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Review on Infectious Diseases in India and their respective diagnostic platforms.

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Abstract: ***India is a lower-middle-income country with improved industrial output and expansion of innovative technologies (information, biopharmaceutical) with some notable health benefits in controlling very few infectious diseases due to an inadequate health system. It mainly focuses on providing medical care for urban population and lacks a common health framework that plays a critical role in illness prevention. However, these diseases are caused not only by a lack of sanitation and population density but also by environmental and behavioural changes.***
This study reviewed the literature on infectious diseases that cause deaths in India, such as tuberculosis, lower respiratory infections, and Transfusion Transmitted Infections (TTIs), diagnostic procedures for treatment and disease burden.
Keywords: lower-middle-income country, Infectious diseases, Transfusion Transmitted Infections (TTIs), disease burden.

I. INTRODUCTION

Predicting the entry of a pathogenic agent is impossible but there is a continuous emergence of new pathogens or already known diseases which weakens significant numbers of people and also increases the risk of a bioterror attack. These infections depend on several factors such as the pathogen's nature, environmental and human behavioral factors[31].
Generally, there are different modes of disease transmission in which the diseases that cause death are grouped as: - communicable (infectious and parasitic diseases and neonatal conditions), non-communicable (chronic), and injuries[31]. This study focuses mainly on infectious diseases which are due to existing harmful microorganisms, transmitted from person to person directly or indirectly. Further communicable diseases are led by faecally transmitted microorganisms[15]. Scope and burden of contagious diseases are high in India therefore predominant infections such as Malaria, Tuberculosis, and HIV infections are controlled through different vertical schemes where the Central Ministry of Health is behind in controlling the disease and its outbreaks[15].
There are different techniques to identify the disease-causing organisms but the recent advances include the use of Electrochemical Biosensor Technology which provides fast response, is highly selective and sensitive, and is portable. It involves the development of point-of-care (POC) devices[22].

A. Disease Burden in INDIA

A series of recent studies have indicated that India saw an epidemic change in percentage of deaths and burden of disease i.e., from 1990 to 2016 with a steady rise in non-communicable diseases (NCDs) burden when compared to communicable diseases in which diarrhoeal, lower respiratory diseases, neonatal conditions, tuberculosis, and measles are the topmost exclusive causes of disease burden in 1990, India whereas diarrhea and lower respiratory infections are the top two disease burden infections that are still prevailing in 2016[27]. Generally, disease prohibition can be obtained by altering or removing the risk components such as elevated glucose levels (fasting) and Body Mass Index (BMI), Air contamination - 9.8%, Dietary hazards - 8.9%, raise in systolic blood pressure - 8.5% or mainly child and maternal undernutrition which accounts for 14.6%[10, 27].
Studies in rural south Rajasthan suggest that the chief causes of burden of infection and deaths in children, youth, and senior group category are due to communicable-malnutrition- maternal-newborn diseases (CMNND), injuries, and non-infectious infections, independently[27].

B. Causes of Deaths over Age Group Distribution

Particularly, the contribution of contagious and non-contagious infections is understood by differentiating the causes of death in India by age group where the elder population (40–69 years) experience and expire (73%) from non-infectious diseases while the younger population die (0–14 years- 81% deaths) from infectious diseases.
However, the middle age group (15–40 years) die due to injuries which imparts nearly 1/3rd of total deaths while infectious and non-infectious diseases deliver uniformly to the remaining deaths[27].

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C. Causes of Deaths by Demographic Distribution

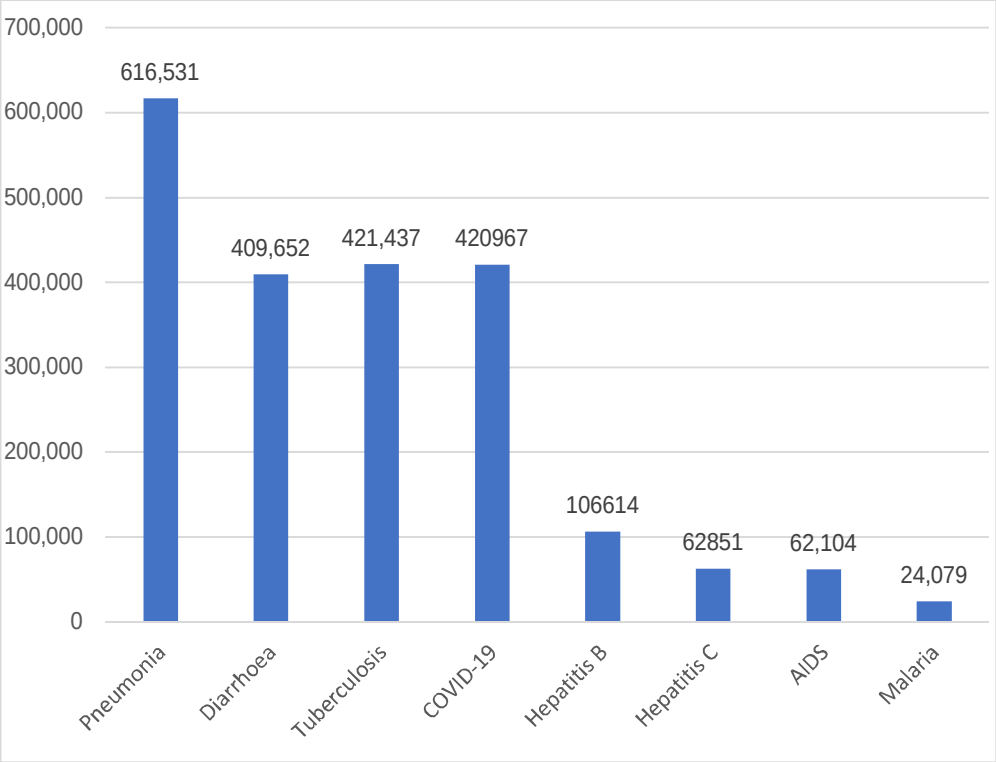
According to social and demographic profiles, a country comprises an expected burden for each disease. Thus, a country exceeds the expected burden due to failure in addressing the health facilities. Therefore, the greater the deviation, the greater is the failure.

