to outbreaks of antimicrobial-resistant infections effectively. Without robust surveillance systems in place, there is a risk of delayed detection and response to emerging AMR threats, leading to increased morbidity, mortality, and healthcare costs.

Nonavailability of antifungal resistance testing

Access to reliable and standardized antifungal susceptibility testing methods remains limited. The emergence of multidrug-resistant *Candida auris*, terbinafine-resistant dermatophytes, and azole-resistant *Aspergillus fumigatus* highlights significant challenges in fungal infection management. These challenges require concerted efforts to raise awareness about fungal infections, improve training and education in mycology, and expand access to diagnostic mycology services.

Economic impacts

In addition to death and disability, AMR has significant economic costs. The World Bank estimates that AMR could result in US$ 1 trillion additional healthcare costs by 2050, and US$ 1 trillion to US$ 3.4 trillion gross domestic product (GDP) losses per year by 2030. Governments should step up to compensate the economic the economic impacts of AMR.

Addressing AMR requires a coordinated effort involving governments, healthcare professionals, researchers, pharmaceutical companies, and the public. Multisectorial collaboration, sustained investments in research and development, strengthened surveillance systems, and robust AMSP are essential for combating AMR and preserving the effectiveness of available antimicrobial drugs for future generations.

Lack of livestock AMR surveillance data

There is concerningly limited data on AMR's quantitative impact on current livestock production, which is mainly due to a lack of AMR surveillance and comprehensive data collection. The intergovernmental public health systems that track cases of resistance in humans offer little data on AMR in livestock, leaving a glaring gap in knowledge. Most imperatively, livestock AMR data deposits do not identify how these hotspots translate to financial and production loss; so, we are likely significantly underestimating AMR's current and future consequences. Without a true understanding of the present impact of AMR on animals, efforts to establish effective preventative measures to mitigate future impacts are stifled.

Implementation of NAP-AMR

Implementation remains fragmented and siloed, and greater political commitment and investment is needed. Marked gaps and variability in maturity of NAP development and operationalization across the domains of: i) policy and strategic planning; ii) medicines management and prescribing systems; iii) technology for optimized antimicrobial prescribing; iv) context, culture, and behaviors; v) operational delivery and monitoring; and vi) patient and public engagement and involvement; and vii) violations in the existing government laws and enforcements were seen. Further, there is a lack of financial allocation across states, and poor enforcement and inadequate multisectoral coordination have hampered progress. Implementation and enforcement of Schedule H1 have lagged far behind and have not resulted in reductions of nonprescription, over the counter (OTC) antibiotic use owing to poor regulatory enforcement by drug inspectors as well as limited capacity.

The gaps, actionability and impact have been summarized in the Table 2a below.

INTERVENTION STRATEGIES FOR CONTROL OF ANTIMICROBIAL RESISTANCE

1. General recommendation

Escalating resistance to antibiotics, including the most potent and last-line agents, is an urgent threat to global public health. The roots of AMR are multifactorial [Table 3]; the emergence of resistant strains has quickly followed the introduction of almost every new antibiotic, beginning with penicillin and continuing to the newest additions, ceftazidime/avibactam, ceftolozane/tazobactam, imipenem/relebactam, meropenem/vaborbactam, and cefiderocol.[45] Arguably, the largest contributor to AMR is the increase in antibiotic prescribing. From 2010 to 2015, global consumption of antibiotics increased by 65%.[46] In addition, climate change is expected to increase water- and vector-borne febrile illnesses, resulting

Table 2a: The gaps, actionability and impact to implement NAP-AMR (+++ means high, + low, ++ in between)

Gaps	Actionability		Impact
	Institutional	Noninstitutional	
Overuse/misuse of antibiotics	+++	+	+++
Inadequate infection prevention & control (IPC)	+++	+	+++
Lack of stewardship (diagnosis, therapy)	+++	+	+++
Lack of rapid diagnostics	++	++	++
Education	++	+	+++
Lack of trained manpower	+++	++	+++
Lack of well-equipped laboratories	+++	++	+++
Delay in availability of newer antibiotics	++	+	+++
Lack of real-time quality surveillance	++	+	++
Lack of public awareness	+	+	++
Economic impacts	+++	+	+
Global coordination			++
Lack of preparedness for outbreaks	-	-	+
New drug development	-	-	+

"+++" very serious concern exist, "++" serious concern exist, "+" concern exist, NAP: National action plan, AMR: Antimicrobial resistance.

Table 3: Factors contributing to antimicrobial resistance

Microbial factors
- New resistance patterns continue to emerge
- Resistance genes on the rise, best control strategies remain unknown
- Transformation by highly fragmented and damaged DNA, environmental cleaning implications
- Climate changes leading to higher bacterial load in environment and higher rates of transmission

Antimicrobial factors
- Dry drug pipeline, disincentives for antibiotic innovation
- Lack of vaccines or other antibiotic alternatives for drug-resistant pathogens

Human factors
- Increase in high-risk patient populations
- Inappropriate prescribing and overuse of broad-spectrum antibiotics
- Inadequate adherence to best infection control practices
- Antibiotic overuse other than medical in veterinary, agriculture, aquaculture, and animal feeds
- Poor human and agricultural sanitation
- Highly mobile individuals and populations

Diagnostics and surveillance
- Inadequate diagnostics and laboratory infrastructure at all healthcare facilities
- Lack of standardized sequencing and bioinformatics protocols
- Insufficient standard-of-care genotyping methods

in increased antibiotic exposure from empirical therapy. There are numerous opportunities for straightforward interventions formulated for the containment of AMR [Table 4].[47] Interventions to deal with AMR, from simple actions to complex ones, from regulatory to behavioral approaches, and from strategies focusing on infection prevention to those focusing on responsible use of antimicrobials, are crucial to consolidate an evidence-based approach to the challenge.[48,49]

2. Interventions for policymakers

Expedited implementation of national action plan on antimicrobial resistance (NAP-AMR) 2.0

The Government of India has formulated a national action plan (NAP) to tackle AMR (NAP- AMR), largely modeled on the World Health Organization (WHO) global action plan on AMR [Figure 1].[50] The 5-year NAP-AMR has been established in three states or union territories, namely Kerala, Madhya Pradesh, and Delhi;[51] financial constraints have also impeded further implementation efforts. The six strategic priorities of the NAP-AMR include:

- Improving awareness and understanding of AMR through effective communication, education, and training
- Strengthening knowledge and evidence through surveillance
- Reducing the incidence of infection through effective infection prevention and control
- Optimizing the use of antimicrobial agents in health, animals, and food
- Promoting investments for AMR activities, research, and innovations, and strengthening India's international, national, and state-level collaboration and leadership on AMR

First, the plan relies heavily on individual knowledge, attitudes, and practice (KAP) surveys across the general population and on behavioral studies. Second, the indicators in the plan rely heavily on training, guidelines, and behavior change interventions with prescribers (doctors, nurses, pharmacists,

Table 4: Areas and actions for monitoring and reducing antibiotic use

Minimize overdiagnosis • Urine cultures: follow guidelines, do not culture for change in urine character, recognizing bacterial colonization of lower urinary tract can be common and benign • *Clostridium difficile* testing: follow guidelines, once positive, do not repeat, do not test for cure, recognize testing cannot distinguish colonization from active infection • Pharyngitis treatment: acknowledge that most is viral in origin, *Streptococcus* is likely and antibiotics recommended only if Centor score >1 • Not performing pan cultures or "fever panels" reflexively, investigate sources on the basis of clinical symptoms • Discourage or remove tests that have suboptimal sensitivity and specificity and are not recommended by WHO for diagnosis eg Widal test for enteric fever and Weil-Felix test for rickettsial infections
Minimize overuse • Do not treat upper respiratory infections with antibiotics • Have low prescribers as role models for high-prescribing colleagues • Confirm that the patient actually needs a discharge prescription for an antibiotic • Prescribe shorter, guideline-based duration regimens for most infections • Restrict surgical antibiotic prophylaxis to a maximum of 24 hrs
Alternative • A global/translational antibiotic stewardship strategy

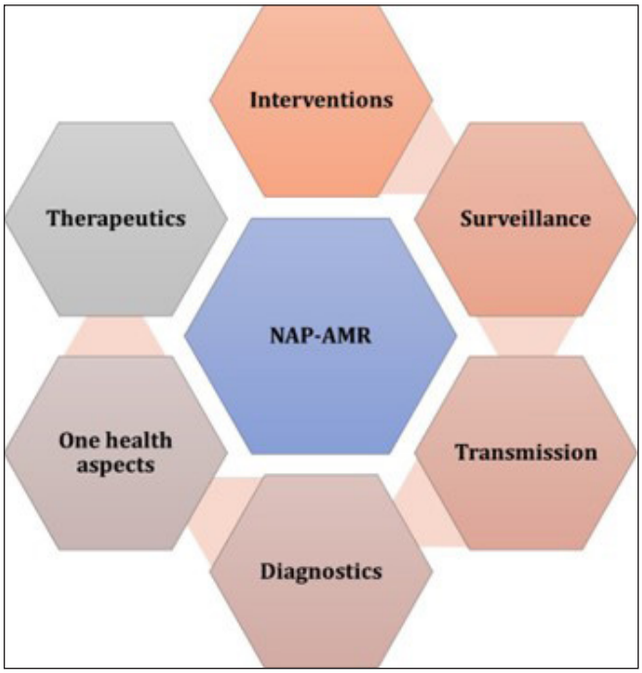

Figure 1: National action plan for the containment of antimicrobial resistance (NAP-AMR).

among others) that have seen limited success in India. Though, the plan mentions the need for antimicrobial stewardship at different levels, it neither recognizes the diversity of outpatient care provision in India nor provides clear mechanisms to coordinate activities between the public and private sectors. For AMR surveillance, the NAP-AMR relies on a national network of laboratory-based surveillance at a few designated reference laboratories in tertiary care medical institutions.

ICMR has taken the initiative to address this gap by establishing antimicrobial resistance surveillance and research network (AMRSN) and implementing AMS programs in tertiary care hospitals.[52] The data collected through these initiatives do not adequately reflect the comprehensive picture of AMR in the country, particularly from community healthcare settings. Limited standardized surveillance data make it even more challenging to monitor the extent and scope of AMR, and most of the data come from published studies of HAIs in inpatient settings, scoping reports, prospective studies, and point prevalence surveys at select, large hospitals. However, antibiotics are routinely prescribed for respiratory infections in primary care and outpatient settings both in the public and private sectors. It is also important to note that secondary care hospitals in India are not well equipped to document the patterns of local antibiograms and monitor antibiotic usage due to the absence of good clinical microbiology labs and skilled staff. From a clinician's perspective in India, recent local susceptibility data would assist in the selection of empirical antibiotics for community-acquired infection management and to support rational choices when treating these bacterial infections. However, India-specific community-acquired pathogen AMR surveillance is lacking.[53] Therefore, public education is vital, covering the misuse of antibiotics, such as not purchasing OTC antibiotics and also the need to complete the full course as prescribed by the physician.

ICMR has identified six nodal centers or each pathogenic group where the organisms with unusual resistance can be confirmed. This includes All India Institute of Medical Sciences, New Delhi, for typhoid fever; Christian Medical College and Hospital, Vellore, for non-fermenting gram-negative pathogens and diarrheal pathogens; Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, for gram-positive pathogens, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, for Enterobacterales and fungal pathogens; and the National Institute of Cholera and Enteric Diseases (NICED), Kolkata, for cholera and diarrheagenic pathogens.

Absolutely, the dynamic nature of AMR demands a flexible and a responsive approach to combat it effectively. Viewing the framework as a cyclical process allows for ongoing assessment, adaptation, and improvement in response to the

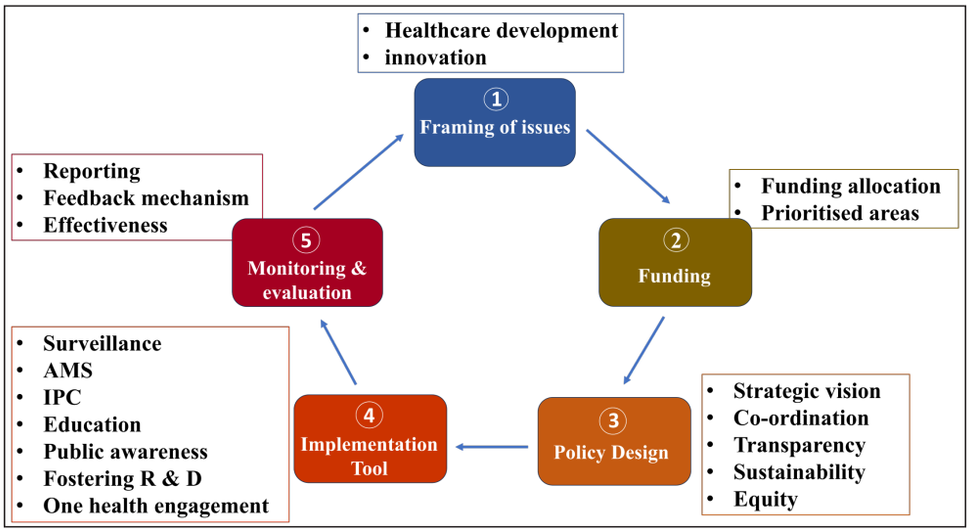

Figure 2: An adapted conceptual framework for assessment of NAP-AMR. AMS: Antimicrobial stewardship, IPC: Infection prevention control, R & D: Research and diagnostics, NAP-AMR: National action plan on antimicrobial resistance.

evolving challenges posed by AMR [Figure 2]. This iterative approach enables policymakers, healthcare professionals, and other stakeholders to continually refine and update NAPs on AMR in line with emerging evidence, changing patterns of resistance, and shifts in healthcare practices. By embracing this cyclical process, it would be helpful to address the multifaceted aspects of AMR and enhance the effectiveness of their strategies to preserve the efficacy of antimicrobial agents.

