Editorial

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Emerging technologies in paediatric laboratory medicine

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Children are the present and future of societies. Globally, the trend of declining birth rates means that they are a diminishing precious resource [1]. Besides socioeconomic factors, having a healthy childhood is a critical prerequisite to unlocking the full potential of children. Moreover, having healthy children pays continuous socioeconomic and healthcare dividends in the future when they enter adulthood [2, 3]. Consequently, every marginal gain in paediatric health is likely to have an amplified positive effect to the society. Recognising this, the World Health Organisation and the United Nations Children's Emergency Fund of the United Nations have specialised their focus on improving paediatric healthcare including prenatal and perinatal care.

Today, we reap the benefits of the many public health measures implemented decades ago that have resulted in remarkable improvements in childhood survival, nutrition, and general health [4]. As we celebrate these achievements, however, there is an ongoing need to continue our investment in them. Indeed, with most of the low-lying

fruits of public health intervention picked, the task of improving and securing paediatric health has never been more challenging and uncertain in our highly globalized, commerce-driven world facing a dramatic climate change [1].

Laboratory medicine is a specialisation in medicine that focuses on the use of science and technology to detect and measure biomarkers for clinical care [5]. It has allowed a data-driven approach for the disease prediction, screening, diagnosis, risk stratification, treatment selection and monitoring as well as prognosis of individual patients. At the same time, the application of laboratory medicine has allowed the collection of important objective data that can be used to inform policy decision making and measurement of health in the community.

Advancements in the technology used in laboratory medicine are critical enablers to achieve further gains in paediatric healthcare. Such advancements need to focus on improving the understanding of physiology and pathophysiology of childhood and diseases, improving the precision of elucidating pathology, improving accessibility of laboratory testing, particularly for under-served community due to either socioeconomic reasons or geographical regions and leveraging on data for informed decision making. Paediatric laboratory medicine is well positioned to play a central role in the quest of improving paediatric health in the rapidly changing world.

This special issue of the Journal focuses on Emerging Technologies in Paediatric Laboratory Medicine and is published on the occasion of the 15th International Congress in Paediatric Laboratory Medicine, where these emerging technologies that will drive the advancement in laboratory medicine will be explored and discussed.

1 Coronavirus disease-2019 (COVID-19) and paediatrics

The COVID-19 pandemic has had a devastating effect on the global health and economy. It has also brought to the

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fore the central role of laboratory medicine in managing this crisis by providing the laboratory results required to identify infected patients and providing critical data in managing the patients and understanding the disease [6–8]. Never before had the general public been more acquainted with various testing modality for infectious agents (e.g. polymerase chain reaction, serology, antigen testing), and they also became more informed about the different clinical characteristics of laboratory tests (e.g. clinical sensitivity, clinical specificity) as well as their implications on health and healthcare policy. This is in a large part driven by the educational efforts promoted by the general press and the daily status updates that are driven by laboratory data.

While (fortunately) death remains a rare outcome of COVID-19 among children, it can cause multisystem inflammatory syndrome in children (MIS-C), which is a severe complication of the infection requiring laboratory evidence of inflammation, multisystem involvement, and laboratory-confirmed COVID-19 infection (or exposure to COVID-19 [9]). The management of these children requires close monitoring aided by appropriate laboratory tests [6–8].

Whilst Long Covid is a recognised in adults it is now slowly being recognised in child and adolescents [10]. What is not known yet is the long term effects of preventative periods of lockdown/isolation on the child long term health. Significant period of inactivity, anxiety, lack of face to face social interaction, increased eating/comfort eating, loss of motivation, mixing, increased screentime, sleep disturbance etc. will surely have long term effects such as increased diabetes, heart disease, obesity which all will put pressure of the healthcare economy now and in the future [11, 12].

2 Mobile health and point-of-care testing

The COVID-19 pandemic also highlighted the need for more easily accessible laboratory test in situations in which healthcare systems dedicate resources to fighting the pandemic or become overwhelmed. During the initial phase of pandemic, laboratories have had to reduce their services to minimise biosafety risks or divert resources to manage the surge in testing demands for COVID-19 [13, 14]. Additionally, non-COVID-19 patients are also advised to refrain from attending healthcare facilities to reduce the risk of nosocomial COVID-19 transmission. This may have the unintended consequence of reducing the service level for paediatric patients who do not have COVID-19.