In India, the real burden of most of the infection conditions far exceeds the anticipated burden due to their social growth profiles, demography, and also slower decline in mortality rate though they include a vast web of primary health care services within a community, they lack resources and accountability[27].

II. INFECTIOUS DISEASES

According to World Health Rankings, the following infections are in the order of top 50 causes of death in India[33]: -

Figure-1: Disease Burden of Infectious diseases, 2018[6,33].



III. PNEUMONIA

Pneumonia, an acute respiratory infection caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib), [4,20,23] with a vast number of polymorphisms in several inflammatory genes have been found as candidates to explain genetic diversity in susceptibility to lung infections[5].

India is responsible for 20% of the pneumonia deaths when compared to other countries[23]. Between 2014 and 2015, Pneumonia cases and deaths were higher in men when compared to women (Figure-2,3)[28]. The total number of cases and deaths were 6,20,167 and 2,534, respectively in India, 2015 with highest number of cases in Rajasthan (1,08,427), least in Lakshadweep (28) and Delhi accounting a greater number of deaths (412) (Table-1)[28]. It holds for 15% of all the deaths of children younger than 5 years where 8,08, 694 children have died in 2017[31].

For over a decade, diagnostic platforms for identifying the disease-causing respiratory agents are rapidly growing. Immunochromatographic-based urinary antigen tests are easily carried out, developed with quick response. Molecular diagnostic techniques are the recent advances in clinical microbiology laboratories which measure the Procalcitonin (PCT) quantity that differentiates between bacterial and viral pneumonia. Moreover, it helps in predicting the survival and severity of the disease[12]. Chest X-rays are been used efficiently to know the severity of infection. It can be treated with antibiotics such as amoxicillin dispersible tablets[31].

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States & Union territories	Number of cases	Number of deaths
Andaman and Nicobar	98	13
Andhra Pradesh	21,606	14
Arunachal Pradesh	477	9
Assam	16,840	80
Bihar	36,642	12
Chandigarh	18,524	97
Chhattisgarh	9,153	16
Dadra and Nagar Haveli	164	20
Daman and Diu	73	1
Delhi	24,599	412
Goa	424	10
Gujarat	2,360	8
Haryana	8,020	2
Himachal Pradesh	22,157	120
Jammu and Kashmir	40,592	5
Jharkhand	6,278	5
Karnataka	18,496	275
Kerala	5,913	57
Lakshadweep	28	0
Madhya Pradesh	70,028	103
Maharashtra	8,820	9
Manipur	2,102	1
Meghalaya	2,216	45
Mizoram	2,175	44
Nagaland	745	0
Orissa	29,134	228
Puducherry	1,009	21
Punjab	11,039	16
Rajasthan	1,08,427	128
Sikkim	145	0
Tamil Nadu	4,191	33
Tripura	2,247	41
Uttar Pradesh	84,428	351
Uttarakhand	17,989	7
West Bengal	43,028	351
TOTAL	6,20,167	2,534

Table-1: Pneumonia- number of cases and deaths in India

(State-wise and Union territories), 2015[28].

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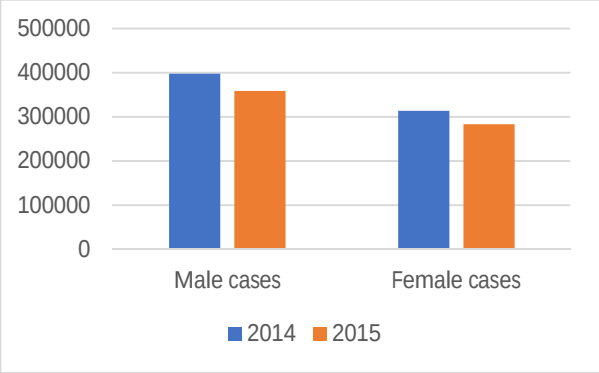

Figure-2: Pneumonia Cases in male and female in India, 2014-2015[28].