Recommendations for action

- Extend the current AMRSN to all tertiary care hospitals in the country, with at least one from each state.
- Start a separate AMRSN network or subcategory for secondary-level or district hospitals to better reflect resistance patterns at the community level.
- Start an AMRSN exclusively for community pathogens from outpatients with representation from each state (e.g., Streptococcus pneumoniae, Neisseria gonorrheae, community-acquired methicillin resistant staphylococcus aureus (CA-MRSA), Salmonella typhi and *S. paratyphi*).

Multisectoral engagement

The multifaceted complexities of AMR require consistent action, a multidisciplinary approach, and long-term political commitment. Multisectoral collaboration is the deliberate coordination of different stakeholder groups—such as government, civil society, the private sector, and sectors such as health, agriculture, trade, and education—and the environment to jointly achieve coordinated and effective action on AMR [Figure 3]. It includes horizontal collaboration

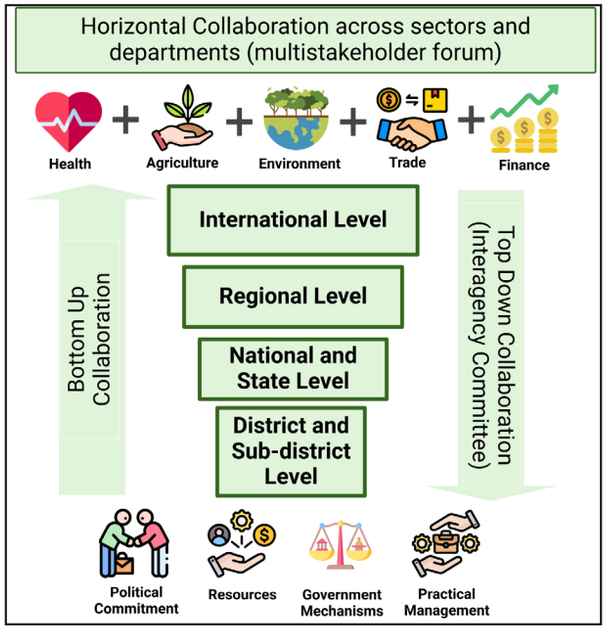

Figure 3: Multisectoral collaboration can be both horizontal across sectors as well as vertical across levels to contain antimicrobial resistance (AMR).

across sectors and vertical collaboration across levels. Vertical collaboration, from local to global levels across sectors, and from on-the-ground practitioners to central policymakers within individual sectors, can be achieved through both top-down and bottom-up approaches. Horizontal collaboration across different government departments and nongovernment stakeholders, can be supported through diverse activities, including knowledge-sharing platforms and multistakeholder forums. A formal, resourced administrative structure at a

level above the implementing ministries is generally required for strategic direction and oversight, however, in practice, there is no one-size-fits-all approach to AMR governance. In the long term, effective multisectoral collaboration requires governments to take ownership of the NAP implementation process and ensure it is appropriately resourced and given sufficient visibility to keep it a national priority.

In a tiered approach, different levels have different functions. At the top lies a high-level, multisectoral, decision-making body that sets the strategic direction and allocates resources. There should also be coordination at an operational level where those implementing interventions come together to ensure coherence. There should be operational-level, active, discrete units within ministries, civil society, and private sector partners responsible for implementing the activities listed in the NAP. Experience at the country level indicates that it is best to keep the top level relatively small, to prevent it from becoming unwieldy and unworkable. One option for keeping the top-level body lean and efficient is to ensure that its members are very well-connected and that they can effectively represent multiple stakeholder groups.

An "AMR champion" authority to work across sectors that galvanizes the interest of high-level policymakers at ICMR, NCDC, and department of biotechnology (DBT) triggers effective action to tackle AMR. Consistent engagement and information sharing between stakeholders working in the AMR space using available government platforms was critical in engaging and sustaining government leadership and commitment.

Recommendation for actions

- Identify and use champions and events to raise the profile of AMR and sustain its visibility on the political agenda
- Use local data on AMR to illustrate likely local and national impacts and convince key decision-makers of the need for action
- Use government platforms to share and promote AMR action
- Manage the risks of changes in leadership to ensure that AMR remains on the political agenda
- Support nongovernment multistakeholder working groups and forums to share information and resources
- Adopt a participatory approach that engages nongovernment stakeholders to develop a shared vision and commitment to tackle AMR
- Understand that AMR initiatives can build on existing programs and activities
- Leverage existing policies and plans to mainstream AMR and optimize resources
- Establish a clear system or structure for coordinating AMR action across all relevant national plans

Funding allocation

Currently, there is inadequate financial support available for the sustainable implementation of NAPs. Increased investment is urgently needed to support the delivery of NAPs. More financial support and incentives are required for effective and affordable innovations across all sectors and stakeholders (including the private sector) to secure a sustainable pipeline for new antimicrobials (particularly antibiotics), vaccines, diagnostics, waste management tools, and safe and effective alternatives to antimicrobials, and to ensure equitable access to them. The antimicrobial resistance multipartner trust fund (MPTF) combats the threat of antimicrobial drug resistance through strategic collaboration, sustainable streams of capital, and sustainable development goal-focused responses that support localized "One Health" NAPs. The studies by the Global AMR research and diagnostics (R&D) Hub to evaluate the scale of challenge of bringing the needed new antibiotics (and diagnostics) into the market in current economic conditions highlighted the astonishing mismatch between global patient needs and the commercial potential of products. The immediate adaptation of existing national health systems tools in combination with pull incentives was called for to support innovation and to ensure that the necessary new products are accessible to those with the greatest need around the world. The Biomedical Advanced Research and Development Authority (BARDA), since its launch in 2011, has provided $1.5 billion in funding. As of June 2021, BARDA's portfolio includes 16 antibacterial programs to address drug-resistant bacteria that the Centre for Disease Control and the WHO consider serious global threats.

Promoting vaccination to minimize infections

Preventing infections using vaccination reduces antibiotic use, which is one of the main drivers of AMR. There are vaccines available against three priority bacterial pathogens: pneumococcal disease (*Streptococcus pneumoniae*), *Haemophilus influenzae* type b (Hib), and Typhoid fever (*Salmonella typhi*).

Unfortunately, most vaccines developed against the main resistant pathogens are still under preclinical and clinical evaluation due to the complexity of pathogens and technical difficulties. Vaccines against these pathogens are unlikely to be available in the short term, and alternative interventions should be pursued urgently to prevent resistant infections due to priority bacterial pathogens. Vaccination also reduces carriage (colonization of an individual in the absence of disease) and shedding bacteria, thus limiting the spread of infections within a community (herd protection) [Figure 4]. It is vital to support the uptake of licensed vaccines by implementing the below strategies:

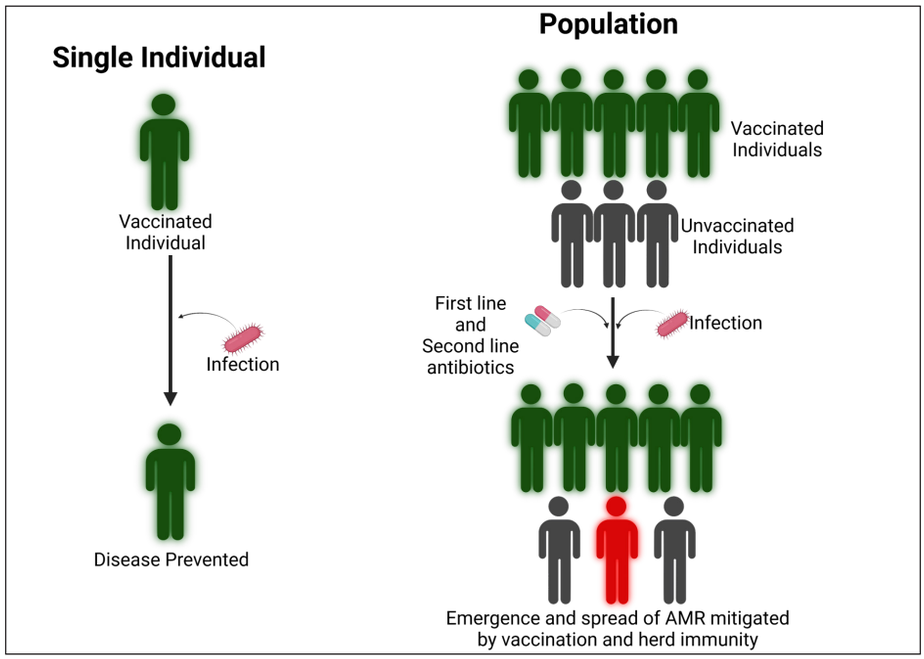

Figure 4: Vaccines against antimicrobial-resistant pathogens could prevent or reduce life-threatening diseases and thus decrease health care costs, and also reduce the use of antibiotics (both first-line and second line drugs) with the potential of decreasing the emergence of AMR. If sufficient vaccine coverage is achieved in a population, indirect protection (herd immunity) further prevents spread of resistant strains. Decreased disease burden would also negate the need for antibiotics.

- Enhance public awareness of the importance of vaccination in the fight against AMR to improve vaccine confidence, uptake, and coverage
- Improve human vaccination coverage in all age groups, with an emphasis of including adult immunization in national immunization plans (NIP) and implementing targeted vaccination of at-risk populations
- Align AMR NAPs with NIPs, and setting clear and defined vaccine uptake targets
- To develop surveillance systems to monitor the impact of both new and established vaccines on AMR

For instance, the introduction of a 13-valent conjugate pneumococcal vaccine has shown the impact of vaccination on the incidence of pneumococcal disease. Antibiotic-resistant invasive pneumococcal disease declined in both vaccinated and unvaccinated populations.[54] The effectiveness in reducing AMR has also been proven by vaccination against Hib. Before the introduction of the Hib conjugate vaccines, 16.6% of all Hib strains worldwide were beta-lactamase positive which reduced the treatment options drastically. With the routine use of Hib conjugate vaccines, disease cases have dropped significantly together with the number of beta-lactamase-positive strains.[55] Influenza vaccination has been demonstrated to reduce the use of antibiotics by 64% in vaccinated individuals by reducing the incidence of disease and thereby reducing the number of associated antimicrobial prescriptions.[56] Notably, during the pandemic, antibiotics were used in 75% of the patients suffering from severe COVID-19, while only 15% of those patients actually developed bacterial superinfections.[57] There are 11 vaccines aiming to address AMR in the vaccine pipelines, targeting six high-threat microorganisms, at different stages of clinical development [Table 5].[58]

The action framework describes a vision for vaccines to contribute fully, sustainably, and equitably to the prevention and control of AMR and identifies a series of priority actions to be taken by different stakeholders in the fields of immunization and AMR.[59] It focuses on three areas:

- Expanding the use of licensed vaccines to maximize impact on AMR
- Developing new vaccines that contribute to the prevention and control of AMR
- Expanding and sharing knowledge on the impact of vaccines on AMR

Recommendations for action:

- Promoting the NIP and improving implementation to reach close to 100% of the childhood population.
- Adding to the NIP vaccines that are efficacious but not currently part of the NIP or not uniformly used across the

Table 5: Vaccines under development tackling antimicrobial resistance (AMR)

Micro-organism	Number of vaccines in the pipeline	Status	Trial population	Technology Platform
C. difficile	3	Phase I, II, III	Adults	Toxoid vaccine Protein subunit
E. coli (ExPEC)	1	Phase III	Adults	Glyco-conjugate vaccine
K. pneumoniae	1	Phase I	Adults	Glyco-conjugate vaccine
Shigella spp.	1	Phase II	Paediatric, Adults	Glyco-conjugate vaccine
S. aureus	1	Phase II	Adults	Glyco-conjugate vaccine

country (e.g., conjugated pneumococcal and conjugated typhoid vaccines)
- Initiating a National Adult Immunization Program for high risk individuals (age > 65, younger persons with comorbidities), starting with influenza and pneumococcal vaccines.

