Africa's response to childhood infection

The AfSPID BULLETIN

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EDITOR'S COMMENT

Dear Colleagues

Welcome to this 13th edition of the AfSPID Bulletin.

COVID-19 remains an important health-related research priority underpinned by a continuous stream of publications cataloguing new and interesting findings. Recent COVID-19 topics that have attracted attention include the immunisation of adolescents and young adults, immunisation during pregnancy and lactation, and the treatment of multisystem inflammatory syndrome in children.

The first phase III placebo-controlled trial that evaluated a COVID-19 mRNA vaccine in young adolescents was recently published. It confirmed that the BNT162b2 vaccine is safe and highly effective among adolescents aged 12-15 years.[1] The findings of this trial resulted in the extension of emergency use authorisation for this vaccine to all individuals 12 years and older in Canada, the USA and Europe. Despite calls to prioritise vulnerable and older adults in low- and middle-income countries for vaccination, the USA proceeded to immunise younger individuals, to date immunising more than 20 million adolescents and young adults.

Myocarditis and/or pericarditis is a rare safety signal that recently emerged during routine immunisation with mRNA vaccines, particularly among adolescents and young adults. It typically manifests within days of immunisation, usually after the second vaccine dose but occasionally after the first dose, and primarily affects male vaccine recipients.[2,3] More than 1000 cases have been reported in the USA.[4]

Although trials to evaluate the safety and efficacy of COVID-19 vaccines in pregnant women are still underway, observational data on more than 35,000 pregnant women who received COVID-19 mRNA vaccines have not shown any safety concerns.[5] Reports have also shown that antibodies to SARS-CoV-2 can cross the placental barrier and be detected in cord blood after maternal immunisation.[6] The first group of vaccine trials also excluded lactating women. However, research has started to shed light on the effect of mRNA vaccines in lactating women and on breastmilk. Antibody responses are similar in lactating and non-lactating women.[7,8] Furthermore, mRNA vaccines do not get into breastmilk and several weeks after immunisation, substantial concentrations of IgA and IgG to SARS-CoV-2 can be detected in breastmilk.[9] These findings suggest that maternal COVID-19 immunisation benefits pregnant and lactating women, and their offspring.

Early outcomes of therapy for MIS-C are the subject of two multi-centre observational studies.[10,11] The first of these studies included 614 participants from 32 countries. It compared three interventions, intravenous immunoglobulin

(IVIG), IVIG plus glucocorticosteroids and glucocorticosteroids alone. The primary endpoints were (1) a composite of inotropic support or mechanical ventilation by day 2 or later or death, and (2) a reduction in disease severity on an ordinal scale between day 0 and day 2. There were no significant differences in the primary outcome measures among participants who received the three interventions, suggesting that either IVIG alone or glucocorticosteroids alone can be used in the management of MIS-C.[10]

The second study included 518 participants who were treated at one of 58 hospitals in the USA. The participants were separated into four treatment categories, IVIG alone, IVIG plus glucocorticosteroids, IVIG, glucocorticosteroids plus a biologic agent, and other treatment interventions. Various outcome measures were evaluated. Furthermore, to compare the effectiveness of IVIG alone and IVIG plus glucocorticosteroids, a composite outcome measure of cardiovascular dysfunction was utilised. This analysis showed that after adjustment for potential confounders, initial treatment with IVIG plus glucocorticosteroids was associated with a lower risk of achieving the composite cardiovascular outcome measure, suggesting that IVIG alone is inferior to IVIG plus glucocorticosteroids.[11]

There are several reasons why these two studies reached conflicting conclusions, particularly regarding treatment with IVIG alone versus the combination of IVIG plus glucocorticosteroids. Of importance is that patient assignment to the treatment groups of both studies was non-randomised, and while statistical methods were used in the analyses to correct for confounding, these methods are less optimal than random patient assignment in balancing confounders. While we await further research findings on the treatment of MIS-C including the long-term outcomes of these interventions, in settings where IVIG shortages exist, clinicians should continue to administer glucocorticosteroids to their patients with MIS-C.

In this issue of the bulletin, five new editorial board members are introduced. Collectively they augment the skill set and expertise of existing board members, and thus we look forward to interesting and stimulating contributions from them.

Ghowa Booley and Hafsah Tootla take us through the laboratory characterisation and susceptibility testing of *Staphylococcus aureus* isolates cultured in routine clinical specimens. This process exploits several virulence characteristics of the organism. The authors then apply these tests to a recent paediatric case of septic arthritis, and in the process provide valuable clinical microbiology insights.

Babatunde Ogunbosi and Stephen Obaro explore whether African countries should invest in specialised infectious diseases hospitals in the wake of the COVID-19 pandemic. Whether or not this suggestion is adopted remains unanswered. However, they acknowledge that substantially improved infection control practices should be a priority for health facilities throughout our continent. The development thereof will require substantial investment, particularly in dedicated personnel, infrastructural modifications to existing facilities, training for all health professionals and changes in health facility culture.

Juanita Lishman, Helena Rabie, Lisa Frigati and Mark Cotton provide a comprehensive review of the prevention of vertical transmission of HIV-1 (PVTH). This paper focuses on research developments over the course of the HIV pandemic that influenced the development of global, regional, and national PVTH policy and practice, and have resulted in the phenomenal reductions in vertical transmission rates that we have all observed. Interventions that may in future enter clinical practice but are currently under investigation, are also discussed.

The case reports & medical images section is starting to gain traction. This edition of the bulletin includes four interesting contributions on severe combined immunodeficiency, herpes simplex virus encephalitis, missed diagnosis of rabies, and intracranial hydatid cyst formation.

Finally, the publication watch section reviews recent reports on immunology advancements during the first year of the COVID-19 pandemic, the new polio eradication strategy, and whether the overall global polio eradication strategy should be changed.

I hope you will find these contributions interesting.

Brian Eley, editor

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SOCIETY NEWS

APPOINTMENT OF NEW EDITORIAL BOARD MEMBERS

Today, we welcome five colleagues to the editorial board.

Figure 1: New editorial board members: Dr Charles Hammond (top left), Dr Norbertta Washaya (top middle), Professor Charles Wiysonge (top right), Dr Hafsah Tootla (bottom left) and Dr Tisungane Mvalo (bottom right)

Charles Hammond is a consultant paediatric neurologist at the Komfo Anokye Teaching Hospital (KATH) in Ghana and a senior lecturer at the School of Medicine and Dentistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana. He is a fellow of the West African College of Physicians and a fellow of the Ghana College of Physicians and Surgeons. He completed his subspecialty training in Paediatric Neurology at the Red Cross War Memorial Children's Hospital from 2014 to 2017 and holds an MPhil (Paediatric Neurology) from the University of Cape Town, South Africa.

He heads the Paediatric Neurology Unit of KATH and serves on various national and international committees such as the Generic Drug Task Force of the International League Against Epilepsy (ILAE), the Training Expansion Task Force of ILAE Africa, and the Ghana National Polio Expert Committee for Polio Eradication. He is a member of the Paediatric Epilepsy Training (PET) International Writing Group and leads PET courses in Ghana.

He has a research interest in paediatric neuro-HIV and has co-authored several journal articles and three book chapters on neuro-AIDS, stroke and moyamoya syndrome in HIV-infected children as well as the neurological complications of antiretroviral therapy in children. He is currently the site neurologist for the WHO multi-centre iKMC Neurodevelopment Follow-up study.

He was a 2010 Frederick and Virginia Smith Stecker Scholar in Paediatric Neurology at the Nationwide Children's Hospital, Columbus Ohio, and the 2017 recipient of the Bernard D'Souza Award by the Child Neurology Society.

Norbertta Washaya, MBChB, FC Paed (SA), MMed (UCT) is a paediatric pulmonology fellow, training under the University of Cape Town and Red Cross War Memorial Children's Hospital. She completed her undergrad education at the University of Zimbabwe College of Health Sciences in 2011. She did her internship in Bulawayo, Zimbabwe and soon after began her journey in paediatric medicine. She trained as a paediatrician at Red Cross War Memorial Children's Hospital after which she commenced her paediatric pulmonology subspeciality training in 2020. Norbertta has a passion for medical education and is a certified APLS instructor. Her current research interests include paediatric respiratory illnesses in low-middle income countries and the use of relevant technology in managing children with respiratory diseases.