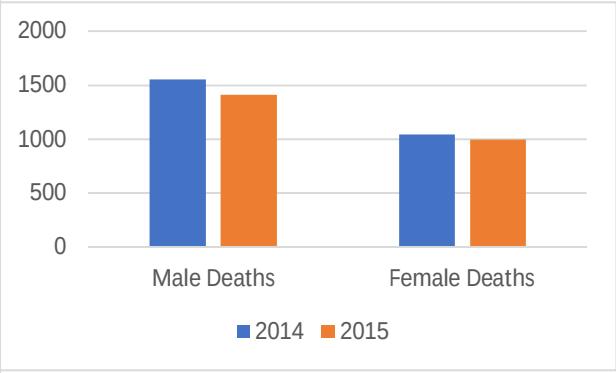

Figure-3: Pneumonia Deaths in male and female in India, 2014-2015[28].

IV. DIARRHOEA

In India, Diarrhoea is the key cause of death in less than five years group of children that is accountable for 13% of deaths, killing about 3,00,000 children every year[18]. This infection can be prevented and treated with oral rehydration solution (ORS) and10–14-day supporting care with 20mg zinc medicines which improved and lessened the duration of diarrhoea[31]. It is also caused due to genetic changes within the genome which develops a protein, GUCY2C where it acts a receptor for bacterial toxins whose activity becomes high in diarrhoea patients[13].

India is accountable for 20% of the global burden since 1.2 million children under the age of 5 years die in India[34]. According to 2017-India-State-Level-Disease-Burden-Initiative-Full-Report, Uttar Pradesh causes a 30% higher burden due to diarrheal infections[10]. There was a stable advancement in decreasing the children's deaths from 2.5 million in 2001 to 1.5 million in 2012 due to novel development of a vaccine against rotavirus[18] but still non-rotavirus diarrhoea is resuming which would be a prime cause for the increase in mortality rate. Prevalence rate of Diarrhoea is high in rural areas, about 15.30% followed by 60 years & above age group, 14.80% and the frequency of the infection is greater in men than women (Figure-4)[21].

Diagnostic platforms for Diarrhoea include the collection of stool samples or blood tests, performing sigmoidoscopy (different costings in various states in India) and colonoscopy (average costing is $128.10-$298.90)[31].

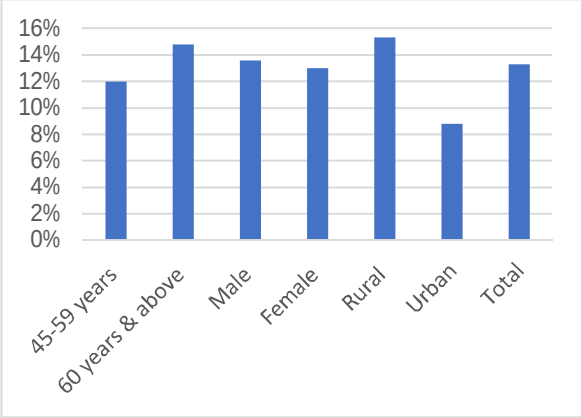

Figure-4: Prevalence of Diarrhoea in India (2017-18) in percentage (%)[21].

V. TUBERCULOSIS

Tuberculosis, led by *Mycobacterium tuberculosis*, mainly attacks the lungs, which disperses through small droplets, whose incidence is elevated in rural areas than urban locality (Figure-4)[21] which can be prevented by early diagnosis and proper management of Tuberculosis patients, awareness about cough etiquettes and residing in properly ventilated atmospheres[31]. It is a curable and treatable disease treated with antimicrobial drugs[31]. The epidemiological research showed that there are certain human genetic, environmental factors are responsible for social variableness over the years. Thus, molecular advancement has been made by detecting the major locus responsible for the resistance to infection with *M. Tuberculosis* and it is demonstrated that in-born mutations of interferon-γ immunity resulted in childhood tuberculosis[1].

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It is the foremost disease burden in India with a 21% frequency rate and 27% of the patients do not acquire proper medical therapy due to lack of uniform health care systems[15]. As per World Health Organization, it is the second prime worldwide killer as a single infectious agent with 30 Tuberculosis highly burden countries rated for about 87% of latest instances and India directing as the top in the count in 2019[31]. Prevalence rate of Tuberculosis is high in men, about 1.30% followed by 60 years & above age group, 1.10% (Figure-5) [21].

In the 1950s, tuberculosis prevalence was proved by surveys using the tuberculin test and miniature chest radiographs[15]. The rapid molecular diagnostic analysis is done as a formal test for patients with signs due to high diagnostic accuracy which will aid in the early detection of the disease. These tests include Xpert MTB/RIF (Mycobacterium tuberculosis (MTB) and Resistance to rifampicin (RIF) but diagnosing multidrug-resistant can be complex and expensive. Truenat is a new molecular assay which is a battery-powered testing platform and cost-effective that quickly identifies the infection and rifampicin-resistance which is a battery-powered testing platform and cost-effective.

