

## Microbiology-The Science behind Cure and Prevention

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### Abstract

Microbiology is a science of ever-changing circumstances and evolutions. There is a constant race between the man and microbes and unflinchingly they try to outsmart each other. Updating our knowledge in all aspects of microbiology can bring out cure from the microbial pathogens and better, their prevention.

### Introduction

Microbiology is a science which deals with organisms, few microns in size but has a scope which is magnanimous. It has two aspects-‘pure’ which deals with microbial properties and ‘applied’, which studies the effects of microbes on other living organisms as pathogens, commensals, or on the environment. The scope of Medical Microbiology starts with physiology of relevant microorganisms, virulence, sources of antibiotics or probiotics, vaccine development, molecular and synthetic biology. It also deals with infection control and bio-medical waste management in patient care areas besides establishing diagnosis of infectious diseases [1].

### The dawn of microbiology

Origin of microbes dates back to billions of years ago with beginning of the very first forms of life, archaeobacteria. Since then these microbes have undergone various adaptations triggered by environmental and genetic stimuli within the confines of a single cell. Man came very late in this evolutionary cycle but has been trying hard to fight bugs that cause infections and utilize many of them for his own benefits. The only known microorganism, a virus that has been eradicated worldwide is small pox.

### History of microbiology

**Microbial existence:** Fracastorius, a physician of Verona, published the concept of ‘contagium vivum’ in 1546 which was later defined by Louis Pasteur. He demeaned the theory of spontaneous generation by his famous ‘swan neck experiment’ and coined the term ‘microbiology’.

**Infection prevention:** The very first idea of disease prevention came when Edward Jenner made a preparation from cowpox (vaccinia virus) to protect against small pox in 1796: a vaccine. In 1847 Semmelweis strongly advocated the concept of ‘hand hygiene’ which was realised after his death when ‘germ theory of disease’ was postulated. ‘Antiseptic regimen’ described by Joseph Lister in 1867 transformed the prognosis of major surgical operations.

**Bacteriology:** Robert Koch (1843-1910), a German Physician brought about technological revolution in bacteriology, known as founder of Modern Microbiology. Koch’s contribution to Microbiology start from visualization of bacteria, their cultivation in animals and

artificial media, discovery of causative organisms of tuberculosis and cholera and ‘Koch’s phenomenon of delayed hypersensitivity; to establishing a causal relationship with infective agents, the ‘Koch’s postulates’.

**Mycology:** The term mycology was first used in 1836 by M.J. Berkeley. Fungi were first classified as infectious agents by Augustino Bassi who in 1835 discovered the mycotic nature of an epidemic disease of silkworms, muscardine. Medical mycology was introduced between 1837 and 1841, when Gruby and Remak discovered the first human mycosis (tinea favosa) [2].

**Virology:** Dmitri Ivanosky in 1892 could reproduce tobacco mosaic virus by applying juice from diseased plants to healthy plants after removing all bacteria through fine filters. Beijerinck, in 1898, coined the term ‘virus’ for such a filterable infectious agent. The first human disease proven to have a viral etiology was ‘yellow fever’.

**Antimicrobial agents:** In 1909, Ehrlich discovered Salvarsan for treatment of syphilis. In 1928, Sir Alexander Fleming accidentally discovered Penicillin.

**Molecular microbiology:** Microbiology advanced to the molecular level with discovery of a chemical–deoxyribonucleic acid (DNA) in 1944 by Avery, Macleod and McCarty who showed that if transferred from virulent pneumococci, it could transform nonvirulent pneumococci to virulent organisms. For the first time, in 1995 the entire genome of a free living organism, *H. influenzae*, could be sequenced. With the advent of recombinant DNA technology, genetic material was used for production of vaccines. The first genetically engineered vaccine was for Hepatitis B, licensed in 1996.

Patrick Collard in 1976 had divided Microbiology into four era [3] as:

- Era of Speculation (5000 BC to 1675 AD)
- Era of Observation (1675 to mid19<sup>th</sup> century)
- Era of Cultivation (mid19<sup>th</sup> century to early 20<sup>th</sup> century)
- Era of Physiological Study (continuing since early 20<sup>th</sup> century)

**Fifth era:** ‘Era of Prevention’ can be added to this list as microbiology aims at prevention of infections by vaccination, public health measures, infection control and synthetic biology methods using microbes or their products against pathogenic microbes.