Charles Shey Wiysonge is a physician with postgraduate training in evidence-based health care and vaccinology. His qualifications include Doctor of Medicine from the University of Yaoundé I in Cameroon, Master of Philosophy from the University of Cambridge in the United Kingdom (UK), and Doctor of Philosophy from the University of Cape Town. He also undertook postgraduate research training at the UK Cochrane Centre and the University of Oxford in the UK and is a Member of the Academy of Science of South Africa.

Charles is the Director of Cochrane South Africa at the South African Medical Research Council, an Extraordinary Professor of Global Health at Stellenbosch University, and an Honorary Professor of Epidemiology and Biostatistics at the University of Cape Town. His previous appointments include Deputy Director of the Centre for Evidence-based Health Care and Professor of Community Health at Stellenbosch University, South Africa; Manager of the Vaccines for Africa Initiative at the University of Cape Town, South Africa; Chief Research Officer at the Joint United Nations Programme on HIV/AIDS in Geneva, Switzerland; Deputy Permanent Secretary in the Central Technical Group in charge of the Expanded Programme on Immunisation at the National Ministry of Public Health, Yaoundé, Cameroon; Medical Epidemiologist at the Pasteur Centre of Cameroon, Yaoundé; and Physician at the University Hospital Centre, Yaoundé.

Charles is the Chair the Vaccine Hesitancy Working Group of the South African National Advisory Group on Immunisation and the Vice-Chair of the Global Research Collaboration for Infectious Disease Preparedness Research. In addition, he is a member of numerous national, continental, and global advisory committees on vaccination, research, and evidence-based health care. He has published more than 300 peer-reviewed journal articles and his current research interests include vaccine hesitancy, acceptance, and uptake.

Hafsah Deepa Tootla completed her undergraduate medical degree at the University of Cape Town in 2006. She trained in clinical microbiology at the National Health Laboratory Service, Microbiology laboratory, Groote Schuur Hospital and the University of Cape Town between January 2014 to December 2019. She has a love for children and works at Red Cross War Memorial Children's Hospital. Her special interests include antimicrobial resistance and stewardship, invasive pneumococcal disease, *Staphylococcus aureus* infection and rapid diagnostic tests for infectious diseases.

Tisungane Mvalo, MBBS, MMED (Paed), FC Paed (SA) is a paediatrician based and clinically practicing at Kamuzu Central Hospital (KCH) in Lilongwe, Malawi. He is a senior clinical research Investigator with the University of North Carolina Project Malawi (UNCPM) a biomedical research institution based in KCH, a research assistant professor with the school of medicine at the University of

North Carolina in Chapel Hill USA and honorary lecturer in the department of Paediatrics and Child Health of the University of Malawi College of Medicine. He trained as a paediatrician with the University of Cape Town graduating with the FC Paed and MMED qualifications in 2014 and 2017 respectively.

He has previously been involved in infectious diseases research in Malawi as a co-investigator for the Phase III Malaria vaccine RTSS/ASO1 trial (MAL 055) and CPAP IMPACT clinical trial. He was a site principal investigator on infectious diseases clinical trials including the Innovative Treatments in Pneumonia (ITIP) and TBM Kids trials. He currently is a Malawi Co-Principal Investigator on the Malaria Vaccine Implementation Program (MVIP) evaluation on the WHO pilot phased introduction of the RTSS malaria vaccine via the EPI program.

His areas of interest include malaria, pneumonia and bacterial bloodstream infections which are the main contributors to the paediatric infectious diseases burden in Malawi.

TWITTER ACCOUNT

The AfSPID twitter account that was opened by Tinsae Alemayehu and Olubukola Idoko in December 2020, is gaining in popularity. It currently has 141 followers, is being used to increase the visibility of the AfSPID Bulletin, draw attention to case reports and medical images published in the AfSPID Bulletin, highlight recent publications, and promote future academic events. Consequently, forthcoming academic events will no longer be published in the AfSPID Bulletin. Please use our twitter account and post information of interest, @afspid.

AfSPID ANNUAL GENERAL MEETING

An AfSPID annual general meeting will be conducted by Professor Mark Cotton on 25 August 2021 between 13h00 and 15h00 South African time. If you wish to participate, please contact Natasha Samuels by email for the Teams link at samuels@sun.ac.za

COMMENTARIES & REVIEWS

STAPHYLOCOCCUS AUREUS: LABORATORY IDENTIFICATION OF A VIRULENT PATHOGEN

Ghowa Booley and Hafsah Deepa Tootla [1, 2]

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Background

Staphylococcus aureus is a bacterium that is commonly isolated in the laboratory. It is a virulent pathogen and the leading cause of bacterial infection. It causes significant disease such as infective endocarditis, bone and joint infection, respiratory infection including cavitatory and necrotising pneumonia, as well as suppurative skin and soft tissue infection (1).

S. aureus possesses several virulence factors which makes it a formidable pathogen. Detection of some of these factors are exploited to identify the organism within the laboratory. These include:

1. Coagulase: This protein, functions to evade host immune mechanisms by converting host fibrinogen to fibrin, which coats the organism and impairs phagocytosis (3).

2. Protein A: This surface protein is either already present on the surface of the organism or is secreted there. It binds directly to the Fc component of host antibodies aiding in immune evasion and preventing optimal phagocytosis from occurring (3).

3. Clumping factor: This protein causes platelet aggregation and can bind directly to fibrinogen and fibrin, playing an important role in adhesion and vegetation formation in endocarditis (1, 4).

4. Nuclease: This enzyme is also referred to as deoxyribonuclease (DNase) and is responsible for breaking DNA bonds and causes host tissue destruction (3).

5. Catalase: This enzyme breaks down hydrogen peroxide which is produced by the host as a defense mechanism. This characteristic is typically used to differentiate *Staphylococcus* species from *Streptococcus* species (4).

Laboratory identification

Gram stain typically reveals gram-positive cocci in clusters. *S. aureus* is not fastidious and can be inoculated onto routine culture media with good growth seen after 24 hours of incubation both aerobically and anaerobically (1). Colonies from culture are typically golden yellow and round. *S. aureus* derived its name from this golden yellow appearance with 'aureus' meaning 'golden' in Latin (5) .
In our laboratory, in conjunction with Gram stain results, we perform manual biochemical and latex agglutination tests to elucidate the presence of catalase, DNase, protein A, coagulase or clumping factor present in isolates. Whilst the presence of catalase is typically used to differentiate *Staphylococcus* species from *Streptococcus* species which are catalase negative, the presence of coagulase is typically used to distinguish *S. aureus* from other *Staphylococcus* species which are usually coagulase negative (1). However, no single biochemical or latex agglutination test is sufficient for identification and most laboratories will use a combination of these manual identification tests with appropriate sensitivity and specificity for diagnostic accuracy (1). Alternatively, automated identification systems such as the Vitek 2 (BioMérieux, Marcy-l'Etoile, France) and MALDI-TOF (Bruker, BioMérieux, Shimadzu), using biochemical reactions or mass spectrometry respectively, may also be used for identification (1). In our laboratory, we use a combination of manual tests and the Vitek 2 (BioMérieux, Marcy-l'Etoile, France) automated system for identification but this may vary between laboratories. Other molecular

methods for identification, not performed at our laboratory include PCR or peptide nucleic acid fluorescent in situ hybridization (1).

Treatment and susceptibility testing

For methicillin-sensitive *S. aureus*, cloxacillin or first generation cephalosporins (cefazolin) are first-line therapy for infection. Penicillin is not recommended due to isolates commonly producing penicillinase, which hydrolyses penicillin, rendering it inactive (2). Sensitivity to cefoxitin or oxacillin is used as a surrogate marker for methicillin sensitivity and can be performed manually using disk diffusion or by determining minimum inhibitory concentrations, which in our laboratory is done using the Vitek 2 (BioMérieux, Marcy-l'Etoile, France) automated susceptibility testing (AST) system. For manual disk diffusion, we use cefoxitin as the surrogate marker for methicillin sensitivity as it is more potent than oxacillin in inducing the *mecA* gene (1, 2), which is responsible for most methicillin resistant isolates. For methicillin resistant isolates, vancomycin is first-line therapy for serious infection and manual disk diffusion is not recommended for susceptibility testing. We test vancomycin susceptibility using the Vitek 2 (BioMérieux, Marcy-l'Etoile, France) automated susceptibility testing system. Other antibiotics, although used with less serious disease, may be considered and include clindamycin, trimethoprim-sulfamethoxazole and linezolid and susceptibility can be performed both manually with disk diffusion and with automated systems (1).