Sensitivity for Tuberculosis detection is done using a microsimulation model along with their costing mentioned in the below table-2: -

1) Truenat for point-of-care testing in primary healthcare facilities (Truenat POC)- 95%.
2) Xpert MTB/RIF in DMCs (Xpert)- 89%
3) Truenat in DMCs (Truenat DMC)- 86%
4) Sputum smear microscopy in designated microscopy centres (DMCs) (SSM)- 84%[19].

Monthly expenditures for treating Tuberculosis for first-line therapy is $28.13, $104.23 for second-line therapy and for retreating it is $32.25, which consists of regular visits, price of medication, observing test reports, clinical visits and hospitalizations throughout the treatment procedures[19].

Diagnostic tests	Base case per test	Range per test
Truenat	$30.93	$27.23 – $34.63
Xpert	$12.63	$11.47 – $14.84
Sputum smear microscopy	$0.86	$0.24–1.58

Table-2: Approximate costing for the above diagnostic platforms per test (USD 2017)[19].

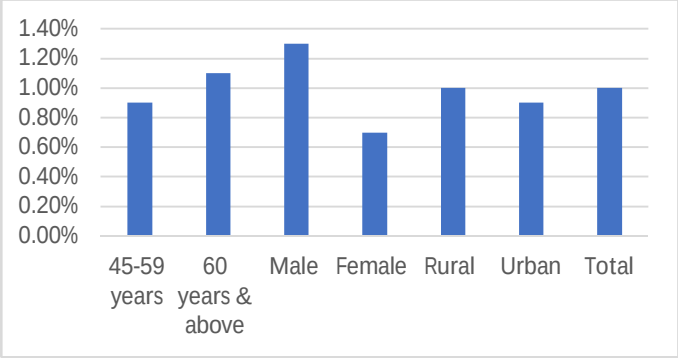

Figure-5: Prevalence of Tuberculosis (2017-18) in percentage (%)[21].

VI. CORONA VIRUS DISEASE 2019 (COVID-19)

Coronavirus (COVID-19), an epidemic caused due to Severe Acute Respiratory Syndrome Coronavirus- 2 (SARS-CoV-2), there are certain Indian vaccines administered to the patients as a layer of protection such as Covaxin and Covishield. Countries also set up a plan to decrease virus proliferation by lessening the social interaction[31]. In Covid-19 infected patients, it was identified that there was an accepted loss of X-chromosomal TLR7 activity which were related to the disability of type I and II Interferon responses[30].

Number of cases and deaths increased gradually from 14th March,2020 till 16th September, 2020 and decreased. Later on, it slowly peaked on 8th may 2021 and gently started lowering in India (Figure-6,7)[7]. As per World Health Organization, 39, 361new cases were registered with 3, 14, 11, 262 confirmed cases and 4, 20, 967 confirmed deaths in India on 26th July 2021. It also led to an economic loss of affected countries including high mortality rate[31].

Virus containing RNA as genetic material is diagnosed using Real-Time- Polymerase Chain Reaction (RT-PCR) by taking swab samples of nose and throat. There is also another way of detecting the virus which is done using rapid kits[31]. Usually, in suspected patients, molecular assays are used as a standard way for detecting the viral genome within a sample[35] and Serology-based immunoassays are used to find the antibodies such as anti-N and anti-S proteins, IgA, IgM, and IgG for SARS-CoV-2 in the infected patient's serum/plasma. Their estimated costing depends on the rules given by the respective states in India[8].

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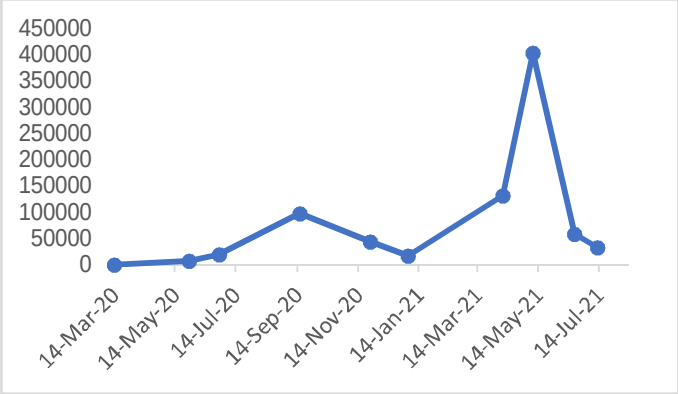

Figure-6: Incidence of Covid-19 cases[7].