Mandatory notification of priority pathogens

The multidrug-resistant (MDR) pathogens should be listed and considered for mandatory notification (isolate needs to be sent to and confirmed as resistant at reference lab). Recently, in 2024, the WHO has revised the priority pathogen list, for which new antibiotics are urgently needed. This includes the critical group (carbapenem-resistant *A. baumannii*), carbapenem-resistant Enterobacterales, third-generation cephalosporin-resistant Enterobacterales), high priority group (fluroquinolone-resistant *S. typhi*, fluroquinolone-resistant *Shigella* spp., fluroquinolone-resistant non-typhopidal Salmonella, carbapenem-resistant *P. aeruginosa*, third-generation and/or fluroquinolone-resistant *N. gonorrhoeae,* MRSA), and medium priority group (Group A Streptococci, macrolide-resistant *S. pneumoniae*, ampicillin-resistant *H. influenzae*, and penicillin-resistant Group B Streptococci). Sending alerts mainly focusing on the critical and high priority group of pathogens would be helpful for infection control and to promote antimicrobial stewardship (ASP) practices.

- Carbapenem- and colistin-resistant *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*
- *E. coli* with presumed PBP insert showing resistance to the triple combination of ceftazidime–avibactam plus aztreonam
- Vancomycin nonsusceptible or resistant *Staphylococcus aureus*
- Penicillin- and cephalosporin-resistant *Streptococcus pneumoniae* using cerebrospinal fluid breakpoints
- Third-generation cephalosporins and azithromycin-resistant *Salmonella typhi* and *S. paratyphi*
- Cephalosporin- and fluoroquinolone-resistant *Neisseria gonorrheae*
- Penicillin-resistant *Neisseria meningitidis*
- Echinocandin-resistant *Candida auris*
- Aspergillus species resistant to voriconazole

Recommendation for action:

- Reporting of the above-mentioned pathogens should be made mandatory on the part of the center from where it is isolated (after confirmation by a reference laboratory).
- Data on the incidence of these MDR pathogens, including spatial and temporal distribution, should be available on a national public website such as NCDC. Spatial and temporal distribution of pathogens provide evidences for public health emergency preparedness.

Public health interventions to improve AMR awareness

A large proportion of AMR infection is linked to community-associated infections, suggesting that interventions set in community settings, including primary care, are urgently needed. When considering the community setting, emergence and amplification of AMR are driven by numerous factors such as the nonprudent use of antimicrobials, lack of access to clean water and poor sanitation, and limited access to quality therapeutics, vaccines, or diagnostics.[59–61] Each of these AMR determinants has unique intricacies that require targeted interventions.

The Indian government has introduced "Red Line campaign" to improve awareness among the public and healthcare professionals about the importance of appropriate use of antibiotics.[61,62] In this initiative, antibiotics and certain other prescription-only medicines had a bold red-colored line on the blister pack to indicate that these drugs were to be consumed only on the advice of qualified prescribers. However, this initiative limited success in regulating OTC antibiotic sales and in creating awareness about antibiotic misuse and overuse in the community.[63] A study conducted in India showed that only 7% of healthcare professionals could describe the significance of the red line campaign and none among patients.[63] General practitioners (GPs) play an essential role in national efforts to tackle AMR, as they prescribe the largest volume of antibiotics. By following best practice prescribing,

they can reduce the amount of antibiotics used and contribute to decreasing antibiotic resistance. Consequently, there is a need for educational activities among GPs to improve the rational use of antibiotics, building on current and planned activities by the Ministry of Health.

Patients presenting in primary care with respiratory, urinary, skin, or dental infections account for the majority of antibiotic prescriptions. It is, therefore, important that primary care physicians be kept well-informed of the AMR landscape and be conversant about the important measures by the government systems in controlling AMR. Also, it is important to strengthen antimicrobial stewardship strategies in the community by implementing and evaluating community interventions to tackle AMR. There have been many interventions targeted at clinicians, patients, and the public [Table 6]. The nonprudent or nonprescribed use of antibiotics is linked to knowledge, attitudes, and practices that may determine inappropriate prescribing, self-medication, and antibiotic use without prescription. Many of these are clearly linked to human behavior, which calls for a need to understand the types of efficient interventions. Clinicians should play an active role in the education of patients, informing of the risks of the acquisition of resistant bacteria.

Public education campaigns have shown to be effective in changing attitudes and knowledge regarding antibiotic use and resistance.[64,65] Clinicians should support the education of patients regarding antibiotic use and resistance. They could use effective strategies, such as shared decision-making, to alert people of the actual risk of acquiring antibiotic-resistant bacteria following antibiotic use. Patients need to stay informed and receive independent information on antibiotics, as better health literacy and a higher degree of knowledge and awareness about the appropriate use of antibiotics are associated with decreased consumption. Social media for health intervention has been widely used during the COVID-19 pandemic, which was found to be the fastest mode of communication for the distribution of preventive information and it could be efficiently be used for education, knowledge dissemination, and healthcare awareness.[66] However, social media in AMR public health interventions is not well explored and potentially underused. Intervention showing animated films and musical or theatre shows had a positive impact on the knowledge gained and attitudes of the participants.

Table 6: Community interventions to optimize antibiotic-prescribing and use

-	Intervention	Target
During the consultation	• Education • Computerized decision support tools • Educational meetings • Audit and feedback • Financial incentives • Point-of-care tests (POCTs)	Clinician-focused
	• Enhanced communication training • Shared-decision making • Delayed prescribing strategies • Patient educational materials	Clinician and patient-focused
Outside the consultation	National antibiotic awareness campaigns	Public

Given the diagnostic challenges in outpatient settings, scaling-up use and access of point-of-care tests, such as C-reactive protein and procalcitonin, may reduce unnecessary antibiotic use.[67] Improving microbiology support, continuous surveillance of antimicrobial resistance patterns, implementation of antibiotic policy at all levels of healthcare, continuous awareness generation among medical students regarding rational use of antibiotics, and regular prescription audits are some of the other widely recommended measures, all of which are seriously lacking in India.[68]

Recommendations for action

- A national education campaign for the public on the dangers of self-medication of antibiotics or their use without a prescription should be introduced in mainstream media, for example, newspapers and television as well as social media (e.g., similar to current campaigns to discourage tobacco)
- Ensure clean drinking water and improve sanitation and personal hygiene (including hand hygiene)
- Develop mechanisms to return unused antimicrobials from households for safe disposal
- Raise awareness of the role of vaccines in limiting the emergence of AMR and use of antibiotics
- Ensure the availability and affordability of preventative testing and counseling services for common infections

Promoting curriculum learning on antimicrobial resistance

Among health workers, a variety of factors can result in the misuse or overuse of antimicrobials, including a lack of knowledge or up-to-date information, inability to identify the type of infection, yielding to patient pressure to prescribe antibiotics, and a preponderance of situations that allow for financial benefit from the supply of antibiotics.[69] Therefore, AMR education and training resources are crucial to support educators, decision-makers, and health policy planners in implementing effective policies to guide actions on AMR control. Implementation of AMR competency framework, which is matrix of the AMR domains, and health worker

Table 7: AMR competency framework

Antimicrobial resistance domainsa	Category 1: All health workersb	Category 2: Prescribersc	Category 3: Non-prescribersd			Category 4: Public health ofAicers/ health services managerse
			Nurses	Pharmacists	Laboratory scientists/ technicians	
Foundations that build awareness of antimicrobial resistance Competency statement: Health worker demonstrates that they have the knowledge and awareness of effective approaches to control AMR, and has the skills/attitudes to implement change according to role and level of training	**Relevance:** High **Knowledge:** 1. Understand the development and main causes of AMR. 2. Understand the basic principles of infection prevention and control, i.e. hand hygiene to prevent transmission of infections. 3. Understand the impact of resistance on choice of antimicrobial therapy for treating infections. 4. Understand the morbidity, mortality and economic threat of AMR to human health. 5. Know the importance of optimizing use of antimicrobials in the human and animal sectors to prevent development of resistance.	**Relevance:** High **Knowledge:** 1. Understand the importance of antimicrobial choice, dosage, interval, duration, preparation and administration of antimicrobials. 2. Know the principles of microbiology in identifying pathogens from clinical samples. 3. Know the basic diagnostic role of the microbiology laboratory. 4. Understand local AMR epidemiology, resistance and susceptibility patterns and use of guidelines. 5. Patient counseling etiquettes, discussion techniques and psychology for patient communication. 6. Understand the principles of empiric, syndromic or culture-based treatment options in relation to the selection of antimicrobials.	**Relevance:** High **Knowledge:** 1. Understand the role of bedside nursing in antimicrobial stewardship programmes.	**Relevance:** High **Knowledge:** 1. Understand the significance of antimicrobial choice, dosage, duration and preparation in the treatment of infections.	**Relevance:** High **Knowledge:** 1. Understand the diagnostic role of the microbiology laboratory in detecting infections, resistance patterns, guiding patient management and informing AMR control strategies.	**Relevance:** High **Knowledge:** 1. Understand the use of quality improvement frameworks to address gaps in AMR education. 2. Understand the potential for cost savings and health gains associated with effective infection control and appropriate antimicrobial use. 3. Understand the roles and responsibilities of different stakeholders in antimicrobial stewardship teams. Members of the team could include, but are not limited to, the roles of physicians, pharmacists, infection preventionists, microbiologists, nurses and hospital administrators or others.

(*Contd...*)

Continued

Antimicrobial resistance domainsa	**Category 1: All health workersb**	**Category 2: Prescribersc**	**Category 3: Non-prescribersd**			**Category 4: Public health ofAicers/ health services managerse**
			Nurses	**Pharmacists**	**Laboratory scientists/ technicians**	
	Skills: 1. Ability to interpret and communicate the use of appropriate policy guidelines on AMR.	**Skills:** 1. Appropriate use of antimicrobials to treat and/or prevent common infections and syndromes. 2. Ability to communicate with patients on the appropriate use of antibiotics. 3. Ability to collect microbiology samples.	**Skills:** 1. Assess the source of infection and identify appropriate measures. 2. Obtain allergy history, perform medication reconciliation, and record this in the medical record.	**Skills:** 1. Advise patients and prescribers on the appropriate use of antimicrobials. 2. Practice safe disposal of unused antimicrobial medicines.	**Skills:** 1. Collect and report data on antimicrobial product quality and sensitivity to national drug registration bodies. 2. Advise prescribers on correct microbiological testing procedures. 3. Ability to carry out bacterial isolation, identification, susceptibility testing and reporting. 4. Provide facility-specific cumulative susceptibility reports for common bacterial pathogens against antibiotics that are recommended in the local or national guidelines. 5. Generate profiles of antimicrobial resistance for identified antimicrobial microorganism for public health decision- making.	**Skills:** 1. Ability to determine and implement best approaches to antimicrobial stewardship interventions on the basis of context. 2. Ability to carry out resource allocation to implement and sustain antimicrobial stewardship programmes. 3. Develop policy advocacy and enforcement to manage AMR programmes.

(*Contd...*)

Continued

Antimicrobial resistance domainsa	Category 1: All health workersb	Category 2: Prescriberssc	Category 3: Non-prescribersd			Category 4: Public health ofAicers/ health services managerse
			Nurses	Pharmacists	Laboratory scientists/ technicians	
	Attitudes: 1. Promote awareness of AMR and appropriate antimicrobial use amongst all health care workers, patient communities and the general public. 2. Act to protect the effectiveness of antimicrobials as an ethical imperative and a public good.	**Attitudes:** 1. Promote a standard for the appropriate use of antimicrobials and manage patient expectations and demands especially when the use of antimicrobials is not indicated 2. According to settings and where appropriate, encourage adherence to antimicrobial formulary/ protocol restrictions. 3. Understand basic principles of behavior change in the context of prescribing antimicrobials and model good prescribing behavior to colleagues.	**Attitudes:** 1. Contribute to a patient centered focus in the clinical team, and monitor and communicate daily patient progress. 2. Contribute to public health literacy and general advocacy on the importance of infection prevention.	**Attitudes:** 1. Advocate for patient safety and compliance in the prescription and use of antimicrobials in compliance with formulary protocols. 2. Critically assess information and pharmaceutical products as part of good procurement practices.	**Attitudes:** 1. Advocate for and comply with laboratory and public health guidelines regarding antimicrobial susceptibility testing.	**Attitudes:** 1. Promote AMR awareness at health system, hospital and community levels. 2. Establish and enforce compliance with antimicrobial formulary/ protocol restrictions at local and national levels according to country policies. 3. Together with civil society, advocate for the responsible development of new antimicrobials and ensure the correct promotion of existing ones.