Below we present a case of *S. aureus* infection and describe how we identified and performed susceptibility testing of the organism in our laboratory.

Case report

An 8-year-old boy presented with a painful, left swollen knee, after a fall a week prior.

He had an elevated temperature (38.2°C) and a warm swollen left knee on examination. Septic arthritis was included in the differential diagnosis and the child was empirically started on IV ceftriaxone (50mg/kg/dose q12h), and blood cultures as well as a joint aspirate was collected aseptically and sent for microscopy and culture.

Gram stain of both the joint aspirate and the signal-positive blood culture, revealed gram-positive cocci in clusters (Fig. 1A) in keeping with *Staphylococcus* species. Round golden yellow colonies were seen on culture after 24 hours of incubation (Fig. 1B). The following biochemical tests were performed on these colonies:

- Catalase was positive (Fig. 1C)
- DNase was positive and can be seen by a clear zone (demonstrating breakdown of DNA) around growth of the organism on DNA-containing media (Fig. 1D), further differentiating *S. aureus* from other *Staphylococcus* species (which are usually DNase negative)
- Latex agglutination was positive indicating the presence of coagulase, Protein A or clumping factor in the isolate (Fig. 1E)

Disk diffusion provided provisional methicillin sensitivity results (Fig. 1F) which was confirmed with the Vitek 2 (BioMérieux, Marcy-l'Etoile, France) AST system, and included sensitivity results for other classes of antibiotics.

The child's knee was washed out in theatre and he completed 4 weeks of IV cloxacillin (50mg/kg/dose q6h) with good clinical outcome.

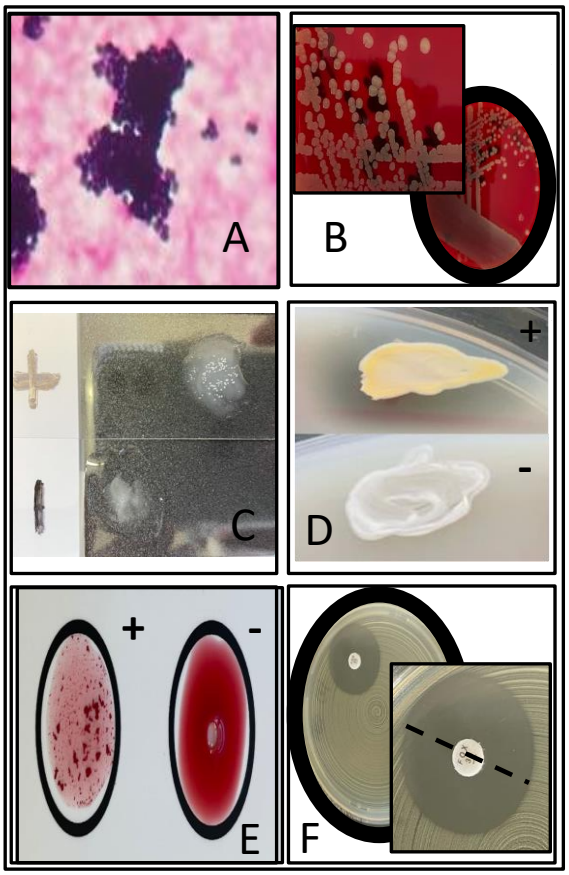

Figure 1: Manual tests performed in the laboratory to aid with identification and susceptibiltiy of S. aureus from culture
(A) *Gram stain showing gram- positive cocci (purple) appearing as grape-like clusters, suggestive of Staphylococcus species*
(B) *Round golden yellow colonies on blood agar media following 24 hours of incubation, suggestive of S. aureus*
(C) *Catalase is usually used to differentiate Staphylococcus species (catalase positive) from Streptococcus species (catalase negative). The (+) test shows the formation of bubbles when an isolate is added to hydrogen peroxide. This occurs with organisms, like S. aureus that produce catalase, which break down the hydrogen peroxide into oxygen (visually seen as bubbles) and water. The (-) test is when an organism does not produce catalase and when added to hydrogen peroxide, there is no visual reaction.*
(D) *DNase is used to differentiate S. aureus (DNase positive) from other Staphylococcus species (usually DNase negative). The test is positive when there is a clear zone around the organism demonstrating DNA breakdown (+). The test is negative when there is no clear zone around the organism indicating that DNA in the media has not been broken down (-)*
(E) *This is a latex agglutination test demonstrating the presence of coagulase, Protein A and clumping factor. The test is positive for isolates like S. aureus that have these virulence factors and is visually seen by agglutination when the isolate is added to the reagent (+). For isolates that do not have these virulence factors, no agglutination is seen (-).*

(F) *Disk diffusion susceptibility testing indicating methicillin sensitivity based on a zone of inhibition ≥22 mm around the cefoxitin disk, which has been used as a surrogate marker for susceptibility (2)*

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INFECTIOUS DISEASES HOSPITALS IN LOW- AND MIDDLE-INCOME COUNTRIES: TO BUILD OR NOT TO BUILD?

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Background

In December 2019, an increased number of patients with pneumonia, not due to common bacterial or viral pathogens, was observed in Wuhan, China. This was later discovered to be a novel disease caused by a new corona virus. The WHO has designated the disease as coronavirus disease 2019 (COVID-19) and the causative agent, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1, 2]. It also declared it a global pandemic, which as at 15 June 2021 has infected over 178 million people and caused more than 3.8 million deaths with cases in all countries of the world on all continents, except Antarctica[3]. Most cases are mild or moderate with 20% having severe disease requiring hospital admission, leading to a surge in requirements for hospital admissions. [4, 5]. Most countries are experiencing second or third waves of the pandemic with countries instituting further periods of lockdown.

Nigeria currently has one of the largest number of cases of COVID-19 on the African continent[3]. The first case of COVID-19 was reported on 27 February, 2020 and has increased to about 68,000 cases as at December, 2020 [3]. This has been partly due to the increased availability of testing platforms from 5 at the onset of the pandemic to over 80 testing sites spread across the country. The index case was managed in the infectious diseases hospital in Lagos, the commercial centre of the country. The Ebola epidemic of 2014 had afforded the state the opportunity of re-vitalizing this long forgotten edifice of the colonial era. This stint with Ebola also led to the establishment of an Emergency Operations Centre, the first in the country, and gradual improvement in diagnostic capabilities and routine training of health care workers in the state on infection prevention and control (IPC) practices [6]. For most parts of the country and probably the continent, this was not the case. Most infectious diseases like Ebola virus disease, Lassa fever and measles are managed within routine hospital care service areas, with patient isolation where feasible. Managing such highly infectious diseases in dedicated infectious diseases hospitals is the exception, rather than the norm in most African countries, including Nigeria.

Challenges of In-hospital Care of Contagious Infectious Diseases

This surge in severe cases, led to a rapid increase in hospital admissions for this highly infectious pathogen [3]. Consequently, in this pandemic, hospital facilities in developed and highly resourced countries were overwhelmed. In Wuhan, China, the government built a dedicated 500 bed facility in 10 days [7]. This is an example of remarkable feats in an effort to address the pandemic. In some developed countries, bio-containment facilities specifically built for managing patients with highly contagious and pathogenic infections have been used. For most developing countries, where the health care delivery system has over the decades been poorly funded or neglected with infrastructural and human resource deficit, the optimal approach to coping with the patient surge occasioned by the pandemic remains unclear. The COVID-19 pandemic has indeed exposed strategic and infrastructural deficits in health care and the economies of most countries, especially in developing nations.

COVID-19 is transmitted mainly through droplets or contact with infected material. Concerns exist of potential airborne transmission, during aerosol generating procedures, with the virus remaining suspended for up to 3-8 hours in the air. Therefore, the need for strict infection prevention and control (IPC) practices and appropriate use of personal protective equipment (PPE) is very important. These requirements are not usually available in the health delivery systems in most developing countries. The question therefore remains, should stand alone infectious diseases hospitals be built in developing countries grappling with COVID-19? Or should treatment facilities be embedded in existing hospital set ups? These two options pose immediate obvious challenges. The COVID-19 pandemic has also brought to the fore the need for institutionalization of IPC practices and specialists, irrespective of the model adopted.