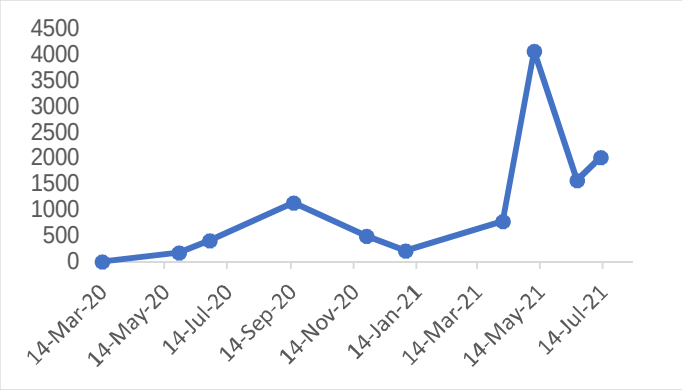

Figure-7: Covid-19 Deaths[7].

VII. HEPATITIS B

Hepatitis B, affects the liver, transmitted through contaminated blood, sexual transmission or sharing needles or syringes which increases the risk of cirrhosis and liver carcinoma[24]. WHO suggests to include oral therapy to lessen the duplication of the virus using tenofovir or entecavir as the effective drugs[31]. Acute hepatitis B cannot be treated but a proper nutritional diet is mandatory whereas chronic hepatitis B can be treated with the help of oral antiviral agents which reduces the process of cirrhosis and thereby, enhances the survival rate. Overall, it can be prevented by a vaccine that is 98-100% safe and effective[31]. It also involves HBV-HIV coinfection and the carrier rate of HBV is 3.0% in India with a high-frequency rate within the tribal community[24].

Each year, around 2.6 crore infants are born in India of which about 1 million show the risk of causing chronic HBV infection[24]. India presents a vast part with greater than 37 million HBV carriers[24]. The number of HBV deaths have been increased gradually between 1990 and 2019 (Figure-8)[5].

Various blood tests are there to diagnose and evaluate the conditions of the patients which distinguishes acute and chronic infections by identifying the presence of surface antigen HBsAg[31].

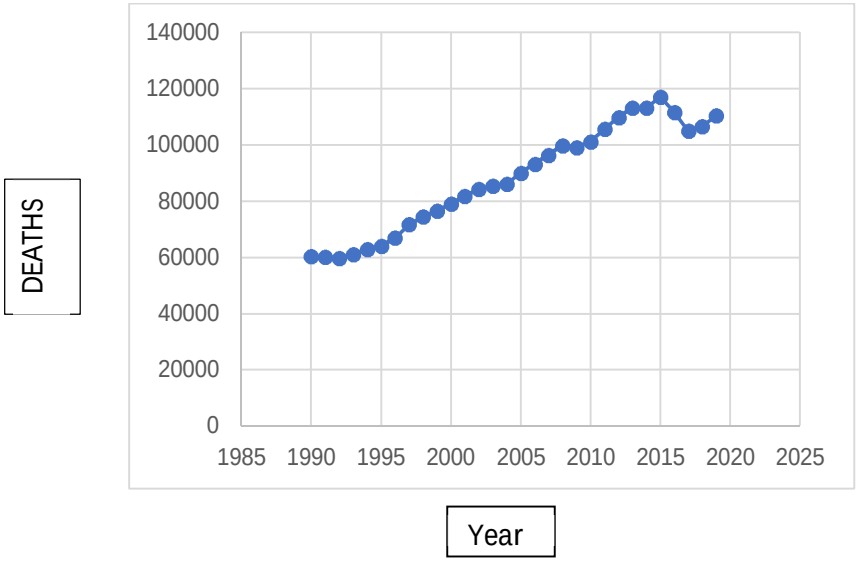

Figure-8: HBV related Deaths[6].

VIII. HEPATITIS C

Hepatitis C, a liver disease caused due to hepatitis C virus (HCV), a bloodborne virus, transfusion-transmitted infection (TTI) through exposure to small quantities of blood i.e., unscreened blood due to unsafe injection practices before transfusion which causes acute and chronic hepatitis that results in liver cancer[3,26,31]. It is marked by high levels of genetic differences which include inaccurate viral RNA polymerase rate and also due to pressure of the infected host's immune system. This led to development of HCV into 7 various genotypes and greater than 67 subtypes[11,14].

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Presently, early diagnosis of HCV infection can only be treated with antiviral drugs, greater than 95% of the infection which depends on the genotype[3]. The severity of liver damage should be evaluated with the aid of non-invasive tests in chronic HCV infected patients[31]. 12-18 million patients are carrying this disease in India with an average prevalence percentage due to the vast population size. Around 30% of the infected patients usually can clear the virus within 6 months of infection in devoid of any treatment whereas the remaining 70% of the patients lead to chronic HCV infection[31]. The number of HCV deaths have been increased rapidly between 1990 and 2019 for over a period of 29years (Figure-9)[5].

Earlier, the serological activity of HCV infection, ELISA is done using Recombinant Immunoblot Assay (RIBA) but at present, the standard method for confirming active HCV infection is achieved by using Nucleic Acid Testing (NAT), a molecular technique that involves amplification and detection of HCV genome within a sample. Rapid assays are also been used as point-of-care testing diagnostic platforms and serological assays help in the identification of anti-HCV antibodies either in the serum or plasma containing samples[3,26, 31].