AMR: Antimicrobial resistance

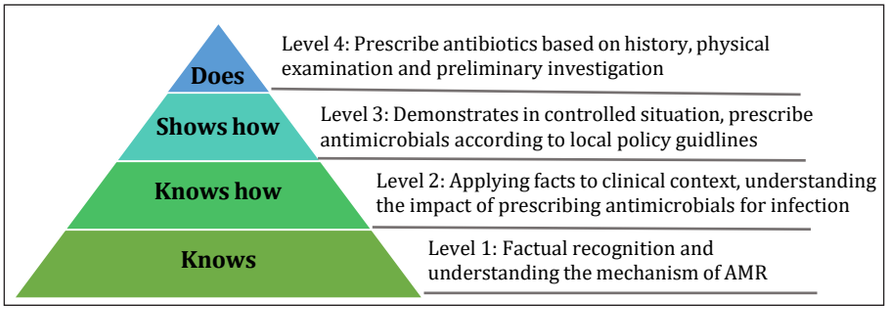

Figure 5: Modified Miller's pyramid to rate level of perceived output for each learning points. AMR: Antimicrobial resistance.

categories and their competencies (the knowledge, skills and attitudes) is necessary to effectively address AMR in practice settings [Table 7].[70] The framework adopts an interprofessional approach based on the principle that addressing AMR requires a shared understanding and an effective collaboration and communication among health workers. Given that a number of different health workers are involved in the sequence of events and scenarios leading to the prescription and use of antimicrobials, the categorization of health workers has been structured to reflect, in a comprehensive manner, the most significant roles impacting antimicrobial prescription and use. In India, the introduction of AMR education in pharmacy curricula showed potential benefit to take key role in antimicrobial stewardship, where postgraduate training for pharmacists remains limited.[71] The following teaching methods or training techniques can be used to deliver the curricula depending on the learning objective, audience type, learning environment, and availability of technology.[72]

- Interactive lectures
- Interactive, small, group tutorials using problem-solving exercises and case-based learning, which encourage the trainee to present, analyze, and discuss
- By apprenticeship, learning by doing (as in in-service training and practical laboratory-based exercises)
- Role playing for preservice and in-service education
- Using e-learning modules such as massive open online courses and webinars
- Project-based learning with creation of project reports, strategic papers, and critical appraisal of the literature

Recommendations for action

- Antimicrobial resistance and strategies to address it should be included in the core curriculum at the MBBS level, preferably at the time Microbiology and Pharmacology subjects are taught.
- Re-education of postgraduates on antibiotic prescribing etiquette should be included in the curriculum to sustain the knowledge, perception, and attitude toward antibiotic resistance as well as proper antibiotic use and prescription. The re-education may be made mandatory during reregistration of doctors.
- Infectious Diseases and Microbiology departments need to be started in each state at all tertiary care hospitals and hospitals that conduct postgraduate training. AMR should be made part of the core curriculum for postgraduates in Medicine and Allied specialties and Microbiology.
- A minimum number of credit hours of continuing medical education on AMR should be introduced for the re-licensure of practicing physicians.
- A modified Miller's pyramid [Figure 5] can be applied to rate the level of achievement of each individual learning point

3. Intervention strategies at regulatory level

Banning irrational fixed-dose combinations

Fixed-dose combination (FDC) definition as per WHO states that, a combination of at least two active ingredients in a fixed proportion of ratio. The FDCs are justified when they demonstrate clear benefits in terms of (a) potentiating the therapeutic efficacy; (b) reducing the incidence of an adverse effect of drugs; (c) having pharmacokinetic advantage; (d) better compliance by reducing the pill burden; (e) reducing the dose of individual drugs; and (f) decreasing the development of resistance. An FDC is described as irrational if these conditions are not met. As per the Rule 122E of the Drugs and Cosmetics Act 1940, the FDCs are considered as new drugs and the Central Drugs Standard Control Organization (CDSCO), after due examination of data on rationality, safety, and efficacy issues approval. Based on this, the State Licensing Authority (SLA) gives the manufacturing and marketing permission. Incidentally, in the past, SLAs issued the license to manufacture and market without asking for non-objection from CDSCO. Thus, the efficacy, safety, and rationality of such FDCs remain questionable. This "disconnect" between the CDSCO and SLAs has precipitated a roadblock in the action against irrational FDCs. The CDSCO, headed by the

Drugs Controller General of India, sought endorsement from infectious diseases physicians, microbiologists, and pharmacologists before FDC became available in the market. The Kokate Committee was constituted by the Ministry of Health and Family Welfare, Government of India, to critically assess the safety and efficacy for the approval of FDCs as rational or irrational.

Manufacturing and marketing of many FDCs play a crucial role in escalating AMR. India has a federal system of government, with drug regulatory functions divided between central and regional authorities.[73] In particular, the WHO does not recommend the use of FDC in clinical practice.[74] Regional authorities (states and union territories) grant licenses for manufacturing, selling, and distributing drugs. Before manufacturing, licenses for new drugs can be granted, however, manufacturers must obtain prior approval from the central regulatory authority, the Central Drugs Standard Control Organization headed by the Drugs Controller General of India (DCGI), for a period of 4 years. FDCs are a hallmark of the Indian drug market. It is estimated that 68% of FDCs containing antimicrobials on the Indian market have not been approved by the central drug regulator.[75] During 2011–2012, the sale of FDC antibiotics in India consisted of 499 million units containing key access antibiotics, 367 million units containing watch group antibiotics, 3 million units containing reserve group antibiotics, and 3 million units containing uncategorized antibiotics.[76] The central government has responded with several measures to control unapproved FDCs, which include the prohibition of manufacturing, distribution, and sales of some FDCs. In 2016, the government issued an official notification banning many FDCs that had been licensed for the manufacturer without prior approval from DCGI, following the recommendations of an ad hoc technical assessment of the Kokate Committee set up by the Ministry of Health and Family Welfare.[77–80]

Recommendations for action:

- A list of irrational FDCs based on the WHO recommendations should be drawn up, and all such FDCs should be banned from the market.
- Both the central and state regulators must harmonize their procedures for licensing FDCs, and the enforcement mechanism needs to be strengthened
- No future antibiotic FDC should be licensed without approval from an appropriate central expert committee

Restricting over-the-counter sales of antibiotics

Over-the-counter (OTC) sales of antibiotics is a common practice. Nearly 52% of Indians were estimated to self-medicate themselves, due to lack of time and to avoid doctors' fees.[81,82] Both access and watch groups of antibiotics are often dispensed for viral and self-limiting conditions, including fever, cold, cough, and sore throat.[83] In India, the sale of antibiotics is regulated by introducing Schedule H1 under the Drugs and Cosmetics rules 1945, to mitigate AMR.[84] This initiative tightens the restrictions on the sales of prescription-only medicines, listed in and covered by Schedule H1 of the Drugs and Cosmetics Rules. Currently, 46 drugs have been placed under this restricted category, which mainly comprises third- and fourth-generation cephalosporins, carbapenems, newer fluoroquinolones and first- and second-line antitubercular drugs. The packaging of these drugs will have a mandatory Schedule H1 warning printed on the label in a box with a red border and the Rx symbol in red. For Schedule H1 drugs, pharmacists are required to maintain a separate register for their sales and retain prescription copies.[74] This act is implemented mainly to avoid OTC sales of antibiotics without a valid prescription or to prevent pharmacists from dispensing antibiotics on their advice to the patient. However, initiatives led by the government have found limited success in regulating OTC antibiotic sales.

Financial and resource constraints may have contributed to inadequate awareness and suboptimal implementation of regulations planned by the government. Alternatively, in the community, OTC sales can be limited by raising the bar for any antibiotic to a higher schedule, the current Schedule H1 included only a few drugs and also with poor implementation. For example, the complete banning of sedatives in OTC that makes it difficult to access.

To address issue of OTC sale of antibiotics, multifaceted strategies are needed, extending beyond administrative or regulatory measures. Moreover, dispensing practices should be better regulated, at least limiting the use of antibiotics to those belonging to the access group. We believe there is an urgent need to foster a proactive attitude among pharmacists through a combination of educational interventions within the community pharmacy sector and increased awareness campaigns targeting proper antimicrobial use among the general population.

Recommendations for action:

- All antibiotics in the WHO watch and restricted categories need to be placed in schedule H1 and should be dispensed strictly with a doctor's prescription only. Safeguards to prevent inappropriate or OTC use that currently exist for sedatives and narcotics need to be extended to all drugs in schedule H1.

Fast-track approval for new antibiotics

In India, many patients lack access to newer antibiotics and are challenged by poor economic incentives, regulatory hurdles,

and poor health infrastructure. There was a significant lag between India and other developed nations in accessing the Food and Drug Administration, United States-approved new antibiotics.[85] Fast Track speeds the development and review of new antibiotics by increasing the level of communication between DCGI and drug developers [Figure 6]. In 2019, to fulfill the objective of fast-tracking the accessibility of new drugs and promoting clinical research in India, the Union Ministry of Health and Family Welfare, India has notified the "New Drugs and Clinical Trials Rules."[86] Phase III of clinical studies can be overlooked in India, if the drugs are already approved in other countries. Clinical studies can only be exempted if there is no serious adverse effect reported for the approved molecule, and there should not be any significant differences in the metabolism pathway in the Indian population. This decision has led to easier access of pharmaceuticals to the Indian population and, hence improving the health status of Indians.[85,86]

Recommendations for action:

- Existing drugs approved abroad need to be given unrestricted accelerated approval in India without further studies (e.g., cefiderocol, sulbactam–durlobactam).
- Drugs not approved abroad that are promising in treating MDR pathogens, such as cefepime–zidebactam, need compassionate or emergency use authorization and pathways to accelerated approval.
- Develop successful approaches to making such antibiotics available as rapidly as possible, through breakthrough therapy (expedite the development and review of drugs which may demonstrate substantial improvement over available therapy); and accelerated approval or fast track (allow antibiotics for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint)

4. Recommendations for hospitals - Where do things currently stand?

Four thematic areas to mitigate AMR in hospitals are as follows: i) antimicrobial stewardship practices, ii) appropriateness of therapy and adherence to treatment guidelines, protocols, and policies, iii) infection prevention control practices and iv) utilization of rapid diagnostic tests

Establishing antimicrobial stewardship team

Antimicrobial stewardship (ASP) is advocated to improve the quality of antimicrobial use. The Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines[3] identify two core proactive, evidence-based strategies for promoting antimicrobial stewardship [Figure 7]: i) formulary restriction and pre-authorization and ii) prospective audit with intervention and feedback.[87] Supplemental Strategies include education,

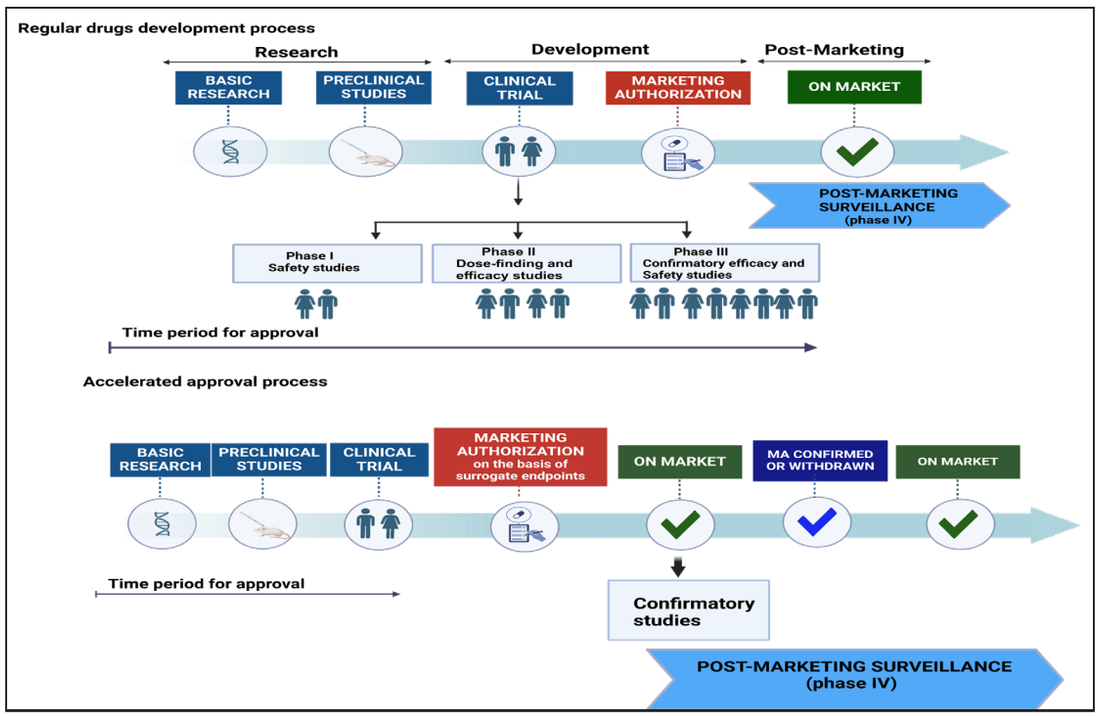

Figure 6: Traditional vs. accelerated development and approval process for novel antibiotics.