What Options Exist for Developing Countries?

The COVID-19 pandemic has not only taken a toll on human lives and health systems, the economies of countries have also been ravaged. This is occasioned by the lockdown of cities and societies limiting wealth generating potentials on communities affected. For developed countries opting to build new treatment facilities, this is an added financial burden. The sustainability of such facilities in the post COVID-19 era is also not guaranteed as with most health care delivery systems in these countries. In those developing countries where treatment centres are embedded in existing health facilities, there will be an urgent need for infection prevention and control specialists and extensive repeated training of health care workers to sustain the needed level of infection prevention and control. In addition to this, significant resources are needed to procure and sustain adequate supply of PPE, of which there is a global shortage. These are mostly produced in developed countries, that are also facing supply challenges, making

the availability of PPE in developing countries a dire concern.

Current trends in hospital design in the developed world is for the building of single patient rooms interlaced with rooms designed for airborne precautions[8]. This is a rarity in most developing countries and existing health infrastructure would need remodelling to meet the present IPC requirements. The current pandemic offers few options and no easy choices for health care systems in developing countries. Innovative funding mechanisms and pragmatic approaches are urgently needed to meet this challenge. In the wake of the COVID-19 pandemic, countries with large outbreaks established COVID-19 isolation and makeshift treatment centres in hospitals, in some cases, schools, hotels, places of worship, community or towns halls. Most have reverted to their original use.

Infectious diseases of public health importance have provided opportunity to harness multi-sectorial resources and collaboration between countries and development partners. These have often formed platforms to address other health care challenges in developing countries. The polio eradication campaign and the role it played in Nigeria's response is a good case in point [9]. Resources from the polio eradication programme were deployed to rapidly contain the 2014 Ebola virus diseases (EVD) in Nigeria. Lessons from this and resources put in place, including an infectious diseases hospital in the mega city of Lagos, were promptly deployed in the early phase of the COVID-19 pandemic in Nigeria. One of the recommendations from the 2014 EVD outbreak was the establishment of infectious diseases treatment in all states of the federation [9]. This never materialized, likely from the aforementioned funding deficits that plague the health sector in Nigeria. Consequently, the response to the COVID-19 pandemic, and indeed prior infectious diseases outbreaks like Lassa and yellow fever in Nigeria, has been faced with proper treatment centre challenges.

Most epidemic or pandemic prone infectious diseases have two phases of transmission, transmission outside the hospital setting and in-hospital transmission, so-called nosocomial transmission. The Ebola and COVID-19 pandemics have typified the risk these pathogens pose to health care workers and the huge death toll which is at times caused by hospital associated infections [10-12]. This highlights the very important role of IPC practices, and infection preventionist and infectious disease physicians in the hospital,; very scarce resources in most developing countries [6]. These resources are fairly-well established in most developed countries with their roles forming a core part of most health care settings.

The pragmatic approach

Irrespective of the care model adopted by developing countries in coping with the surge associated with COVID-19 or future such epidemics or pandemics, there is an urgent need to pay greater attention to and direct resources to infection prevention and control activities in hospital settings. This should be ingrained as a culture in all healthcare settings, irrespective of the designation of such facilities, whether infectious diseases hospitals or not. Also, this is the time to invest in personnel and expertise that will drive and sustain the process [13]. The infectious diseases sub-specialty is still a budding specialty in most developing countries, despite sharing a disproportionately higher burden of infectious diseases compared to the rest of the world. Few hospitals, if any, in developing countries have an infection preventionist. These critical healthcare workers are urgent value-added investments in all hospitals in low- and middle-income countries irrespective of whether they choose to build or not to build infectious diseases hospitals.

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RESEARCH

PREVENTING VERTICAL TRANSMISSION OF HIV-1

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Introduction

The acquired immunodeficiency syndrome (AIDS) caused by the Human Immunodeficiency Virus-1 (HIV-1) was first described in 1981 and remains one of the worst global health pandemics in recorded history, having claimed

almost 33 million lives so far.[1] With increasing access to prevention, diagnosis, treatment and care, HIV has become a manageable chronic health condition. People living with HIV can now lead long and healthy lives.[1] In the past three decades, there has been tremendous progress in preventing mother to child transmission (PMTCT) of HIV-1. Owing to sensitivity about implicating the mother alone and awareness that mothers usually acquire HIV from a male partner, we prefer the term vertical transmission (VT), and its prevention as VTP. UNAIDS (2019) estimates a 63% decline in new child HIV infections since 2000.[2] This can be attributed to improved access to HIV testing and combination antiretroviral treatment (ART) with better implementation of VTP services.[2] In the absence of any interventions, rates of HIV transmission from parent-to-child can be between 15% and 45%.[3] Vertical transmission can almost be eliminated if the mother is on ART from preconception or from early pregnancy. The newborn infant also requires one or more antiretrovirals (ARV), depending on the level of risk.[1]

The current World Health Organization (WHO) guidelines recommend lifelong ART for all people living with HIV, regardless of CD4 count and the clinical disease stage. In 2019, approximately 85% of the estimated 1.3 million pregnant women living with HIV received ART globally.[1] Increasing numbers of countries have been formally validated for eliminating HIV VT including several countries with large HIV burdens progressing to elimination (Cuba, Thailand, Armenia, Belarus, six Caribbean territories and states, Malaysia, Sri Lanka and Maldives). Africa remains the continent with the highest number of people living with HIV and the highest number of new infections.[2] Regrettably, the pace of VT reduction is less rapid than hoped. Notably, in 2018 (6 years after WHO introduced triple ART for VTP globally), 160 000 new paediatric HIV infections were diagnosed, far above the target of below 40 000 new paediatric HIV infections from 2015 onwards.[2]

This review briefly addresses five aspects of HIV-1 VTP: its history, some key studies informing guidance, the current practice in South Africa, barriers to achieving the goal of VTP elimination and a look at some exciting new prospects in VTP.

History of VTP – a timeline

Vertical transmission is the primary means for infants to acquire HIV-1. This can be in utero, during labour and delivery (intrapartum) or during breastfeeding (post-natal).[3] Without any interventions the estimated rate of VT is between 15% and 40%, with breastfeeding increasing transmission.[4] The landmark AIDS Clinical Trial Group (ACTG) 076 took place from April 1991 to December 1993. This double-blind, placebo controlled, randomized study enrolled pregnant women living with HIV-1 between 14 and 34 weeks of gestation with a CD4 count above 200 cells per mm^3. They concluded that an intensive regimen of zidovudine (ZDV) started at 14-34 weeks' gestation, given intravenously during labour and delivery, and orally to babies for the first 6 weeks of life lowered HIV-1 vertical transmission by two thirds.[3]

As ACTG 076 was complex and unsuitable for resource-limited settings, the HIVNET 012 randomized trial was designed. This study compared single dose Nevirapine (NVP) in mother and infant to an oral loading dose of ZDV during labour, continued intrapartum every 3 hours and the first week of life.[5] NVP lowered the risk of HIV-1 transmission during the first 14-16 weeks of life by nearly 50% in a breastfeeding population. NVP has potent antiviral activity, is rapidly absorbed when given orally, and quickly passes through the placenta to the fetus. The drug also has a long half-life in pregnant women and babies. At the time single-dose NVP was also considered to be a cost-effective intervention that would be deliverable and sustainable in resource-poor settings that had yet to develop ART programs.[5]

Exclusive breastfeeding protects the integrity of the intestinal mucosal barrier, presenting a more effective barrier to HIV.[6] Exclusive breastfeeding is also associated with reduced diarrheal morbidity and all-cause mortality in infants.[7] Between October 2001 and April 2005 Coovadia et al assessed the risk of HIV transmission and survival associated with exclusive breastfeeding and other types of infant feeding in KwaZulu Natal, South Africa[6] when ART was not available through the provincial health services. In exclusively breastfed infants the cumulative infection rates were 14.1% at six weeks of age and 19.5% at 6 months of age. Infants who received both breastmilk and formula milk, were almost twice as likely to acquire HIV infection than those exclusively breastfed. Infants who were breastfed, but also received solids were nearly 11 times more likely to acquire HIV infection.[6] This emphasized the need to develop feeding policies that considered overall survival and not only avoidance of HIV infection.[7]