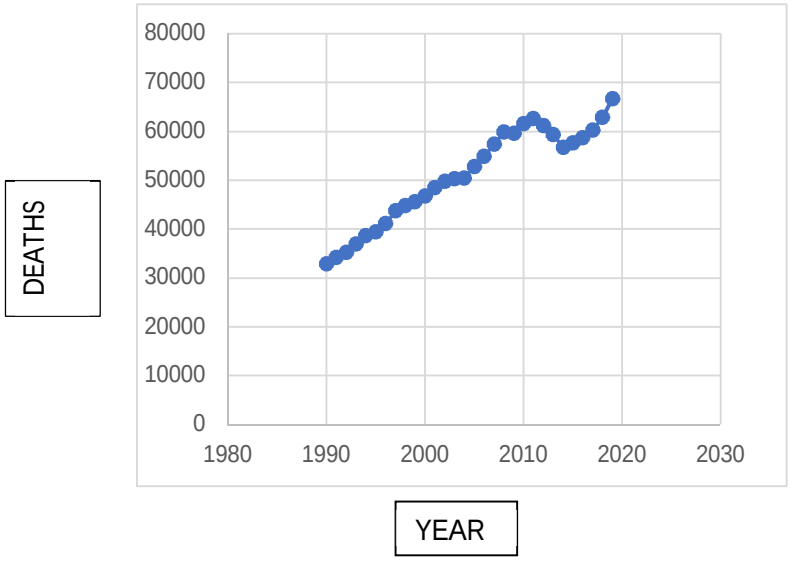

Figure-9: HCV related deaths[5].

Hepatitis virus type	Source of Infection
Hepatitis A	Contaminated water or food.
Hepatitis B	Exposure through body fluids (Infected blood) or contaminated injection practices.
Hepatitis C	Exposure through body fluids (Infected blood) or contaminated injection practices.
Hepatitis D	Infected body fluids.
Hepatitis E	Contaminated water or food.

Table-3: Types of Hepatitis virus and their source of infection[31].

IX. ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Human immunodeficiency virus (HIV) attacks the immune system of the body whose treatment is complex, mutations in human genetic content result in HIV infection where 40% imbalance is found in the env gene, and 8–10% difference in the pol/gag genes[29]. HIV disease treatment involves antiretroviral therapy (ART) which only suppresses the viral replication within a person's body[16,17,25,31].

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Of the estimated Human Immunodeficiency Virus burden in India, women and girls are responsible for about 40% whereas children are about only 4%. The proportion of HIV infected patients has elevated in the states such as Andhra Pradesh about 21% and 20% Maharashtra with 1%, 0·7% prevalence rate in adults, respectively[15]. Rate of adult HIV prevalence has been reduced from 0.45% to 0.35% and also a slight decrease in number of HIV cases between 2002 and 2007 (Figure-11)[5]. A progressive decline of HIV-positive persons (in both children and adults) has been observed from 2003–2005 to the years 2010–2015 (Figure-10)[25] and even a decrease in its prevalence in female sex workers (5.06% in 2007 to 2.67% in 2011) due to HIV prevention programme[2]. HIV trends were recorded which did not show any change between drug-injecting users (7.23–7.14%)[25].

HIV can be diagnosed through different Immunoassays such as rapid, ELISA (Enzyme-Linked Immunosorbent Assay), Western blot and NAA testing. For children less than 18 months of age, along with serological testing, virological testing is also required to identify HIV. Limiting antigen (LAg)-avidity assay and BioRad avidity assay helps in identifying the recent HIV infection in HIV seropositive patients which estimates the bond strength of HIV- specific antibodies and HIV proteins[16].

