Tackling Infectious Diseases

Subjects: Primary Health Care

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Infectious diseases (IDs) are a leading cause of death. The diversity and adaptability of microbes represent a continuing risk to health.

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1. Infectious Diseases Global Annual Mortality

According to the World Health Organization (WHO), worldwide, the top three leading causes of deaths are cardiovascular diseases, cancer, and infectious diseases (IDs) [1]. Global annual deaths from IDs have been declining steadily over the past 20 years from 208 deaths per 100,000 people in 2000 (12.7 million deaths in a total world population of 6.1 billion people at the time) down to 106 deaths per 100,000 people in 2019 (8.2 million deaths in a total world population of 7.7 billion people at the time) [2]. The main reasons for this reduction include affordable therapies and preventive measures.

2. Deaths Due to Resistance to Antibiotics/Antimicrobials

Antimicrobial (antibacterial, antiviral, antifungal, and antiparasitic) resistance (AMR) of infections is a growing global threat causing significant mortality. An estimated 4.95 million deaths were associated with AMR in 2019 [3]. The World Economic Forum predicts that global mortality due to antimicrobial resistance could reach 10 million people worldwide (4.73 M in Asia, 4.15 in Africa, 0.39 M in Latin America, 0.39 M in Europe, 0.317 M in North America, and 0.022 M in Oceania) [4]. The World Health Organization (WHO) is calling for a One Health approach to fight AMR and this is articulated around the appropriate use of antimicrobials [5].

3. Multifaceted Transdisciplinary Approach to Tackle Infectious Diseases

From the beginning, the research group envisioned a multifaceted approach (prevention, diagnostics, and therapeutics) to tackle and ultimately improve the management of IDs. Researchers built a transdisciplinary team where an array of specialists focused on common tasks and exchanged knowledge on a weekly basis during the course of a series of parallel research projects each spanning 3–7 years. This was possible by combining several funding sources, involving multiple public and private organizations covering different sectors, ranging from fundamental and clinical research to applied engineering, industrialization, business models, and legal partnership frameworks. Researchers believe that patient-oriented applied medical research providing data within a clinically actionable timeframe is the future to better serve unmet patients' needs. Patients should be in control of prevention; giving women control of their protection against sexually transmitted infections (STIs)/Human Immunodeficiency Virus (HIV) is crucial. The team has been devoting their medical research to closing the loop, from identifying patients' problems at bedside, to finding solutions in the laboratory through product development and clinical testing, to finally bridging the gap of unmet needs at the patients' bedside. Researchers also believe that in the future, researchers should be trained on the basics of business management and technology transfer. Licensing revenues help offset the decline in research support by funding government agencies, philanthropies, and the pharmaceutical industry.

4. New Vision That Is Changing ID Diagnosis Medical Practice

Since the mid-1990s, the team has been working to revolutionize the diagnosis of infectious diseases, which until then would have required at least two days because it relied on traditional microbial culture techniques dating from the time of Louis Pasteur. The first molecular diagnostic tests used in clinical practice were probe-based assays without nucleic acid amplification, but still required microbial culture [6]. The invention of the polymerase chain reaction (PCR) in 1985 [7] and its practical application through the use of thermostable polymerase [8], followed by the availability of PCR thermocyclers, paved the way for major changes in the culture-free molecular diagnosis of infectious diseases due to its high sensitivity