By 2004 there was an urgent need to reduce VT of HIV through breastfeeding in resource-limited settings. In the PEPI-Malawi trial (Post-exposure prophylaxis in Infants in Malawi), ART was just becoming available for mothers with CD4 counts <250 cells per mm^3 with approximately 3% of mothers on ART by 14 weeks postpartum.[8] The infants were randomized to one of three regimens at birth: single-dose NVP plus 1 week of ZDV (control regimen) or the control regimen plus daily prophylaxis either with NVP (extended nevirapine) or with NVP plus ZDV (extended dual prophylaxis) until the age of 14 weeks. The frequency of breastfeeding did not differ significantly between the groups. The study concluded that extended prophylaxis with NVP or with NVP and ZDV for the first 14 weeks of life reduced the post-natal HIV-1 transmission from 10.6% to 5.2% or 6.4% in 9-month-old infants.[8]

Taha et al conducted an observational data analysis from the PEPI-Malawi trial conducted from April 2004 to December 2007 to determine the effect that maternal ART on postnatal HIV-1 transmission.[9] For women eligible for but not receiving ART, HIV transmission rate was 10.6 per 100 person years versus 1.8 transmissions in those on ART, thus confirming the importance of maternal ART during breastfeeding.[9] To address the best regimen to prevent intrapartum infection in neonates in mothers whose HIV was determined in labour, 1684 infants were enrolled in the Americas and South Africa. All received ZDV for 6 weeks, either alone, or with nevirapine (3 doses within the first 8 days) or with nelfinavir (an old protease inhibitor with erratic absorption) and lamivudine (3TC).[10] For ZDV alone, there were 24 transmissions (4.8%; 95% confidence interval [CI], 3.2 to 7.1) versus 11 (2.2%; 95% CI, 1.2 to 3.9; P=0.046) for ZDV plus nevirapine and 12 (2.4%; 95% CI, 1.4 to 4.3; P=0.046) in the three drug group. This study provides the rationale currently recommended for high-risk pregnancies.[10]

Based on emerging but seemingly equivalent trial data, the WHO introduced two approaches for women with CD4 counts above the threshold for ART (≥350 per mm^3) in 2013: Option A included ZDV and single dose nevirapine to mother and infant and Option B recommended maternal ART during pregnancy and breastfeeding.[11] The Option B+ approach is the most notable recent development in HIV VTP globally with the introduction of lifelong ART for all pregnant and breastfeeding woman.[12] Option B+ greatly simplified the VTP strategy by introducing a test and treat approach, eliminating the complexity of needing CD4 counts to guide maternal therapy (Options A and B).[13]

Despite the clear benefits of ART for the mother and infant, it does not come without risk. The PROMISE (promoting Maternal and Infant Survival Everywhere) trial compared the efficacy and safety of various proven VTP antiretroviral strategies for asymptomatic pregnant women living with HIV and high CD4 counts.[14] Enrollment began in 2011. Women at 14 or more weeks of gestation with CD4 counts ≥ 350 cells per mm^3 were randomly assigned to ZDV and single-dose nevirapine plus a 1-to-2-week postpartum "tail" of tenofovir and emtricitabine (to protect against NVP resistance); ZDV, lamivudine and lopinavir-ritonavir (zidovudine-based ART); or tenofovir, emtricitabine, and lopinavir-ritonavir (tenofovir-based ART). Transmission rates were significantly lower for ART than ZDV alone. However, the rate of maternal grade 2 to 4 adverse events was significantly higher for both ART regimens than with zidovudine alone. A birth weight <2500g was also more frequent with both combination ART regimens than with zidovudine alone.[14]

After the period of transmission risk was over in PROMISE, women were randomized to either continue or discontinue ART. Theron et al compared the subsequent pregnancy outcomes of non-breastfeeding women randomized to continue ART after delivery or breastfeeding. The intention-to-treat analyses showed increased incidence of low birth weight (<2500g) and also a higher risk of spontaneous abortion, stillbirth, or neonatal death in women who conceived while on ART than those who restarted ART during subsequent pregnancy. This emphasizes the need for improved obstetric and neonatal care for women conceiving on ART.[15]

Dolutegravir is an integrase inhibitor with many benefits. These include rapid viral suppression, a high genetic barrier to resistance, no interaction with hormonal contraceptives and mild or rare side-effects.[16] Botswana became the first African country to shift from efavirenz-based to dolutegravir-based ART as first-line for adults with HIV in 2016.[17] In May 2018, a review of data to inform the WHO ARV guidelines revealed a potential early signal for neural-tube defects associated with dolutegravir exposure at conception, with 4 defects found among 426 exposures.[18] Based on these findings, many countries, advised pregnant women and women of childbearing potential to take efavirenz instead.[17] Since this safety signal was raised, recent data noted a decline but not absence in risk. Updated results showed that the risk of neural tube defects among newborn babies exposed to dolutegravir at conception was 0.3% (0.13-0.69) compared with 0.1% among those exposed to non-dolutegravir ART.[17,19] In 2019 the WHO recommended dolutegravir in preferred first-line and second-line treatment for all populations, including pregnant women and those of childbearing potential as the benefits outweighed potential harm.[20] It is also worth noting that folate fortification of essential foods e.g. flour is associated with very low rates of neural tube disorders but was not standard in Botswana.[21]

Williams et al evaluated HIV exposed uninfected (HEU) children enrolled in the Surveillance Monitoring for ART Toxicities (SMARTT) study for the development of microcephaly.[22] They demonstrated a concerning association between in utero exposure to efavirenz and microcephaly. The risk was more evident in children also exposed to ZDV and 3TC rather than tenofovir and emtricitabine.[22] The children with microcephaly also had worse neurodevelopmental scores at age 1 and 5 compared to those without microcephaly. They emphasized the need for alternatives to efavirenz as part of first line ART for pregnant women.[22]

Table 1: Timeline of VTP

1994	A regimen consisting of Zidovudine given ante partum and intra partum to the mother and to the newborn for six weeks reduced the risk of maternal-infant HIV transmission by approximately two thirds.	Connor EM et al, New England Journal of Medicine
1999	Nevirapine lowered the risk of HIV-1 transmission during the first 14-16 weeks of life by nearly 50% in a breastfeeding population.	Guay LA et al, Lancet
2007	Exclusive breastfeeding carries a significantly lower risk of HIV transmission than do all types of mixed feeding.	Coovadia HM et al, Lancet
2008	PEPI-Malawi trial concludes that extended prophylaxis with nevirapine or with nevirapine and zidovudine for the first 14 weeks of life significantly reduce postnatal HIV-1 infection in 9-month-old infants.	Kumwenda NI et al, New England Journal of Medicine
2009	Maternal HAART reduces postnatal HIV transmission in infants.	Taha TE et al, Journal of Infectious Diseases
2013	Option B+ approach implemented globally with the introduction of lifelong ART for all pregnant and breastfeeding woman.	Nielsen-Saines K et al, New England Journal of Medicine
2016	Promise trial showed that antenatal ART resulted in significantly lower rates of transmission than zidovudine alone but a higher risk of adverse maternal and neonatal outcomes.	Fowler MG et al, New England Journal of Medicine
2018	Safety signal with Dolutegravir in early pregnancy – increased risk of neural tube defects.	Zash R et al, New England Journal of Medicine
2019	WHO recommends Dolutegravir as the preferred treatment option in all populations.	World Health Organization
2020	Increased risk for adverse pregnancy outcomes in women conceiving on ART.	Theron G et al, Clinical Infectious Diseases

Current practice in South Africa

South Africa has made great progress in reducing HIV VT in the first two months of life from 23% (2003) to 0.7% (2019).[23] Maternal HIV acquisition late in the third trimester of pregnancy or postpartum, chronic untreated maternal HIV infection and suboptimal postnatal adherence to maternal ART have led to the increase in the relative contribution of breastfeeding to the overall VT rate.[24] Due to the benefits of breastfeeding and the risks associated with not breastfeeding, mothers are encouraged to breastfeed their infants for the longest duration possible, while maintaining virological suppression.[23]

The 2019 South African National VTP Guideline suggests three strategies to improve the National program:[25]

1. Prevent unintended pregnancy and primary HIV infection in woman of childbearing potential.
2. Improve maternal viral suppression rates at delivery and in the post-natal period through potent, well-tolerated antiretroviral regimens, strategic use of maternal viral load monitoring, linking of mothers to post-delivery HIV care and integration of mother-infant health care.
3. Provision of enhanced prophylaxis to infants of mothers with elevated viral loads during breastfeeding.