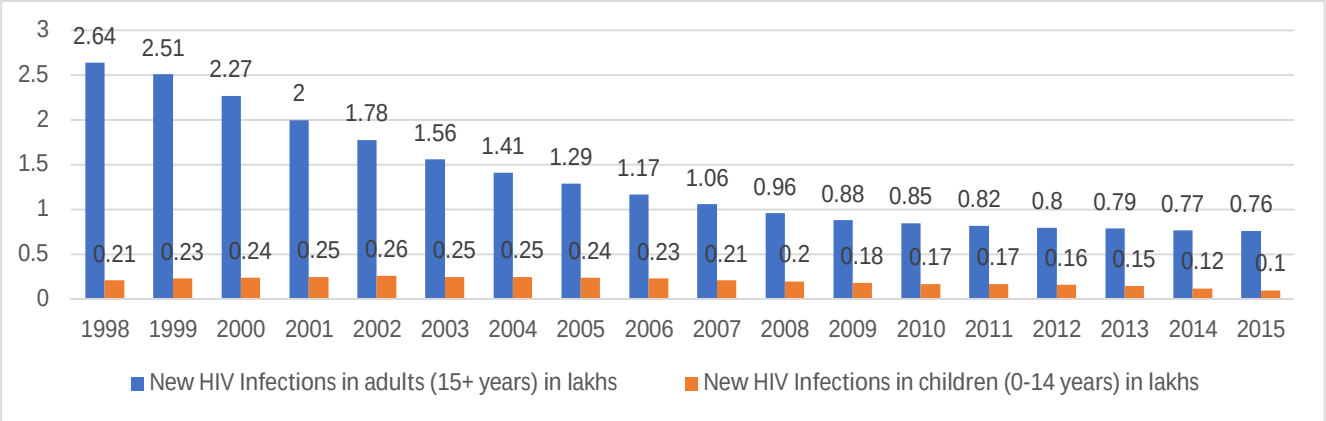

Figure-10: New HIV infections in India 1998–2015 (2 different age groups)[25].

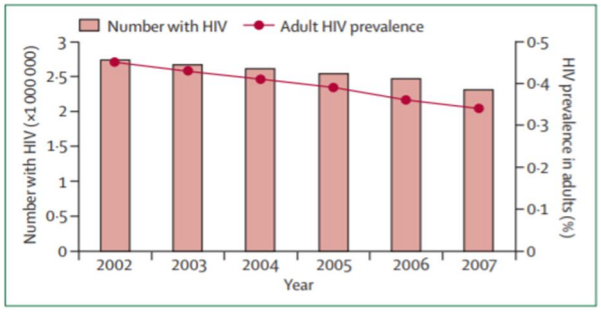

Figure-11: HIV Burden estimation and adult prevalence in India (National AIDS Control Organization)[15].

X. MALARIA

Malaria, a lethal disease transmitted by *Plasmodium* parasites that spread through the bites of malarial vectors[31]. It can be prevented by using antimalarial drugs such as sulfadoxine-pyrimethamine[31]. It is resulted due to gene selective pressure within the genome and is associated as a transformative force for genetic diseases, such as sickle cell disease (SCD), thalassemia[9]. The primary vector for malaria in India is *Anopheles culicifacies* which is resistant to numerous insecticides and the secondary vector is *Anopheles fluviatilis* which proliferates during monsoon season and increases the disease burden[15,31]. Malaria treatment is not sustained because the malarial vectors are becoming resistant to the old drugs which were developed in 1950-1960s such as chloroquine and sulfadoxine-pyrimethamine (SP). Malaria caused by *Plasmodium falciparum* can be cured using Artemisinin-based combination therapy (ACT)[31]. In future, proteomics technologies will play an important role in eradicating the spread of malaria[26].

Malaria mainly affects the rural and poor urban communities in India with 1,144 deaths in the year 2009 and the number of cases (*P. vivax and P. falciparum* cases), deaths has been decreased from 2000 to 2020 till October with few fluctuations (Figure-12)[32]. In 1973, *P. falciparum* showed stability towards chloroquine and sulfadoxine-pyrimethamine which was raised from 12% in 1984–92 to 24% in 1997–2007[15,31]. Prevalence rate of malaria is high in rural, about 10% followed by 60 years & above age group, 8.60% and the frequency is higher in men than women (Figure-13)[21].

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Suspected cases of malaria can be confirmed within 30 minutes with the aid of parasite-based diagnostic testing either microscopy or rapid diagnostic test prior starting the treatment[31].

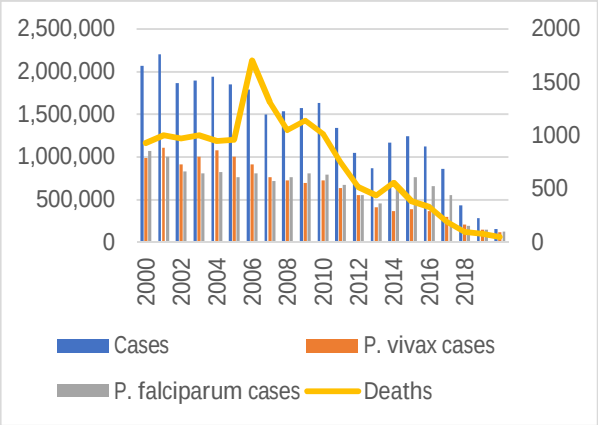

Figure-12: Epidemiological shift of Malaria in India (2000-2019) *P. vivax* and *P. falciparum* cases[32].

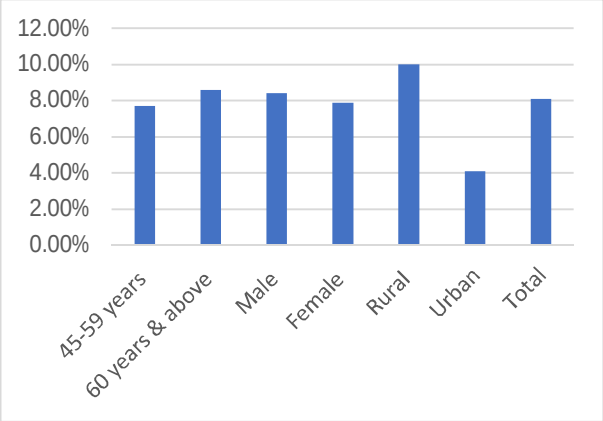

Figure-13: Prevalence of Malaria (2017-18) in percentage (%)[21].