and specificity, and ability to produce billion-fold copies of nucleic acid from a small number of microorganisms present in a sample. However, the widespread use of PCR in clinical microbiology laboratories has been made feasible by the introduction of closed-tube assays based on real-time PCR (rtPCR) detection using fluorescent technologies and new rapid PCR cycle instruments [9][10][11][12]. This eliminated the need for complex multi-step post-PCR analysis while reducing hands-on time and the risk of contamination by carryover amplification of previously generated amplicons [13][14]. This also resulted from a better understanding of the rules for designing efficient primers and probes and optimal PCR components [13][15][16], and the development of pre-PCR processing to extract microbial nucleic acid and remove PCR inhibitors in clinical samples [15][17][18]. By combining rtPCR and multiplex rtPCR molecular detection technology with the then emerging microbial genomics and rapid sample preparation process, researchers demonstrated that it was possible to detect microbes and their antibiotic resistance genes directly from clinical specimens in approximately one hour. Bringing these technological innovations into medical practice, Dr. Michel G. Bergeron created the company Infectio Diagnostic Inc. (IDI) (Quebec, QC, Canada) in 1995 and developed with his team the very first rtPCR test to receive approval from the Food and Drug Administration (FDA) in USA for detecting Group B *Streptococcus* directly from clinical specimens in less than one hour [IDI-Strep B™ (2002—FDA)] [19], a major breakthrough for the rapid diagnosis of infectious diseases. This was followed by another FDA-cleared test for detecting methicillin-resistant *Staphylococcus aureus* (MRSA) [IDI-MRSA™ (2004—FDA)] [20][21]. Furthermore, in collaboration with Becton Dickinson (BD), which acquired IDI in 2006, the group developed more rtPCR tests such as vancomycin resistance [BD GeneOhm™ VanR (2011—FDA)] and enteric pathogens on the fully automated BD MAX system [BD MAX™ Enteric Bacterial Panel (2014—FDA)]. Several tests have been developed on this automated system or adapted to this system such as the MRSA assay. rtPCR tests are now used all over the world for the diagnosis and rapid detection of infections. The clinical impact of rapid rtPCR tests has been evaluated in the years since they were introduced, and they have been shown to reduce hospital-acquired infections, save lives, and reduce health care cost. For example, MRSA transmission rates while using standard MRSA culture (3 days) was 13.9 per 1000 patient days versus 4.9 while using IDI-MRSA^{TM} (same day). This in turn allowed for an economy of USD 243,750 per 1000 patient days [22]. Rapid rtPCR tests have proven to be a powerful tool not only for the diagnosis of infectious diseases, but also for the prevention and control of infections, reducing the spread of antimicrobial-resistant pathogens.

The last two decades following the introduction of the first rtPCR tests in the clinic have seen the development of several commercial and laboratory-developed rtPCR and other molecular tests for the detection of a wide range of microorganisms and antibiotic resistances [23][24]. The list of nucleic acid-based tests (close to 400 tests) that have been cleared or approved by the US-FDA is available [25]. The automation of molecular tests has been an important step towards their wider use in clinical microbiology laboratories. Automated systems for nucleic acid extraction and purification were first introduced to reduce the labor associated with the manual sample preparation steps prior to molecular assay, making the recovery of nucleic acids more reproducible and reducing the risk of the cross contamination of samples [15]. Then, fully automated systems were developed that carry out all the steps from sample preparation to nucleic acid amplification and detection, saving labor time, making them easier to use, and, for some systems, enabling multiple samples to be analyzed at once to achieve the high throughput required in clinical microbiology laboratories for certain types of samples [26]. A new innovative approach was introduced in 2011 which includes commercial molecular assays that simultaneously detect and identify the multiple pathogens and resistance genes associated with a clinical syndrome in a single test such as bloodstream, respiratory, gastrointestinal, and central nervous system infections [27][28][29].

Nucleic acid amplification technologies (NAATs) other than PCR have also been developed, the most widespread being a variety of isothermal amplification (IA) methods that do not require temperature cycling, thus providing a simpler and less costly procedure for the rapid detection of nucleic acids from clinical samples. Some IA-based tests are now incorporated into a variety of commercial molecular tests [23][30][31][32][33]. However, an important advantage of rtPCR fluorescence detection over other molecular technologies is its ability to detect microorganisms quantitatively or semi-quantitatively, based on a standard curve [15]. Knowledge of microbial load can be used to infer a patient's response to treatment, or to provide information to distinguish infection from colonization [34]. Digital PCR (dPCR), the latest generation of PCR, has emerged as a promising new PCR technology which provides absolute quantification without the need for a standard curve. dPCR involves partitioning the PCR solution into a large number of droplets, and the reaction is carried out in each partition individually, with endpoint fluorescence detection and Poisson statistics for the absolute quantification of nucleic acid targets. It has been shown to be more tolerant to PCR inhibitors and more sensitive and reproducible compared to rtPCR [35]. Different commercial dPCR systems are available which are based on chamber/chip-based dPCR (cdPCR) platforms and droplet-based dPCR (ddPCR) platforms, and at least three dPCR SARS-CoV-2 tests have been granted emergency use authorization (EUA) approval [35]. Several studies have shown the potential of dPCR for the detection and clinical management of infections [35][36][37][38]. However, the use of dPCR in clinical settings is limited due to the high cost of instruments and consumables compared to rtPCR, as well as the complexity of the workflows which require greater

hands-on time [35]. Continuous improvement aimed at reducing complexity and costs should enable the wider use of this powerful technology in the future.