## Scope of microbiology

Microbiology affects our day to day lives in multiple ways. Microbes are useful for the food industry, agriculture, dairy, brewing, pharmaceuticals, vaccines, enzymes, antibiotics, etc. From the presence of microbes in our body as normal flora helping and defending the body, to their role in causing infections, they perform various roles outside the body. The thin line between commensals and pathogens is getting blurred day by day after the advent of immunosuppressive agents used for various autoimmune and malignant diseases. The role of medical microbiologists starts with the epidemiology of infection, to trace the source, transmission and entry of organism, to understand the physiology of microorganisms, their pathogenicity determinants and role in disease so that a proper diagnosis can be arrived early. This follows establishing correct diagnosis which should be fast and affordable. Antimicrobial susceptibility aids in managing the cases and bringing about cure. The role of a microbiologist doesn't stop here. Major role is prevention of infectious diseases at hospital level by infection control surveillance activities and biomedical waste management. Research is focused on targets for preparation of effective vaccines. Medical microbiologists can serve as important links between public health epidemiologists, pharmacologists, and infectious disease physicians. Clinical microbiology laboratories form the first line for rapid and appropriate diagnosis, outbreak diagnosis and control, hospital acquired infections, controlling antibiotic usage, infection control policies and in emerging infectious diseases. For this close interaction with clinicians is required with consultative services. Usual hindrances are financial resources and outsourcing of services. Functions of clinical microbiology laboratories may be enhanced by considering new technologies though they may not serve as magic bullets, by dissemination of laboratory information, evidence-based laboratory practices, pre-emptive cultures as part of infection control and by patient centric approaches. These include direct advice on care and management and by forming multidisciplinary anti-infective teams in the hospital. Challenges for a clinical microbiologist therefore remain the knowledge of automation, immunodiagnostics, Biomarkers in infectious diseases, molecular diagnostics, clinical coordination, infection control, surveillance of infectious diseases and antimicrobial resistance.

**New diagnostic technologies:** New diagnostic technologies are the need of hour as infectious diseases are on a rise. Of an estimated 58.8 million annual deaths worldwide, approximately 15.0 million (25.5%) are believed to be caused by infectious diseases [4].

Molecular technology for rapid diagnosis includes PNA-FISH (Peptide Nucleic Acid Fluorescent *in Situ* Hybridization) RT-PCR, MALDI-TOF MS (Matrix-assisted laser desorption/ionization Mass Spectrophotometry), SeptiFast, etc. to guide appropriate therapy in time [5].

**Antimicrobial resistance:** Antimicrobial resistance is increasing and no new drugs are sustaining against the microbes for long. Resistance markers must therefore be identified in all bacteria isolated in laboratory to guide the therapeutic outcome. These markers include MRSA (*Methicillin Resistant S. aureus*), VRE (*Vancomycin Resistant Enterococci*), ESBL (Extended Spectrum Beta Lactamase), AmpC, Carbapenemase, multidrug resistant tuberculosis, etc. resistance may be considered a man-made phenomenon resulting from inappropriate prescribing, poor quality drugs, poor patient compliance. There is a paradigm shift from 'drug development' to 'regimen development'. Innovative drug delivery systems are being made available in the

market to improve compliance, improved action on-site and reduce side effects.

**Evolution of probiotics/immunobiotics:** Probiotics are live microbial food ingredients to be used as health supplements. They stimulate cell mediated immunity, increase interferon gamma and complement receptors on phagocytes. These may have local or distant effects as has been hypothesized in the hygiene theory of allergy development [6]. Recently 'lugdunin' isolated from *Staphylococcus lugdunensis* has proven efficacious against *Staphylococcus aureus* in in-vivo studies [7]. This could have a long term effect against treatment of MRSA for which treatment options are limited.