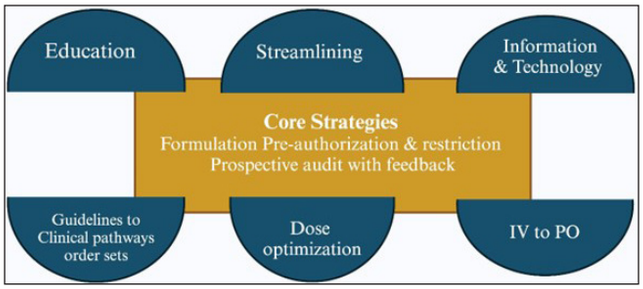

Figure 7: Infectious Diseases Society of America (IDSA) recommended antimicrobial stewardship strategies. IV to PO: Intravenous to oral..

guidelines, and clinical pathways, antimicrobial order forms, streamlining or de-escalation, dose optimization, and intravenous to oral switch interventions considered as part of ASP are listed in Table 8. Several studies have demonstrated the positive impact of antimicrobial restriction policies and procedures; however, there is limited guidance on the optimal criteria and measures needed to develop an effective process and ensure adherence to the established policy.

Current stewardship efforts in India are few, and there is a significant dearth of trained personnel in most hospitals in addition to the absence of facility-specific antimicrobial guidelines and infection control measures.[88] Pre-authorization for restricting high-end antibiotics has shown the beneficial effect of ASP in optimizing and reducing antibiotic use besides achieving improved patient outcomes.

Instituting a prior authorization program requires the ASP to consider many operational and logistic challenges. Because prompt antimicrobial therapy is extremely important in critically ill patients, approval logistics need to be addressed before starting a prior authorization program, particularly in facilities that cannot provide around-the-clock reviews.[89] The Directorate General of Health Services (DGHS) recommends the establishment of a hospital pre-authorization committee for reviewing and approving watch and reserve category antibiotics to ensure that their usage aligns with established guidelines and justifies on the clinical needs.

Perioperative antibiotic prophylaxis is considered one of the most effective measures for the prevention of surgical site infections (SSIs). Restricting perioperative antibiotics increased the rational use of prophylactic antimicrobial use, with substantial improvement in the risk-benefit trade-off. A randomized control trial demonstrated that three doses of perioperative antibiotic are equally effective in preventing infective complications.[90] Prospective audits and feedback (PAF) are often initiated based on the antimicrobials prescribed or by clinical results obtained from the microbiology laboratory. Post-prescription review (PPR) provides recommendations to change the agent, to adjust the dose or duration of therapy, to convert intravenous to oral formulations, and to evaluate drug–drug interactions.[91] This review can be performed immediately after prescription or within 24–72 hours after prescription when more clinical information is available. In India, the implementation of PPR decreases antimicrobial use from 831.5 during the baseline phase to 717 DOT per 1000 in the intervention phase. Notably, 73.3% of antibiotic prescriptions were inappropriate,

Table 8: List of interventions considered as part of antimicrobial stewardship

Intervention	Description/comment	Healthcare setting
Formulary restriction	Antibiotics may be prescribed only: • For certain approved clinical indications • By certain physicians (i.e., infectious diseases specialists)	inpatient/ outpatient
Drug preauthorization	Permission (from ASP team member or infectious diseases specialist) required for release of certain antibiotics. often implemented together with formulary restriction	inpatient/ outpatient
Prospective audit and feedback	Case review by trained asp team member and feedback of recommendations if reviewed antibiotics are deemed to be inappropriately prescribed. Labor-intensive.	inpatient
Prescriber education	More effective as a supplementary strategy to other interventions	inpatient/ outpatient
Patient education	usually focus groups or mass media campaigns.	outpatient
Clinical guidelines	treatment protocols for various infections – may be institution-specific	inpatient/ outpatient
Clinical decision support systems	Information technology systems for improving antibiotic prescription. Requires existing electronic records and electronic prescribing system to be effective	inpatient/ outpatient
Point of care diagnostic tests	Diagnosis of non-bacterial etiologies may help reduce antibiotic prescription.	inpatient/ outpatient
Microbiology laboratory susceptibility reporting	Selective reporting of susceptibility profiles for positive cultures may dramatically alter prescribing patterns of physicians	inpatient/ outpatient
Antimicrobial cycling	Substitution of selected antibiotics over pre-defined periods. Little clear evidence for efficacy	inpatient

de-escalation according to culture susceptibility has improved significantly with PPR.[88] Physicians and pharmacists trained in infectious diseases are ideally suited to perform PPR and to provide recommendations.

However, a lack of trained infectious disease physicians and pharmacists makes it challenging to establish antimicrobial stewardship in India, especially in public sector hospitals. DGHS also suggests conducting regular audits to evaluate the patterns and trends of antibiotic prescribing and usage at hospitals. This audit provides valuable insights into prescribing practices, identifies areas of improvement, and enables us to track progress in ASPs efforts.

A compilation of consumption in the form of defined daily doses (DDD) or days of therapy (DOT) may be used to determine high prescription areas to maximize the effect of interventions and this should be reviewed and updated over time.[92] This strategy also provides opportunities for education through the feedback mechanism and promotes individualization of therapy. Compliance to institution-specific antibiotic guidelines showed marginal improvement in PPR intervention phase. Importantly, in 28.5% of the cases, antibiotic guidelines were not applicable, suggesting a need for comprehensive national- and institution-specific antibiotic policy guidelines based on the local antibiogram.[92] The establishment of facility-specific treatment guidelines for optimizing empiric antimicrobial selection, de-escalation, duration of therapy, and also including recommendation of source control are warranted. In addition, continuous updates of the policy or treatment guidelines is necessary based on the national AMR surveillance data or cumulative antibiogram that reflects institution-specific antimicrobial usage.

A significant number of studies have assessed the quality of antibiotic prescribing in the outpatient settings. Up to 80–90% of antibiotics are prescribed in outpatient settings, with high levels of inappropriate use.[93] Increasing attention has been paid to antibiotic stewardship efforts in the outpatient setting. Encouraging doctors to include clinical diagnosis and investigations in each case and the reason for antibiotic usage prescription by default helps identify the interventions that prevent inappropriate use. A major cause of misuse is insufficient knowledge of prescribing of antimicrobials in many categories of professionals, and education is the fundamental component of ASPs. Implementation of an education-based ASP was shown to improve antimicrobial prescriptions and consumption, even when restrictive measures were not implemented.[94] However, current guidelines suggest that educational interventions should not be used alone but to support other stewardship interventions. A theme-based educational program provides a platform for stressing facility-specific issues and influencing prescribers' behavior. Such interventions are most commonly directed toward prescribers and less likely educate pharmacists, nurses, or even members of the stewardship team.

Moreover, teaching of the principles of ASPs at the undergraduate and postgraduate level improves antibiotic use. Currently, in India, no structured provision of education and training exists for AMS.[95]

Studies evaluating the impact of implementing infection control and antibiotic stewardship practices on nosocomial infections are limited. In addition, the impact of studying the appropriateness of intervention measures in antimicrobial stewardship and infection control practices are urgently needed for Indian settings. Interestingly, a study from India has documented that improving basic infection control practices, rapid diagnostics, and antimicrobial stewardship practices as key tools for the reversal of AMR.[96] There was a notifiable reduction in the incidence of priority pathogens, including VRE (43.5% in 2016 to 12.2% in 2021); carbapenem-resistant *E. coli* (21.6% in 2016 to 19.4% in 2021), carbapenem-resistant *P. aeruginosa* (23% in 2016 to 20.6% in 2021); carbapenem-resistant *A. baumannii* (66.6% in 2016 to 17% in 2021).The incidence of reduction in VRE and carbapenem-resistant *A. baumannii* was significant, but the reduction was found to be marginal in case of carbapenem-resistant *E. coli* and carbapenem-resistant *P. aeruginosa*. In addition, the rate of isolation of *Candida* spp. from non-sterile sites also showed a reduction, from 1.68 to 0.65 per 100 patients. Importantly, the incidence of HAIs also fell from 2.3 to 1.19 per 1000 line days for CLABSI and 2.28 to 1.88 per 1000 catheter days for complicated UTI.

In hospital or community, certain innovation strategies have been proposed to promote ASPs. It is an urgent appeal to all the doctors to make it a mandatory practice to write indication/reason/justification while prescribing antimicrobials. The OPD cards should be designed and structured to compel the clinicians to make note of clinical diagnoses and reasons for prescribing antibiotics. A person-centered practice for prescription can be promoted by recognizing the best prescriber team or individual. The essential recommendations are as follows:

- Develop and maintain antimicrobial policies, procedures, and clinical pathways for antimicrobial treatment and prophylaxis.
- Define and maintain a formulary restriction and approval process that include restricting broad-spectrum antimicrobials to patients in whom their use is clinically justified.
- Develop and implement interventions and educational strategies for medical officers, nurses, pharmacists, and

other clinical employees on appropriate antimicrobial prescribing and AMS principles, and monitor outcomes.
- Maintain an awareness of local antimicrobial resistance patterns among local pathogens and relevant local outbreaks of infection, and to consider whether these may need to influence antimicrobial prescribing guidelines.
- Monitor antimicrobial usage, including appropriateness of prescribing relative to evidence-based recommendations.
- Participate in activities that permit benchmarking and comparisons of prescribing between facilities where appropriate and provide guidance on proper interpretation of these findings.
- Ensure antimicrobial stewardship process, and outcome indicators are measured and reported to the hospital management and relevant committees.
- Ensure that there is feedback of clinically relevant data regarding prescribing behaviors to prescribers and to other stakeholders, for example, nurses and pharmacists in a way that they can understand.
- Ensure that APS activities are aligned with other hospital activities
- Regular meetings should be established with defined objectives, action plans, and measurement of progress and outcomes. AMS committees will often meet monthly, or, for smaller centers, every second or third month. Any less often than quarterly (3 monthly) is rarely acceptable but might be relevant for a small center with a limited spectrum of diagnoses managed (e.g., a day-procedure hospital).

Recommendations for action

- National Accreditation Board for Hospitals & Healthcare (NABH) accreditation should be made mandatory for licensure of all public and private hospitals: an AMSP program is one of the components of NABH accreditation.
- An ID physician should be the convener for the AMSP program in all tertiary care hospitals: where no ID physician or department currently exists, a senior physician or surgeon or microbiologist can be the convener. In secondary and primary care hospitals, any physician or microbiologist with an interest in this area and who has a good rapport with other antimicrobial prescribers can be the convener.

Diagnostic stewardship

Inappropriate testing can also result in overdiagnosis of HAIs. Rapid and accurate diagnosis of infection is critical for appropriate antimicrobial initiation and subsequent optimization. The goal of diagnostic stewardship is to select the right test for the right patient, generating accurate, clinically relevant results at the right time to optimally influence clinical care and to conserve healthcare resources [Figure 8].[97,98] The process of diagnostic stewardship begins with the evaluation, selection, and implementation of appropriate diagnostic tests for the clinical setting, incorporates guidance for health care providers regarding judicious use of testing for appropriate patients, and ensures timely sample collection, transport, and processing and timely reporting of results. Diagnostic stewardship and antimicrobial stewardship are both critical components of healthcare aimed at optimizing patient outcomes while minimizing the emergence of antimicrobial resistance. By integrating diagnostic stewardship with antimicrobial stewardship, healthcare providers can ensure that diagnostic tests are used judiciously to guide appropriate antimicrobial therapy, leading to improved patient outcomes and reduced AMR [Figure 9]. Key considerations and strategies for each step of the diagnostic stewardship process are outlined below and summarized in Table 9.

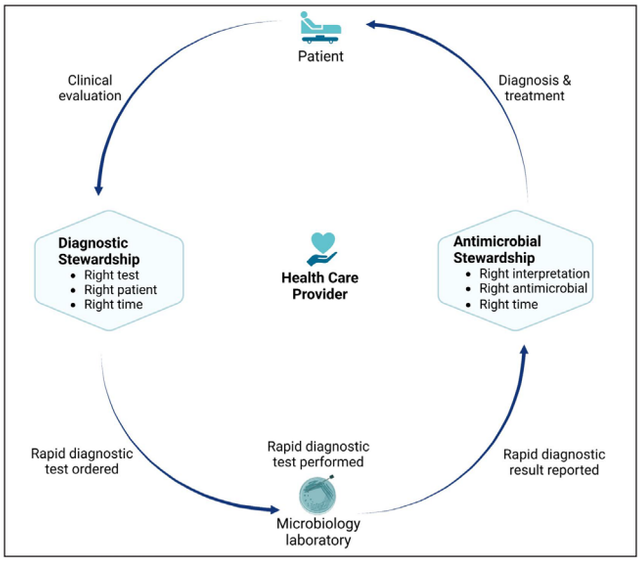

Figure 8: Roles of diagnostic and antimicrobial stewardship in the implementation of rapid molecular infectious disease diagnostics in the clinical setting.