Molecular diagnostic technologies were later taken to a new height, bringing diagnosis to the point of care (POC) as portable, simple, and fast tests, an effective way of further reducing the turnaround time (TAT) for rapid molecular tests, which depends on the diagnostic cycle, i.e., the number and duration of steps in the diagnostic process required from prescribing the test, collecting, and transporting the clinical sample to the laboratory, to transmitting the result to the physician [39][40][41]. With this goal in mind, Dr. Bergeron established GenePOC Inc. (Quebec, QC, Canada) in 2007 (acquired by Meridian Bioscience Inc. (Cincinnati, OH, USA) in 2019). The transdisciplinary R&D team assembled experts in chemistry, instrumentation, microbiology, medical device manufacturing, microfluidics, molecular biology, nanotechnology, medicine, optics, physics, and regulatory affairs, whose work has been integrated by engineers. This translated into designing and building state-of-the-art Revogene®, Meridian Bioscience, Quebec City, QC, Canada (**Figure 1**), a fully automated molecular platform integrating clinical sample processing with single and multiplex testing capabilities while requiring minimal hands-on time [42]. Revogene® automates sample homogenization, dilution, cell lysis, the conversion of RNA templates into DNA using reverse transcription, nucleic acid amplification, and the detection of the amplified PCR products [41].

Figure 1. Revogene®—Automated molecular testing platform.

In 2015, four nucleic acid-POC tests based on PCR amplification and isothermal amplification received for the first time a Clinical Laboratory Improvement Amendment Certificate (CLIA) of Waiver, Compliance, or Accreditation status in the USA. CLIA-waived tests are defined as “simple tests that have an insignificant risk of an erroneous result” [43], and thus can be performed by less skilled personnel [41][44]. Today, there are more than thirty nucleic acid tests for the detection of single or multiple microorganisms (syndromic panels) which have received CLIA-waiver, including twenty-five SARS-CoV-2 tests under FDA EUA authorization [44][45][46]. The CLIA-waiver represents a major step towards opening-up molecular diagnostic tests close to patients for use in decentralized (laboratory) settings in hospitals such as close to the emergency department (ED), intensive care unit, and delivery room, or outside of hospitals such as in outpatient clinics, physicians’ offices, pharmacy laboratories, and remote area facilities (dispensaries of developing countries) [41]. For example, the use of a CLIA-waived POC test for SARS-CoV-2 in an ED has recently been shown to accelerate clinical decision-making, improve patient management, and significantly reduce the length of stay in the ED for patients requiring outpatient care [47].

The COVID-19 pandemic triggered remarkable advancements in molecular diagnostics, leading not only to the widespread laboratory adoption of rtPCR and other molecular innovative testing technologies coming from both existing and new manufacturers without previously available tests, but also to a greater public awareness of the importance of rapid molecular test performance, such as high sensitivity, high specificity, and rapid TAT, in the management and control of infectious and highly transmissible pathogens [48][49]. More than 260 molecular SARS-CoV-2 tests have been granted FDA EUA approval [45]. Molecular tests have now become an integrated component of guideline-recommended practices for a variety of infections, being accepted as the standard of care, replacing conventional methods, and routinely applied

to detect the presence of these infection-causing pathogens, [23]. For example, rapid nucleic acid tests have replaced culture for the detection of respiratory virus infections in the majority of virology laboratories, which have chosen to abandon viral culture because of its lower sensitivity, long TAT and hands-on time, and the need for technical expertise [50]. However, the cost of molecular tests can be an obstacle to their implementation in some clinical settings, particularly in developing countries. However, demonstrating the health care cost-effectiveness and the availability of affordable molecular POC tests, with their simplicity, short TAT, and wide accessibility, could help overcome this obstacle, especially in resources-limited settings [51]. Furthermore, in developing countries, price can be subsidized by contributions from richer countries and international organizations. By offering more powerful tools for the earlier and more accurate detection of infectious diseases, molecular diagnostics represents a veritable revolution whose considerable clinical impact is constantly being demonstrated for several infections, with advantages including a more appropriate use of pathogen-target therapies, a reduced length of hospital or emergency department stay, decreased unnecessary antibiotic use, improved infection control practices and antimicrobial stewardship, and reduced overall health care costs [52].

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