**Microbes and cancers:** In 2008, around 2 million new cancer cases were attributable to infections, around 30% of these cases occurred in people younger than 50 years [8]. Oncogenic infectious agents include hepatitis B and C viruses and *clonorchis sinensis* and opisthorcic which cause liver cancer, human papilloma virus (HPV) which causes cervical or anogenital cancer, *Salmonella* infections may cause gall bladder carcinoma, *Helicobacter pylori* in stomach cancer, Epstein Barr virus (EBV) and HTLV-1 in nasopharyngeal carcinoma and Hodgkin's lymphoma, schistosoma in urinary bladder carcinoma and human herpes virus (HHV-8) in Kaposi's sarcoma. Colorectal carcinoma usually has a host predisposition along with environmental factors. Microbes cause inflammation, release mutagenic toxins and free radicals. Organisms incriminated in colorectal carcinoma are *Streptococcus bovis*, *Helicobacter pylori*, *Bacteroides fragilis*, *J.C virus*, *EBV*, *CMV* and HPV. It has been speculated that there is a role of *Tubercule bacilli* in causing lung cancer. In a study conducted by Vento et al., the incidence of Lung cancer 11-times higher in patients with tuberculosis, and the hazard ratio (HR) was 3.32 [9].

**Emerging and re-emerging infectious diseases:** Microbiologists also owe the responsibility of diagnosing and reporting the emerging and reemerging infectious diseases and spread their knowledge in the community. Such category of viral infections include Influenza viruses (H5N1, H3N2v, H7N9), Avian Influenza (H1N1), Coronaviruses-SARS (Severe Acute Respiratory Syndrome), MERS (Middle East Respiratory Syndrome), Norwalk virus, Rotavirus, Hepatitis viruses, HIV-TB syndemic, resistant HIV infections. Bacterial emerging pathogens include Ehrlichia/Anaplasma, Bartonella, Rickettsia and *Tropheryma whipplei* [10], MDR, XDR or TDR *Mycobacterium tuberculosis*, XDR *Neisseria gonorrhoeae*, *Enterohemorrhagic Escherichia coli serotype O157:H7*, *E.coli non-O157 STEC*, *Vibrio vulnificus*, other vibrios, *Listeria monocytogenes*, *Yersinia pseudotuberculosis* O3, *non-typhoidal salmonellae*, *Clostridium perfringens*, *C. bolutinum*, *Campylobacter jejuni* and *C. coli* [11]. Parasitic agents in this category are drug resistant malaria, *C. parvum*, *C. cayatanensis*, and emerging fungal pathogens include *Fusarium*, *Curvularia*, *Alternaria*, *Trichosporon beigelli*, other agents of phaeohyphomycosis and hyalohyphomycosis, yeasts like *Candida non-albicans*, *Rhodotorula*, *Trichosporon* spp., *Rhodotorula* spp., and *Geotrichum capitatum* [12,13].

## Role of bacteriophages

They have been used for prevention, treatment (phage therapy) and diagnosis of infectious diseases. They have been utilized as vaccines, gene therapy, antimicrobial action (holy waters), detection of pathogenic bacteria; tools for screening libraries of proteins, peptides or antibodies [14]. They have also been used for drug delivery in cancer patients [15].

**Vaccines:** many infectious diseases are preventable by vaccines and for many others active research is going on. Improved vaccines, new vaccines, multivalent, expanded and novel vaccines are being made available. The delivery systems and targeted antigens are used for vaccine preparation to minimise side effects. Purified adjuvants are available which increase the vaccine delivery at target sites and improve bioavailability.

**Microbial Engineering:** Craig Venter was the first to sequence human genome in 2005. In 2010 he produced a synthetic bacterial chromosome which could self-replicate and express in a new host [16]. Saeid et al. designed a synthetic biological system, which comprised of quorum sensing, killing, and lysing devices, that enabled *Escherichia coli* to sense and kill a pathogenic *Pseudomonas aeruginosa* strain through the production and release of pyocyanin which was released subsequent to *E. coli* killing [17]. Microbes can thus be designed for cure in oncology patients. JX-594, an oncolytic poxvirus was genetically designed to selectively infect, replicate and expresses transgene products in cancer tissue after intravenous infusion followed by cell lysis and anticancer immunity, without affecting normal tissues [18].

Microbiology is witnessing co-evolution of humans and microbes. This is attributable to urbanization, deforestation, hunting, commercial farming, livestock production, bush-meat, animal trafficking, environmental change, global travelling, War and famine, Bioterrorism, under-nutrition, impaired governance and public health neglect. Pandemics can be prevented by means of technology, geographical information system, global viral forecasting and intercontinental coordination.

Today's microbiologist has to be as dynamic as the Microbiology itself to keep with the pace. In an era of infectious agents, many of which are emerging and re-emerging, knowledge of microorganisms and their role in diseases should be known so that they can be prevented, controlled and treated in time. Future opportunities for Medical Microbiologists are thus Vast, Scenic and Rocky.

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