XI. CONCLUSION

Improvements in diagnostic platforms, vaccination schemes against various illnesses, identification and knowledge of genetic origins, and pharmacological treatment are all strategies to reduce the death rate associated with infectious diseases. Children can be protected from diarrhoeal infections if prevention techniques are implemented, which include social factors such as appropriate sanitation. Similarly, preventive and control efforts, as well as education about vaccine timings, must be effectively aimed for each infectious disease. It is suggestive that government's need to be prepared for any type of disease by researching cures and medications that can be stockpiled or manufactured quickly.

Therefore, in India, communicable diseases, which include infectious diseases, cause significant disease burden and mortality as a result of inadequate nutrition, sanitation, human genetic variations, behavioural and environmental changes, and limited access to health care systems.

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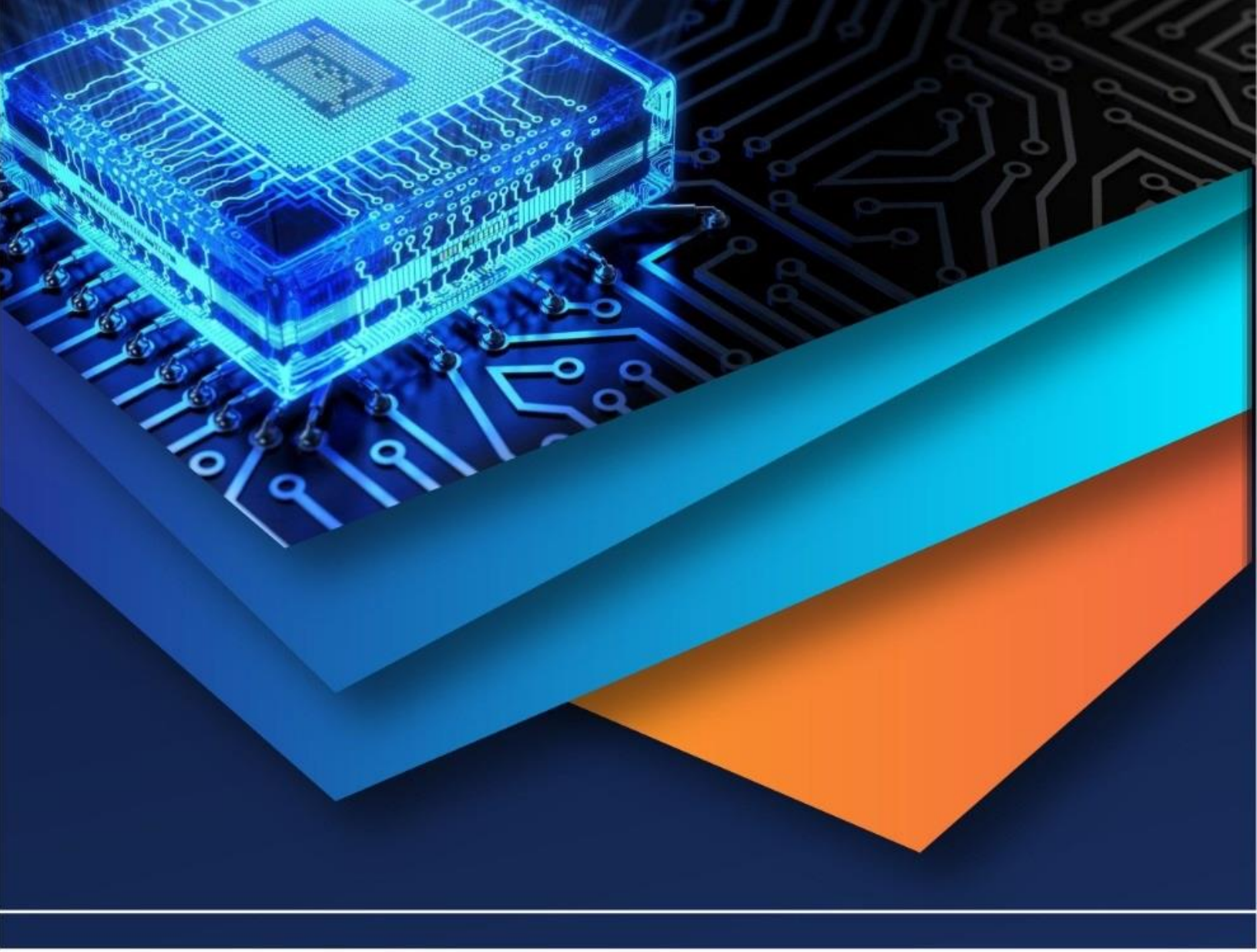

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