Maintaining suppressed maternal viral load remains the most critical intervention in preventing transmission. ARVs that rapidly and safely achieve viral suppression during pregnancy and breastfeeding are of great importance.[25] Dolutegravir is excellent in this regard. As mentioned previously, the WHO recommended dolutegravir as the

preferred first-line agent for all populations (weight >20kg).[20] South Africa has taken a more conservative approach and recommends that dolutegravir should be used with caution in women wanting to conceive and avoided in the first six weeks of pregnancy.[25] As more information becomes available, South Africa's position is likely to change.[19,25] Table 2 summarizes the South African 2019 VTP guideline and compares it to the 2010 guideline.[25,26] Other African countries had similar evolutions, following WHO guidance.

Table 2: Evolution of South African VTP guidelines between 2010 and 2019

	2019[25]	2010[26]
Prevention	Universal infection precautions preventing infection in HIV-negative women and serodiscordant couples. PrEP is routinely available for adolescent girls and young women, as well as for sex workers.	Primary prevention of HIV among women of childbearing age and prevention of unintended pregnancies among women living with HIV.
Maternal HIV testing	At first visit and at every subsequent antenatal clinic visit, and three-monthly during breastfeeding.	At first visit and repeated at 32 weeks gestation.
Maternal ART	All HIV positive woman to be initiated on lifelong ART. The preferred first-line ART regimen is TLD. Due to concerns around safety of TLD in the first 6 weeks of pregnancy, TEE is recommended for women of childbearing potential wanting to conceive. ART should ideally be initiated on the same day as diagnosis.	Lifelong ART commenced if CD4 count ≤350 cell per mm^3 and clinical stage 3 or 4 disease. If not eligible for ART, ZDV prophylaxis started at 14 weeks gestation. First line regimen: TDF + 3TC/FTC + NVP. ART to be initiated within 2 weeks
Maternal HIV VL monitoring	<u>Scenario 1 - HIV positive women already on ART:</u> Do VL at first antenatal visit <u>Scenario 2 - Newly-diagnosed HIV positive:</u> Do first VL at 3 months on ART VL done at delivery in all mothers and at six months post-partum for all women, and six-monthly during breastfeeding.	VL monitoring done only in mothers on lifelong ART at month 6, 1 year on ART and then every 12 months.
ART for the mother presenting in labour	Stat dose of NVP and a stat dose of TDF, 3TC, and DTG in a fixed-dose combination (TLD). Start ART next day (TLD preferred), after appropriate counselling	<u>Scenario 1 - HIV infected Mother on AZT regimen or no treatment:</u> • At onset of labour stat dose NVP and 3 hourly ZDV till delivery • Post-delivery provide stat dose TDF and FTC <u>Scenario 2 – Mother on lifelong ART</u> • Continue ART regimen throughout labour
Infant HIV testing	• HIV PCR test at birth and 10 weeks • Six-month HIV PCR test for all HIV-exposed infants • At six months of age, establish the HIV status of all infants not already known to be HIV-exposed by offering an HIV test to the mother. If a maternal HIV test is not feasible, consent should be obtained to perform a rapid HIV test on the child. • Age-appropriate HIV testing at six weeks post-cessation of breastfeeding. • 18-month rapid test/ ELISA for all children regardless of HIV exposure (universal testing) • HIV PCR test used as a confirmatory test for any HIV-positive result up to age two years	No HIV PCR test at birth <u>Scenario 1 - Infants exclusively formula fed:</u> PCR at 6 weeks Discontinue infant NVP <u>Scenario 2 – Exclusively breastfed and lifelong maternal ART:</u> PCR at 6 weeks Discontinue infant NVP Repeat HIV test 6 weeks post-cessation of BF <u>Scenario 3 – Exclusively breastfed without maternal lifelong ART:</u> PCR at 6 weeks Continue infant NVP until BF stopped Repeat HIV test 6 weeks post-cessation of BF Rapid HIV test at 18 months for all exposed infants
Definition of high-risk infant exposure	High-risk infant at birth: • Maternal VL ≥ 1000 copies/mL at delivery, or in the last 12 weeks of pregnancy • No maternal VL result available in the last 12 weeks • Unknown maternal HIV status because the infant is orphaned or abandoned High-risk infant during breastfeeding (> 72 h after delivery): • New maternal HIV diagnosis during breastfeeding • Maternal VL ≥ 1000 copies/mL after previous viral suppression on ART	No risk stratification of infants
Infant post-exposure prophylaxis	<u>High risk infants at birth, exclusively breastfed:</u> ZDV for six weeks and NVP prophylaxis for a minimum of 12 weeks. NVP is stopped after 12 weeks only if the maternal VL is proven to be < 1000 copies/mL. If the maternal VL is not suppressed by 12 weeks, continued NVP is given until maternal VL suppression is achieved, or until four weeks after breastfeeding cessation. High risk infant exclusively formula fed: NVP and ZDV for 6 weeks Low risk infants (breastfed or formula fed): NVP for 6 weeks	Daily NVP for 6 weeks or for duration of breastfeeding

Breastfeeding	Breastfeeding recommended for 24 months or longer whilst ensuring maternal ART and viral suppression, in line with recommendations for the general population.	Mothers can breastfeed provided the child is taking NVP during breastfeeding period. Exclusive breastfeeding for 6 months.

Pre-exposure prophylaxis (PrEP); tenofovir disoproxil fumarate-lamivudine-dolutegravir (TLD), tenofovir disoproxil fumarate-emtricitabine-efavirenz (TEE), tenofovir disoproxil fumarate (TDF), Emtricitabine (FTC), lamivudine (3TC), Zidovudine (ZDV), Nevirapine (NVP), viral load (VL)

Current challenges in achieving the goals of eliminating vertical HIV transmission

Retention of women and infants within the VTP services remains challenging. Option B+ was first introduced in Malawi[13] where a study using aggregate data from 540 health facilities and patient-level data from 19 facilities found 17% loss-to-follow-up at 6 months in women who started ART under Option B+.[27] A qualitative study investigating the causes for loss-to-follow-up, early refusal of ART and stopping ART, identified concerns about partner support, feeling healthy and needing time to think. The main reasons for discontinuing ART were side effects and lack of partner support. They concluded that long term health outcomes might be improved by providing consistent pre-ART counseling, early support for patients experiencing side effects, and targeted effort to bring women who stop treatment back into care.[28]

A study from Tygerberg Hospital in Cape Town, South Africa linked the clinical profile of hospitalized young children living with HIV to maternal HIV diagnosis and care.[29] Fifty-seven mother-child pairs were enrolled of whom 31 mothers (56%) were diagnosed with HIV prior to the index pregnancy. Only 20/31 (65%) of mothers aware of their HIV diagnosis attended antenatal clinic. In women with known HIV prior to pregnancy, lack of antenatal clinic attendance, ART interruption and failure to suppress HIV were the drivers of HIV transmission. They concluded that it is important to gain a better understanding of the barriers to care for women who know their HIV status but fail to attend either antenatal clinic or HIV services.[29]

Olakunde et al explored the challenges in the elimination of vertical HIV transmission in Nigeria.[30] Challenges identified included difficulty in identifying HIV positive pregnant women due to low uptake of antenatal care; interrupted supplies of medical commodities, knowledge gaps among health care workers; and lack of a national unique identifying system to enhance data quality. They concluded that a successful program in Nigeria would require feasible, culturally acceptable and sustainable interventions to address the health system-related challenges.[30]

Two-thirds of people living with HIV, reside in Sub-Saharan Africa (SSA). A review article investigating the challenges faced by VTP programmes in SSA found the most common barriers were non-disclosure of HIV status, late ART initiation, adherence to ART, screening for sexually transmitted infections, long clinic waiting times, non-involvement of men, infant feeding methods and sensitizing community members on antenatal clinic or vertical transmission programs.[31] This paper emphasized the need to expand VTP coverage and implementation of the 90-90-90 programme toward eliminating vertical HIV transmission in SSA[29] defined as: ≥90% of pregnant and breastfeeding mothers knowing their HIV status; ≥90% of those with HIV on ART and ≥90% of those on ART being virally suppressed.[31,32]

What does the future hold?