Diagnostic stewardship is more challenging for direct-from-specimen rapid diagnostic tests, for which the responsibility for appropriate ordering traditionally rests on the clinician. Development of diagnostic algorithms and inclusion of computerized order entry (CPOE) decision support can be used to direct clinicians toward the appropriate test for the clinical situation and curb unnecessary duplication of diagnostic testing.

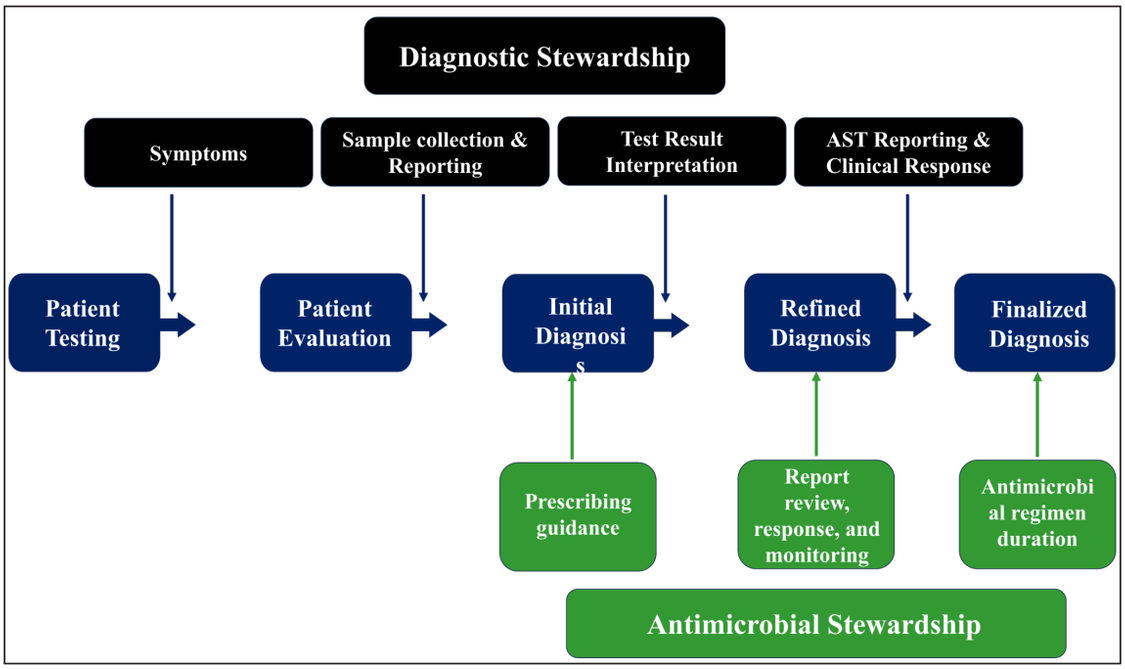

Figure 9: Relationship between diagnostic stewardship (dark green) and antimicrobial stewardship (light green) on patient diagnosis and treatment.

Table 9: Key diagnostic stewardship considerations for implementation of rapid infectious disease diagnostics

Goal	Key question	Key considerations and potential strategies
Right test	Is the test appropriate for the clinical setting?	• Sensitivity and specificity • Predictive values • Testing volumes • Diagnostic yield • Laboratory feasibility • Cost • Clinical impact
Right patient	Will the clinical care of the patient be affected by the test result?	• Laboratory test utilization committee • Automatic laboratory reflex • Appropriate use criteria • Indication selection • Prior authorization • Benchmarking • Specimen rejection
Right time	Will the result be available in time to optimally affect care?	• Time to specimen receipt • Centralized vs point-of-care testing • On-demand vs batched testing • Specimen preparation time • Run time • Result reporting time

Recommendation for action

- All Microbiology laboratories (both stand-alone and hospital-associated) need to be mandatorily NABL accredited: this will automatically ensure a basic level of optimum practice and diagnostic stewardship
- Diagnostic stewardship should be taught and emphasized in the core curriculum on Microbiology at the undergraduate and postgraduate levels.

Hospital infection control practices and NABH accreditation for tertiary care centers

Healthcare facilities are high-risk environments for the development and spread of resistant pathogens and frequently have the highest burden of multidrug-resistant pathogens, including carbapenem-resistant and difficult-to-treat gram-negative pathogens. In India, the burden of HAIs is high, with an estimated pooled prevalence of 15.5 per 100 patients.[99] Most HAIs are preventable through effective infection prevention and control (IPC) measures [Figures 10 and 11]. They are, therefore important to efforts to contain AMR. At present, however, a lack of adequate systems and infrastructure for infection prevention and control in many healthcare facilities contributes to the development of HAIs and the spread of resistant pathogens.

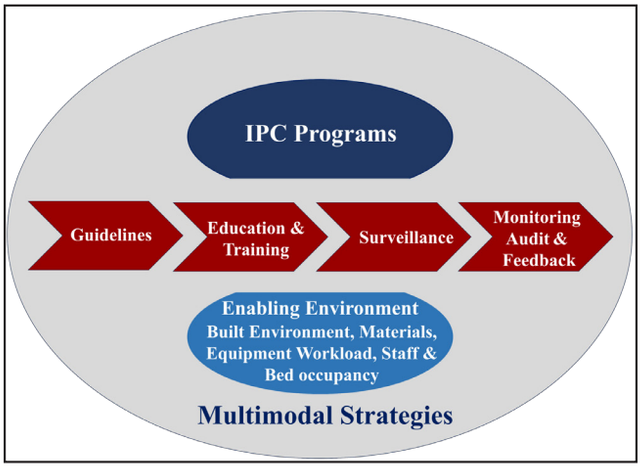

Figure 10: Multimodal strategy for infection, prevention and control implementation and to improve IPC practices in hospitals. IPC: Infection prevention control.

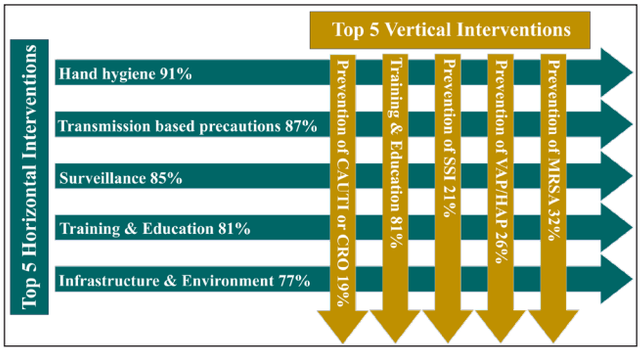

Figure 11: Top 5 horizontal and vertical interventions suggested as a minimum requirement at the facility level.

Accreditation is an important strategy to improve and assure the quality of health care. Although hospital accreditation is not mandatory in India, groups such as the autonomous National Accreditation Board of Hospitals and the National Health Mission's National Health Systems Resource Center have incorporated programs on infection prevention and control, including surveillance of HAIs, as a core part of the review and certification process.[100,101] At the national level, there has been growing recognition of the need for policy and guidance documents, and in 2016 the ICMR released guidelines on infection prevention and control.[102] Despite these initiatives, the successful implementation of an infection prevention and control program in Indian healthcare settings faces some important challenges, including insufficient funding and human resources, hospital overcrowding, and low nurse-to-patient ratios even in ICUs.[103,104] Implementation and improvement of IPC programs are critical to reducing the impact of HAIs and the spread of multiresistant pathogens. The annual plan for prevention and control of HAIs are:

- Actions to promote appropriate hygiene measures
- Guidelines for empirical and targeted therapy based on national recommendations and local epidemiology, especially in life-threatening emergencies
- Actions against the spread of nosocomial infections driven by specific local situations
- Monitoring of alert microorganisms, including MRSA, VRE, ESBL-producing Enterobacterales, carbapenem-resistant isolates belonging to Enterobacterales, *P. aeruginosa,* and *A. baumannii*). The process starts from the microbiology laboratory: when an alert organism is isolated an alert is sent to the local IPC team.
- Monitoring of antimicrobial use as provided by the hospital pharmacy with a focus on broad-spectrum antimicrobials
- Annual one-point survey to establish the local prevalence of HAIs
- Epidemiological reports on circulating pathogens and antimicrobial resistance
- Educational annual program pointed to an appropriate antimicrobial use for all the hospital personnel

Active and passive surveillance programs should be implemented to assess and monitor the extent and trends of HAIs, inform alert and precautionary programs, and improve performance, strategy, and skill development. Active surveillance for multi-drug resistant organisms (MDROs) includes targeted screening to identify colonized patients on hospital admission which should be epidemiologically determined, such as performing entry rectal swabs for prevention and control of carbapenem-resistant Enterobacterales infections and nasal swabs for prevention and control of methicillin-resistant *S. aureus* in high-risk units.[105] Active surveillance may be more directly associated with monitoring and controlling the risk of drug-resistant pathogen outbreaks. Monitoring should include all gram-negative and gram-positive organisms that represent a relevant threat according to local or national epidemiological assessment. Passive surveillance consists of data that are routinely generated from patient registration, laboratory or pharmacy data, or data from discharge. Quality microbiology and laboratory capacity are essential to enable reliable HAI surveillance, and laboratory reporting of alert organisms, usually multiresistant, is a due act of surveillance within the facility.[106] The role of pharmacy and the antimicrobial stewardship team is to track trends in antibiotic consumption (DDD/100 hospital days) that is also measured for economic

reporting purposes. Surveillance should provide information for:

- Description of the status of HAIs (i.e., incidence and/or prevalence surveys, type, etiology, and ideally, data on severity and attributable burden of disease)
- Identification of the most relevant AMR susceptibility patterns
- Identification of high-risk populations, procedures, and exposures
- Early detection of clusters and outbreaks (contact tracing)
- Evaluation of the impact of interventions.

Education and training programs should be audited against predefined checklists that are revised over time to take into account local barriers and behavior.

Education and training should be combined with knowledge tests, competency assessments, or both. In order to reduce the incidence of nosocomial infections, compliance with interventions is mandatory.

Recommendations for action

- Encouraging public hospitals to get NABH accreditation: a hospital infection control program is one of the NABH accreditation.

Promoting in-hospital formulary

An antimicrobial formulary is a simplified list of available antimicrobials, with accepted indications for use, dosing schedules, drug interactions, and adverse events. A robust formulary can allow for easier maintenance of guidelines, and provision of education and training. Available antimicrobials have been evaluated in a systematic manner and meet strict criteria for inclusion. This can benefit prescribers by limiting the number of antimicrobials that they will be learning how to utilize and therefore, should improve the appropriateness of prescribing [Figure 12]. The formulary should include a subset of restricted antimicrobials. The use of these restricted antimicrobials requires strict monitoring and adherence to the antimicrobial prescribing policy of the hospital. The WHO AWaRe classification of antibiotics could be used as the base for a formulary restriction policy, mainly targeting Watch and Reserve groups of antibiotics.[107] Auditing compliance with the in-hospital formulary restriction is important to ensure the adherence of policies.

A hospital's drug and therapeutic committee (DTC) has the responsibility of creating and managing the antimicrobial formulary list but may involve an antimicrobial subcommittee or rely on the AMS team to advise on the need for adding

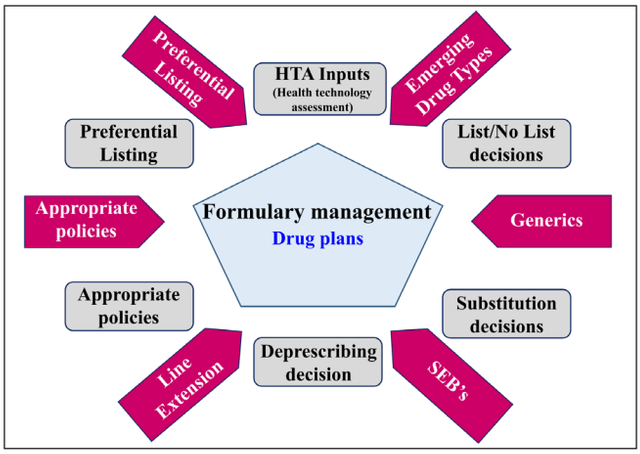

Figure 12: Managing formularies in hospitals.

new antimicrobials or indications to the current list.[108] The management of the antimicrobial formulary should involve periodical review at least monthly to quarterly would be preferable.[109,110] This process should involve medical and pharmacy staff knowledgeable about the spectrum of activity of antimicrobials, pharmacokinetics, and pharmacodynamics, hospital antibiograms, and common infectious diseases. New antimicrobials should be added if they meet the criteria for inclusion, including acceptable data on safety, pharmacological action, adverse drug reactions, and drug interaction; reasons why this is superior to current formulary-listed antimicrobials; scientific evidence and literature to support its addition; updated clinical guidelines or treatment pathways; altered hospital infection patterns and antibiogram; acceptable cost-efficiency; and approved and quality source of supply.[109] Current antimicrobials should be removed from the list if they meet the deletion criteria, including if the antimicrobial is no longer used; recent data on lack of safety and efficacy become available; the antimicrobial does not meet the requirements for cost-effectiveness if an acceptable alternative is identified.[109] Antimicrobial formulary management includes:

- The formulary should be consistent with any national formulary or approved standard infection treatment guidelines.
- The formulary should be reviewed and revised periodically
- Combination or fixed-dose antimicrobials should only be used in specific proven infections
- The ability to prescribe antimicrobials is restricted to only those practitioners with appropriate prescribing skills
- In Hospitals strict measures across the country to limit prolonging perioperative prophylaxis by stop orders after three IV doses and no oral doses. This should be audited.