Mobile healthcare and point-of-care technologies are potential solutions to such challenges. Indeed, telemedicine consultation has gained prominence as a way to bridge the clinical gap at a time of physical segregation. Point-of-care testing has also enabled continuation of clinical care while minimising the risk of infection for vulnerable groups. An example of this is the use of point of care testing (glucometer) for gestational diabetes testing that avoid exposing pregnant women to higher risk environment in the hospital [15]. Additionally, innovations in sample collection methods such as use of dried blood spots promises to improve accessibility to laboratory testing for geographical regions that may be under-served.

3 Mass spectrometry

Mass spectrometry is an important tool in paediatric laboratory medicine. The high specificity and the ability to measure multiple biomarkers (multiplex) has made it a key technology in the diagnosis of many paediatric conditions. These include newborn screening for inborn metabolic disorders and steroid profiling for disorders of sexual differentiation [16, 17]. The multiplex capability of mass spectrometry has made it the ideal tool for screening as it can detect multiple biomarkers for multiple conditions at the same time in a highly cost-effective manner. At the same time, multiplex mass spectrometry methods also allow laboratory practitioners to better elucidate pathology by examining multiple biomarker changes across biological pathways and diagnose a condition with a higher degree of confidence.

With the changing dietary and lifestyle habits, children are increasingly exposed to high carbohydrate and high fat diet. This predisposes them to metabolic diseases including obesity, lipid disorder and diabetes. The application of mass spectrometry technique in paediatric lipidomics can provide insight into this worrying trend of chronic conditions that can have significant complications at later life [18]. The lipidomics study may also inform treatment options for this group of patients.

Important emerging technologies in the area of mass spectrometry include instruments with higher sensitivity that allow very high number of biomarkers to be detected at the same time or the detection of molecules with very high molecular mass (e.g. proteins), increasing pre-analytical, analytical and post-analytical automation. Pre-analytical and analytical automation in mass spectrometry lowers the adoption barrier for routine clinical laboratory. On the other hand, post-analytical automation (i.e. automated bioinformatics/data processing) is particularly important

as the instruments generate greater details and amounts of data, powerful bioinformatics strategy is required to take full advantage of the benefits of the instrument advancements [17].

4 Next generation sequencing in pediatrics

A complimentary tool to mass spectrometry for newborn/inherited disorder is next generation sequencing, which can determine the genetic sequence of large sections of a gene/genome with high fidelity (read depth) [19–21]. The application and proliferation of this tool has revolutionised the approach of diagnosing inherited diseases. With the ability to sequence large sections of genetic codes rapidly and economically, significant biological insights have been gained in many inherited disorders, some of which have been incorporated into clinical care [19–21]. In some centers, next generation sequencing has become the first- or second-line screening tool for certain inherited disorders in favour of mass spectrometry.

Another emerging use of next generation sequencing is the area of investigating the gut microbiome in neonates and studying the interaction between the gut microorganisms and the health of the host (the neonate). Genomic sequencing of the gut microbiome has provided insights into how the microbiome is formed *in utero* and how it changes as the fetus develops and after the introduction of post-utero neonatal diet [22]. The dysregulation of the neonatal gut microbiome has been implicated in obesity and necrotising enterocolitis and it is an area of great interest and activity [21, 22].

5 Data mining

The interpretation of numerical laboratory results requires appropriately defined reference values including reference intervals and medical decision limits. However, it is extraordinary challenging to derive reference intervals in the paediatric population owing to the need to obtain blood samples from otherwise healthy children [23]. Moreover, multiple partitioning is often required for paediatric reference intervals to account for the changes during growth and development as well as between sexes. This poses significant ethical, operational and resource challenges that cannot be overcome by most clinical laboratories.

At the same time, laboratory medicine generates an increasingly large volume of data that are often stored discretely in electronic databases. These databases are invaluable resources that can be interrogated to derive useful clinical values for interpretation of laboratory results as well as to provide insight into the physiology of a growing child. The indirect approach (also known as data mining approach), where careful statistical analysis is applied on historical laboratory data to derive clinical values in paediatric laboratory medicine, is increasingly used to generate and verify paediatric clinical reference values [24]. Using the indirect approach on large databases has resulted in continuous paediatric clinical reference values and biological variation data across age that better reflect the physiology of growing children [25–29].

In summary, emerging technology in paediatric laboratory medicine plays a crucial role in safeguarding the health of the next generation, now and future. Emerging technology can take the form of breakthrough advancements or novel, better utility of current technology and resources to improve outcome. It is expected that the continued advancement in technology will bring about new insights into the physiology and pathophysiology of childhood diseases that will enable new treatment opportunities and models of care.

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