In a recent Health Policy paper by Van de Perre et al[24], the need for complementary biomedical interventions to eliminate HIV transmission in high incidence areas was discussed. The transmission rate from breastfeeding is increasing relative to other transmission modes. The need for urgent action to evaluate and implement additional preventive biomedical strategies is emphasized. Three preventative strategies are discussed: pre-exposure prophylaxis (PrEP) in breastfeeding women who have an increased risk of acquiring HIV; postnatal reinforcement strategies, such as maternal retesting for HIV, maternal care reinforcement, and prophylaxis in infants exposed to HIV via breastmilk; and active (vaccine) or passive immunoprophylaxis with long-acting broadly neutralizing antibodies.[24]

PrEP for pregnant or breastfeeding women at high risk of acquiring HIV infection

The WHO released guidance and a policy brief in 2017 that recommends pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil fumarate for pregnant and breastfeeding women at substantial risk of acquiring HIV.[32] The effectiveness of oral PrEP is highly dependent on adherence. The adherence and consistent use of PrEP amongst women in clinical trials are initially high (84%) in the first three months but tend to decrease thereafter.[33] Two new modalities delivering long-acting antiretroviral regimens for PrEP are in phase 3 clinical trials for women who are not pregnant or breastfeeding. Long acting cabotegravir (a strand transfer integrase inhibitor) given by intramuscular injection every 8-12 weeks (vs daily oral tenofovir disoproxil fumarate plus emtricitabine) is being evaluated for safety and efficacy for HIV prevention amongst women aged 18-45 years in Botswana, Kenya, Malawi, South Africa, Eswatini, Uganda, and Zimbabwe (HPTNo84 study; NCT03164564).[24,34] Rilpivirine (a non-nucleoside reverse transcriptase inhibitor), the only other long-acting injectable, was well tolerated in healthy people who were not pregnant and HIV uninfected.[35] Finally, the monthly self-insertion of a vaginal ring containing 25mg dapivirine (a non-nucleoside reverse transcriptase inhibitor) resulted in a 30% lower HIV incidence in pregnant women over a 2 year period than pregnant women on placebo.[36]

Reinforcement approaches

These approaches are intended to improve existing policies and are based on maternal HIV retesting during late pregnancy or breastfeeding and should be supported by high-performance point-of-care (POC) qualitative and quantitative molecular testing.[37] The POC testing will identify infant infection and determine maternal HIV viral load. This will identify two groups: infants with HIV requiring prompt ART initiation and infants without HIV whose mothers have detectable HIV in blood or breastmilk. In the second group, reinforcement of maternal ART adherence and infant PrEP might be a safe intervention to protect the infant against HIV acquisition. The current WHO guidelines recommend 3 monthly testing, starting in the third trimester of pregnancy until the end of breastfeeding.[38]

Passive immunoprophylaxis by means of long-acting broadly neutralizing antibodies (bNAbs)

More than 40 human monoclonal bNAbs against HIV have been identified and target different epitopes of the HIV envelope.[39] The VRC01 bNAb is the most studied bNAb in humans and the only one evaluated in efficacy trials. Two phase 2 trials using VRC01 or the closely related VRC07-523LS subcutaneously are ongoing in infants exposed to

HIV and HIV positive infants on ART.[40] A modelling exercise derived from data in animal models suggest high efficacy and tolerability for VRC01.[41]

Active vaccination to induce neutralizing or non-neutralizing antibodies to protect breastfed infants

An HIV vaccine that induces T-cell sensitization non-neutralizing antibodies binding to HIV envelope administered during the neonatal period could become a crucial component in the strategy to eliminate paediatric HIV.[24] Antibody-mediated immune responses (antibody-dependent cellular phagocytosis and antibody dependent cell cytotoxicity) have been correlated with reduced HIV infection in non-human primates and in humans.[42] Efficacy trials in southern and eastern Africa are evaluating approaches to trigger antibody-mediated immune responses to prevent HIV acquisition through sexual intercourse.[24]

Long-Acting Cabotegravir and Rilpivirine to Maintain HIV-1 Suppression

A phase 3 multicenter trial included adults who had plasma HIV-1 RNA levels of less than 50 copies per mm^3 for at least six months on standard oral ART.[43] Participants were randomly assigned to either continue their oral therapy or switch to monthly intramuscular injection of long-acting cabotegravir or rilpivirine. The primary outcome was the percentage of participants with an HIV-1 RNA level of 50 copies per milliliter or higher at week 48. They concluded that monthly injections of long-acting cabotegravir and rilpivirine were noninferior to standard oral therapy for maintaining suppression of HIV-1 and that injection-related adverse events were common but only infrequently led to medication withdrawal.[43]

The HPTN 084 study announced recently that a PrEP regimen consisting of long-acting cabotegravir injections every eight weeks was safe and superior to daily oral FTC/TDF.[44] HPTN 084 enrolled 3223 cisgender women from seven sites in Africa. The incidence rate of HIV without any intervention is approximately 3.5% per year. In the cabotegravir arm the incidence was 0.21% compared to 1.79% in the FTC/TDF arm. The researchers believe that the results are related to poor adherence to daily oral PrEP.[44]

Long-acting injectables such as cabotegravir are an exciting option to improve ART adherence. However, when information was made available in May 2018 regarding periconception dolutegravir exposure and neural tube defects this approach stalled. Future studies will have to be conducted to ensure safety of the long-acting injectable ART during pregnancy and breastfeeding.

Conclusion

Major advances have been made in preventing vertical HIV transmission over the past three decades, saving the lives of many children. Rigorous implementation of guidelines can move the global population closer to eliminating vertical transmission and realizing a HIV-free generation. However, challenges remain in retaining mother-and-infant pairs within care in Africa and other low- and middle-income countries. Global strategies to overcome these challenges are imperative. Individualized attention to women in socially fragile situations is imperative. Exciting new prospects include the use of complementary biomedical interventions and long-acting injectable ART.

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CASE REPORTS & MEDICAL IMAGES

SEVERE COMBINED IMMUNODEFICIENCY CAUSED BY A MUTATION IN THE RAG-1 GENE

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Abstract

Primary immunodeficiency diseases are a group of conditions that affect the innate and adaptive immune system. The burden of these conditions is under-recognised and under-diagnosed in Africa. In this paper we discuss a 4-month-old infant with severe combined immunodeficiency.

Background

Primary immunodeficiency diseases (PID) result from failure in the development and functioning of the immune system. It affects different components of the innate and adaptive immune system including neutrophils, macrophages, dendritic cells, complement proteins, natural killer cells and B and T lymphocytes. The spectrum of PID in children is under-diagnosed and under-reported more so in the developing countries of Asia and Africa. The worldwide prevalence derived from regional PID registries, is estimated to be 1:8500 to 1:100000 for symptomatic patients.[1] The exact prevalence of PID in Africa is unknown. It is estimated that in Africa 988 000 adults and children have PID, of whom only 2500 have been diagnosed. Secondary immunodeficiency due to HIV infection, malnutrition, immunosuppressive therapy, measles, vitamin A deficiency, and exposure to aero-pollutants often overshadows the clinical recognition of primary immunodeficiency diseases in childhood and certainly accounts for the bulk of immunodeficiencies encountered in daily clinical practice in Africa. In addition, specialised immunological and genetic laboratory services, as well as clinical immunologists needed for the accurate diagnosis and treatment of PID are only available at a few referral centres in Africa.[2] As with many PID, affected infants have an increased susceptibility for infections and may have multiple visits to healthcare facilities with recurrent, unusual or non-resolving infections before a diagnosis is made.[3] Here follows a case of a young infant who was diagnosed with severe combined immunodeficiency, a life-threatening disease, in an under-resourced area of South Africa.

Case Presentation

A 4-month-old HIV unexposed uninfected male infant was referred from a district level hospital after a 2-week admission with a severe pneumonia. He had had no previous admissions and had received routine childhood immunisations at 6 and 10 weeks of age, which included live attenuated BCG, OPV and rotavirus vaccines. No growth faltering was noted. There was no history of parental consanguinity. At the referral hospital, the infant was not clinically improving on the first line antibiotics of ampicillin and gentamicin as well as empiric anti-tuberculous treatment. Prior to transfer he experienced increasing oxygen requirements and was subsequently

admitted to the intensive care unit at the tertiary hospital for ventilatory support in the form of high frequency oscillation ventilation. This was continued for the duration of his stay in hospital.