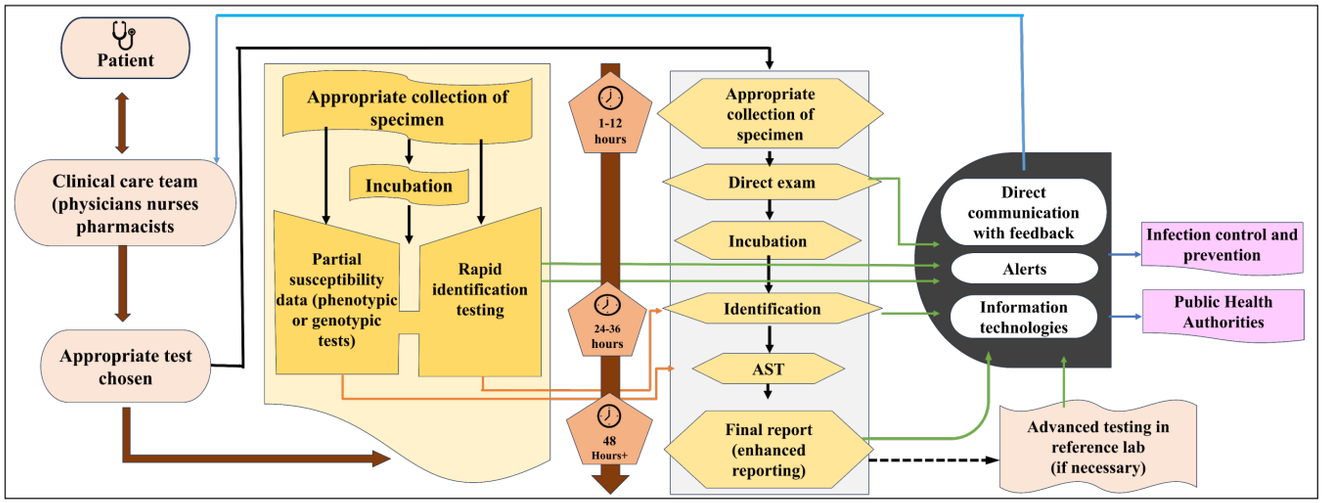

Figure 13: Workflow pathways for conventional microbiology and RDT. Implementation of RDT increases laboratory workflow complexity but can hasten the availability of results. Communication of results is a key factor. Blue arrows represent the conventional microbiology pathway, orange arrows represent the RDT pathway, and green arrows represent opportunities for the laboratory and antimicrobial stewardship teams to improve communication of results. AST, antimicrobial susceptibility testing. AST: Antimicrobial Susceptibility testing, RDT: Rapid diagnostics tests.

Recommendations for action

- NABH accreditation for licensure should be made mandatory for all public and private hospitals: optimum hospital formulary practice in regard to antibiotics is one of the components of NABH accreditation.
- AMR and AMS should be introduced in the core curriculum of trainees in Pharmacy. Parenteral to oral switch of antibiotics should be rational and a nation-wide policy can be developed for this purpose

5. Interventions at clinical microbiology laboratory level

Integrating microbiology laboratories to ASPs is important in the area of diagnostic stewardship, the development of antibiograms to support optimal antibiotic use, the introduction of new diagnostic tests into the laboratory, the implementation of new antibiotic susceptibility testing interpretative criteria, and education of clinicians on laboratory testing practices. Strengthening clinical microbiology laboratories across the country in performing diagnosis and antimicrobial susceptibility testing, including rapid molecular diagnostics testing, supports ASPs [Figure 13]. Institution-wide antimicrobial resistance surveillance reported in the form of antibiograms informs decisions for empiric antimicrobial therapy, and timely and accurate patient-specific pathogen isolation, and susceptibility data inform directed antimicrobial therapy.

Coupling clinical microbiology laboratory information with ASP interventions leads to the best antimicrobial use for individual patients and on an institutional level.

Maintaining high-quality clinical microbiology laboratories is the current best approach for diagnosis and treatment of infectious disease. The clinical microbiology laboratories, accredited under the National Accreditation Board for Testing and Calibration Laboratories (NABL), ensure quality infrastructure, laboratory operations, quality assurance, and continual improvement. Furthermore, regular participation in an external quality assessment scheme (EQAS) is crucial for ensuring acceptable laboratory performance in facilitating optimal patient care.

Tailoring susceptibility test performance and reporting to formulary decisions and the stewardship principle of encouraging narrower spectrum antibiotic use whenever possible is recommended. Use cascade reporting to promote preferential use of narrowest spectrum antibiotics [Figure 14].[110] Update institution antibiograms following published guidance in the M39 CLSI document, at least on annual basis.[111] Antibiogram helps the prescribers for selecting effective therapy when culture results are pending, and informing and update local guidelines for empirical treatment of common infection syndromes. From the antimicrobial stewardship standpoint, cascade or selective reporting can be used to promote the judicious use of antimicrobials. Cascades consist of algorithm-driven reports that provide only a limited number of tested antimicrobial susceptibilities based

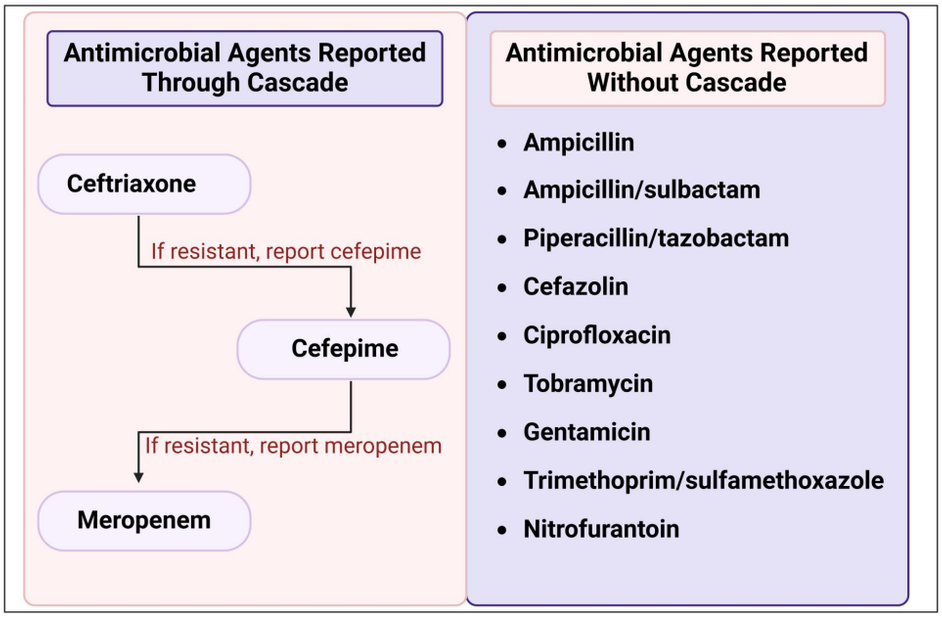

Figure 14: Cascade reporting for Enterobacterales.

on formulary availability, local cumulative susceptibilities, and cost for isolates with no or low levels of resistance and reporting of susceptibility to broader-spectrum drugs only when isolates are resistant to drugs in the first "cascade." Careful selection of reported susceptibilities and frequent re-evaluation are necessary to ensure the continued value and reliability of the cascade and the quality of the reporting. Unreleased susceptibility data should also be readily available upon clinician request.

Molecular rapid diagnostic tests (mRDTs) have emerged as a key technology to decrease the time to identification and antimicrobial susceptibility of pathogens.[91] These tests can decrease the time to effective therapy and antimicrobial optimization, and they also decrease the length of stay in patients with bloodstream infections. The clinical impact of mRDTs is most pronounced when reviewed and acted upon by the ASP in real time. Successful implementation of mRDTs is dependent on workflows supporting antimicrobial stewardship review of mRDTs results and on communicating recommendations to frontline clinicians.[112,113]

Incorporating mRDTs results into the ASP workflow should be a high priority in hospitals that utilize this technology.

Clinical microbiology laboratories are key to AMS programs, providing specimen collection and testing, rapid diagnostics, susceptibility testing, and production of antibiograms and education activities. The usefulness of clinical microbiology laboratories are as follows:

- The clinical microbiology laboratory and the clinical microbiologist can play a pivotal role in any AMS program.
- Clinical laboratories can provide diagnostic stewardship
- The microbiology laboratory should ensure that all antimicrobial susceptibility results are reported in a selective manner; "cascade reporting" should be considered as part of an effective AMS program.
- Early and direct communication with the treating team regarding the interpretation of results and offering clinical advice can help support AMS initiatives and optimize antimicrobial therapy.
- Antibiograms can be used to help guide the local antimicrobial formulary, empiric antimicrobial guidelines and inform specific AMS interventions.
- WHONET is a software program available from the WHO to assist in the development of cumulative antibiograms.

Recommendation for action

- All Microbiology laboratories (both stand-alone and hospital-associated) need to mandatorily be NABL accredited: this will automatically ensure a basic level of quality control and optimal reporting.
- State of the art microbiological practices that impact AMR should be included in the core curriculum of Microbiology at the undergraduate and postgraduate levels.
- An early updated CLSI document should be distributed to all accredited laboratories by the government. This can prevent the use of obsolete breakpoints for susceptibility

interpretation and therefore quality of AMR data can be maintained

6. Research and development

Promoting research for new antibiotics and rapid diagnosis

- Promoting research for development of new antibiotics and validated point-of-care or rapid test for diagnosis of infectious disease can prevent misuse of antibiotics in the community.

  New agents displaying innovative chemistry and modes of action are desperately needed worldwide to tackle AMR. Researchers developed an artificial intelligence (AI) model that designs novel, synthesizable antibiotic compounds, several of which showed potent in vitro activity against priority pathogens.[114,115] Initially, researchers used predictive AI models to identify antimicrobial properties of existing drug compounds, but these models are not very efficient. Generative AI models can go a step further to design brand new drugs, but these tend to be difficult to synthesize. However, additional studies on the newly identified antibiotics are warranted. While there is room for growth and improvement, India's position in antibiotic development is poised for advancement. With its strong pharmaceutical industry, research capabilities, and ongoing initiatives, India has the potential to play a significant role in addressing the global challenge of AMR through the development of novel effective antibiotics.

  Lack of easy access to diagnostic testing, in fact, has made the diagnostic step one of the weakest links in the cascade of patient care. Moreover, timely and accurate diagnosis through rapid tests can reduce the time to pathogen identification and facilitate faster, optimized antimicrobial treatment. The most common identified gaps include inadequate near-patient testing for identification, susceptibility testing and biomarkers.[116] The R&D priority for rapid diagnostics against AMR includes
- Improved near-patient testing for ID and susceptibility
- Host response tests, identifying biomarkers
- Multiplex diagnostic platform to identify bacterial pathogens and perform susceptibility testing directly from samples
- Simple, easy-to-use test or platform for antimicrobial susceptibility testing (AST) only

Recommendations for action

- Both investigators initiated and ICMR-initiated projects concerning diagnostics and therapeutics impacting AMR need to be accorded priority with fast-track approval and increased funding.

Promoting one-health approach

One Health is an integrated approach that recognizes the health of humans, animals, and the wider environment as closely linked and interdependent [Figure 15].[117] It requires multidisciplinary collaboration, adequate surveillance systems, and strong laboratory capacity, many of which are challenges for Indian settings. Several integrated approaches have been proposed to reduce antibiotic misuse in human, environmental, and animal health [Table 10].[118]

Restricting the use of antibiotics in food-producing animals

There is growing concern that nonprudent use of antibiotics is linked with the escalating emergence of human infections with antibiotic-resistant pathogens of zoonotic importance. In farm animals, antibiotics are commonly used to promote more rapid growth quickly, however, there is evidence to suggest that use of antibiotics at low- or sub-therapeutic levels fosters the development of resistant bacteria. Additionally, high levels of antibiotic-resistant genes have also been identified in soils fertilized with manure and river waters contaminated by runoff from animal farms. Therefore, the presence of resistance and residues of antimicrobials in foods of animal origin constitutes a potential risk to the health of consumers and are also recognized as an emerging environmental problem. In India, regulations controlling the use of antibiotics in animals are very weak and in the initial phases.

Low doses of antibiotics to promote growth are often used to compensate for poor farm hygiene and crowded conditions.[119] In India, projected financial losses for a proposed ban on subtherapeutic antibiotic use were 1–3% of annual meat production, with the greatest losses by poultry farmers.[120]

Fewer intervention strategies have been proposed to address the contributions of animal reservoirs to the dissemination of antibiotic resistance. First, antibiotic use in the livestock and aquaculture industries should be evaluated.[121] Little is known about the quantity, frequency of administration, or types of antibiotics used in animal production. Survey results can be used to identify which types or aspects of animal production are most in need of oversight, and once identified, comprehensive monitoring programs could be designed to address them. A systematic review and meta-analysis showed that reducing antibiotic use decreased the prevalence of antibiotic-resistant bacteria in animals by about 15% and multidrug-resistant bacteria by 24–32%.[122] Second, administration practices that result in veterinary drug residues at slaughter must be restricted.[123] Third, any antibiotic classes that are of critical importance to human health (e.g., colistin) should be banned for animal use.[119]

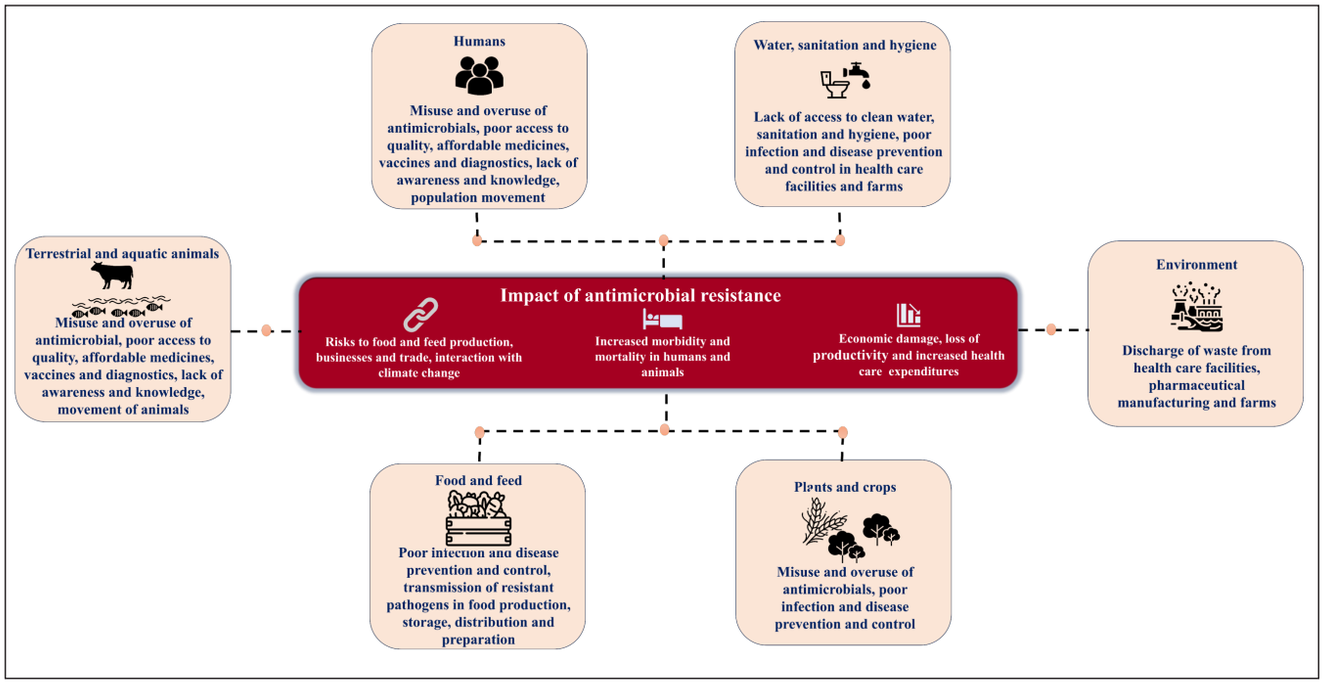

Figure 15: Drivers of antimicrobial resistance (AMR) in one health aspect.

Table 10: Recommendations for action to address one health challenges related to antibiotic misuse

Strategies	Specific actions
Manage antibiotic use in animal agriculture	Survey antibiotic use in livestock and aquaculture production
	Create antibiotic resistance action plans that address antibiotic use in agriculture
	Improve farmer education about best practices in animal agriculture, including vaccine use and antibiotic withdrawal periods before slaughter
	Improve waste disposal from farms
	Ban use of antibiotics that are critically important to human health eg cephalosporins, fluoroquinolones, tetracyclines, colistin
Livestock antimicrobial resistance (AMR) surveillance	Generating surveillance-based AMR data from the veterinary practice is required to counteract resistance and preserve the efficacy of antimicrobial agents
Treat highly contaminated waste effluent before disposal	Enforce minimum treatment levels for hospital and drug manufacturer waste
Improve access to clean water and sanitation	Consider water and sanitation initiatives

Fourth, considering alternative options to using antibiotics for disease prevention in animals include improving hygiene, better use of vaccination, and changes in animal housing and husbandry practices.[124] Importantly, farmer education is also necessary to reduce animal antibiotic misuse.

Recommendations for action

Interventions strategies that help to reduce the need of antimicrobials in farm animals are as follows:

- Restricted preventive use of antimicrobials both in groups of animals and medicated feed
- Restriction on metaphylactic use of antimicrobials
- Antimicrobials should be strictly avoided for the purpose of promoting growth and increasing yield
- Reserve certain antibiotics for humans only. A list of such antibiotics may be drawn up after inputs from medical and veterinary experts.
- Make obligatory for state government to collect data on antibiotic sale and use of antimicrobials in farm animals

Interventions to reduce environmental antimicrobial resistance

The environment acts as a mixing pot of drug-resistant bacteria from many sources such as pharmaceutical, biomedical, veterinary, and agricultural sectors. There are three main emission sources in the environment includes animal farming, hospital or community sewage, and pharmaceutical industry. Wastewater discharge from antimicrobial production is a hotspot for AMR development. Because antibiotics present in pharmaceutical wastewater have not been metabolized, their concentrations may be manyfold higher than in human waste.[125] Subsequently, a study on wastewater treatment plant treating discharge from 90 pharmaceutical companies in India has reported to release a huge amount of ciprofloxacin in 1 day that equals to an amount prescribed to humans in Sweden over 5 days.[126]

Additionally, hospitals discharge antibiotic-resistant bacteria, which propagate in the hospital setting due to poor infection control.[119] Moreover, inadequate sanitation and poor hygiene practices amplify the propensity for increasing antimicrobial pollution in the environment. Thus, prompt interventions are urgently needed to address the emergence and transmission of AMR in the environment.

Wastewater serves as a pivotal juncture for the dissemination of antibiotic-resistant organisms and functions as a pathway through which strains of human and animal origin can infiltrate the environment and potentially colonize new hosts. Even if present, the wastewater treatment plants are not designed to remove antibiotics or antibiotic resistance genes. The proposed predicted no effect concentrations (PNECs) for resistance selection ranges from 8 ng/L to 64 μg/L.[127] However, the lack of optimal wastewater treatment increases its overall risk in India. The high cost associated with regular monitoring of antimicrobial levels in pharmaceutical waste water makes it a low-priority objective, and a strict vigilance on the effluent produced is also needed.[128] Pharmaceutical companies may be able to reduce antibiotic discharge by improving manufacturing practices and on-site industrial waste treatment systems.[129] Noncompliance penalties, such as fines or revocation of operation permits, may be necessary for enforcement.

Hospital wastewater containing disinfectants, antibiotics, and microbial and organic compounds can be very harmful for the environment and humans. The existing evidence indicates inadequate microbial treatment emphasizing the need for improvement in healthcare waste management. Over the years, various treatment technologies, including biological methods, such as activated sludge process, membrane bioreactor, moving bed bioreactor, constructed wetlands, the advanced oxidation processes, such as photocatalysis and Fenton process, have been implemented to treat the effluents. Noticeably, high proportions of multidrug-resistant and carbapenem-resistant gram-negative pathogens have been reported in the treated hospital effluents in India.[130–133]

Recommendations for action

The following are the interventions to prevent the dissemination of resistant pathogens and release of antibiotic residues into the environment.

- Decontamination of human and animal wastewater and sewage from hospitals, farms, urban sewage, treatment plant discharge, sewage overflow, run-off manure-fertilized agricultural fields and livestock farms
- Surface microbial decontamination of floors and equipment in hospitals and farms.
- Prevention of environmental releases and deconta-mination of antimicrobial substances, including biocides, metals, and industrial pollutants, as influencing the environmental selection of resistant organisms
- Sublethal concentrations of biocides can increase the pool of resistant organisms in the environment. Another important aspect is the sharing of resistance mechanisms between biocides and antimicrobial agents, thus facilitating their co-selection. Biocides as a route of AMR need to be listed in the NAP-AMR of India.

Inequity in priorities and agendas between the Global North and the Global South

The term "Global North" typically refers to the more economically developed countries, while the "Global South" encompasses less economically developed countries. The division between these regions extends beyond economic factors and influences priorities and agendas related to AMR. In the Global North, where access to healthcare and resources for research and development is generally higher, there is often a greater focus on developing new antimicrobial drugs and technologies to combat resistance. However, this approach may not be feasible or effective in the Global South due to financial constraints and different healthcare infrastructures.

Conversely, the Global South often faces more immediate challenges related to access to basic healthcare, sanitation, and clean water, which are critical for preventing infections in the first place. Therefore, their priorities may lean toward strengthening healthcare systems, improving sanitation, and promoting responsible antimicrobial use to prevent the spread of resistance. This disparity in priorities and agendas between the Global North and South poses a significant

threat to global efforts to mitigate AMR. Collaboration and coordination between these regions are essential to address the multifaceted challenges posed by AMR effectively.

Thera are three examples that illustrate these differences. In European countries, a direct correlation between outpatient penicillin use and the *S. pneumoniae* resistance rate to penicillin has been demonstrated. However, in a study on low-income countries, the direct association between resistance to and use of fluoroquinolones or third-generation cephalosporins on *E. coli* was not demonstrated. However, a study on LMICs demonstrated no direct association between resistance to and use of fluoroquinolones or third-generation cephalosporins on *E. coli*. This study examined the impact of universally applicable interventions such as governance, health expenditure, gross domestic product per capita, education, infrastructure, and climate on AMR. The findings indicated that infrastructure interventions, which included adequate sanitation, access to improved water sources and electricity, and urbanization, contributed significantly to the reduction in AMR. Further, environmental sources, such as water, soil, and surfaces within the household, are critical reservoirs for ESBL-producing bacteria. These contaminated environments facilitate the transmission of resistant bacteria between animals and humans. This research underscores the interconnectedness of human, animal, and environmental health, a concept central to the One Health approach. Further, no correlation was observed between country-level antibiotic usage and total AMR gene abundance, suggesting that non-antibiotic-use factors play a more significant role in driving the presence of AMR genes in sewage.

The danger of the Global South falling short of opportunities to fundamentally mitigate AMR is further exacerbated by the focus of global funding toward research and development of new antibiotics. However, there is a risk of neglecting these holistic and preventive measures, which are vital for sustainable AMR mitigation. A balanced approach that includes significant investments in these areas is essential to effectively combat AMR, especially in the Global South. Less funding for vaccines for research and development in diagnostics further complicate AMR issue in the Global South. The inequality in global pharmaceutical procurement, where the Global North dominates over 60% of the market, contrasts sharply with antibiotic production, which is primarily concentrated in countries like China and India. This distribution poses significant environmental risks, particularly concerning water contamination, due to the discharge of antibiotic residues into nearby water sources. Such disparities underscore the complexities of the global pharmaceutical landscape, highlighting not only economic divides but also environmental concerns that require attention and cooperation on a global scale.

Recommendation for action

- The United Nations Secretary General play a pivotal role in accelerating the establishment and funding of this panel by advocating for its importance on the global stage, Additionally, leveraging existing platforms and initiatives within the UN system, such as the WHO and the Food and Agriculture Organization (FAO), could amplify efforts to address AMR holistically.
- By prioritizing AMR, G77 leaders can take proactive measures to mitigate these risks and promote sustainable development. This includes strengthening healthcare systems, promoting responsible antibiotic use in agriculture, investing in research and development of new antimicrobial drugs, and fostering international collaboration to address this urgent threat.
- Linking equitable AMR mitigation interventions to the attainment of country-level sustainable development goals (SDGs)
- Negotiations on knowledge transfer and capacity development for antimicrobials, vaccines, and diagnostics should indeed involve the UN, given its convening power and its ability to coordinate efforts among member states.

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