Multiple pathogens were identified including *Pseudomonas aeruginosa* on blood culture, *Pneumocystis jirovecii* detected via polymerase chain reaction (PCR) on a tracheal aspirate, a mildly elevated CMV viral load of 187 IU/ml and rotavirus on a stool sample. The infant was treated with meropenem, trimethoprim-sulfamethoxazole and gancyclovir. The respiratory viral panel as well as a rapid antigen test for SARS-CoV-2 infection were negative. The chest radiograph on admission showed extensive bilateral perihilar infiltrates, consistent with severe pneumonia.

The number of positive microbiological tests and the severity of the clinical presentation in an HIV uninfected child prompted investigation for a possible primary immunodeficiency. The white cell count during the admission was not raised and ranged from 1.5 to 6.2 x 10^9/L with a lymphocyte count persistently less than 3 x 10^9/L. There is a limited onsite laboratory at our hospital. Therefore, blood samples for immunological tests were couriered to a referral centre. The total immunoglobulin levels were sub-normal (IgG < 3 g/L, IgA <0.05 g/L and IgM <0.01 g/L). The lymphocyte subset analysis showed low T and B cells (total T cells (CD3) 75 cells/µL, helper T cells (CD4) 57 cells/µL, cytotoxic T cells (CD8) 13 cells/µL and B cells (CD19) 0 cells/µL) and the natural killer cell concentration (CD16/CD56) was normal for age.

A diagnosis of severe combined immunodeficiency (SCID) with the B-T-NK+ immunological phenotype was made. Testing for a genetic mutation was arranged through a private diagnostic laboratory in South Africa. A mutation in the recombination-activating gene (RAG 1) was detected, inherited by Mendelian X-linked inheritance. Intravenous immunoglobulin replacement therapy was commenced but unfortunately the infant demised a few days later due to progression of his pneumonia. Haematopoeitic stem cell transplantation (HSCT) was discussed but not pursued, as the infant failed to respond to the treatment administered for his severe pneumonia.

Discussion

Severe combined immunodeficiency is the severest form of the PID described. The infant with SCID may not always present with the clinical warning signs associated with PID[4] and the only presenting manifestation may be severe invasive infection. Unusual and unexpected infections, as in the patient above, should raise the suspicion of a PID. If not diagnosed early enough, the disease is fatal.

In developed countries, newborn screening for SCID is widely available.[5] T-cell receptor excision circles (TRECs) ± kappa-deleting recombination excision circles (KRECs) are measured using PCR. This detects T cell ± B cell lymphopenia at birth and allows for the earlier diagnosis and definitive treatment of SCID and other severe combined immunodeficiency diseases. Unfortunately, on the African continent, newborn screening is not widely available and the complications of disseminated disease due to live attenuated BCG and oral polio vaccines may be evident in infants with an undiagnosed SCID.[6]

There are now 430 single-gene inborn errors of immunity listed by the International Union of Immunological Sciences expert committee.[7] Table 1 outlines the immunological phenotypes of SCID classified with their corresponding genetic abnormality. Almost all are associated with low T cells with or without decreased B cells and/or natural killer (NK) cells. Except for common γ-chain deficiency which has X-linked inheritance pattern and activated Rac2 defects which are acquired by Mendelian autosomal dominant inheritance, the other SCID types are acquired by Mendelian autosomal recessive inheritance. Genetic counselling for future pregnancies should be included as part of the ongoing care. Parental consanguinity has been reported in 40-60% of cases in the countries of northern Africa.[1]

Table 1: Immunodeficiencies affecting cellular and humoral immunity. Severe combined immunodeficiencies defined by CD3 T cell lymphopaenia

Immunological phenotype	Genetic abnormality
Normal CD19+ cell concentration (T-B+ SCID)	
NK+	IL-7 receptor α-chain deficiency CD45 deficiency CD3δ, CD3ε and CD3ζ deficiencies Coronin-1A deficiency LAT deficiency
NK-	Common γ-chain deficiency Janus kinase-3 deficiency
Low CD19+ cell concentration (T-B- SCID)	
NK+	RAG-1 / RAG-2 deficiency DCLRE1C (Artemis) deficiency Adenosine deaminase deficiency DNA PKcs deficiency Cerunnos deficiency DNA ligase IV deficiency
NK-	Adenosine deaminase deficiency AK2 deficiency (reticular dysgenesis) Activated Rac2 defect

T cell lymphopaenia defined by CD3+ T cells < 3000 cells/µl, DNA PKcs deficiency = DNA-dependant protein kinase Catalytic subunit deficiency, DCLRE1C deficiency = DNA cross-link repair 1C deficiency, LAT = linker for activation of T cells RAG = recombination activation gene

Without early intervention with HSCT, enzyme replacement therapy, or gene therapy, a patient with SCID is unlikely to survive beyond the first 2 years of life due to secondary infections, failure to thrive, or immune dysregulation.[8] SCID was first successfully treated with allogenic HSCT more than 50 years ago with the overall 5-year survival rate now improving to more than 70%. Predictors for long term survival post-HSCT include early transplantation, good clinical condition at the time of the HSCT i.e. no active infection, and the underlying SCID phenotype or genotype. Infants in the United States less than 3.5 months who had HSCT were found to have better outcomes than those older than 3.5 months.[9] This was due to the absence of infection pre-transplantation. HSCT is available at only a few centres on the African continent, so with limited resources and the expense of the procedure and medications, even the small number of children diagnosed with SCID may not be able to access this life-saving intervention.

In the interim, children with SCID are best managed by a dedicated team with particular attention to infection control practises, good nutrition and hand hygiene, aggressive management of infections, antimicrobial prophylaxis (trimethoprim-sulfamethoxazole, fluconazole and acyclovir), avoiding administration of live vaccines and the administration of regular immunoglobulin replacement therapy. More detailed guidelines on the management of SCID and other PIDs is available.[3]

In conclusion, even though the burden of childhood HIV and malnutrition is high in Africa, there remains a group of the population who may have underlying PID. Recognising and treating these conditions relies on clinical suspicion, a diagnostic laboratory and access to specific treatment.

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PRESUMED HERPES SIMPLEX VIRUS ENCEPHALITIS

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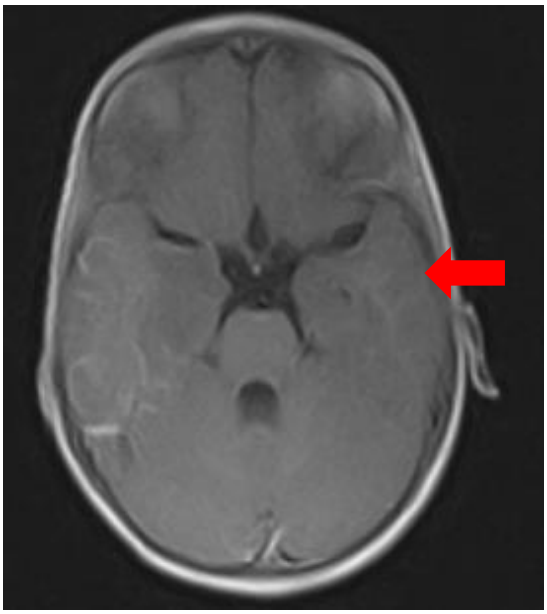
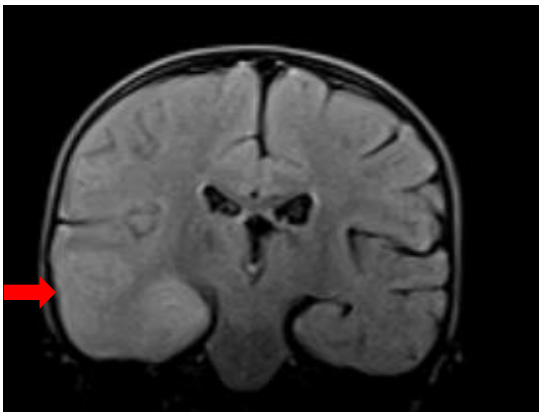
A two-years and two months old boy presented with high grade fever of seven days duration. This was accompanied by a few episodes of focal abnormal body movements lasting for less than five minutes. He also experienced few episodes of vomiting and loose stools and sleepiness with irritability if disturbed. He had no further symptoms. He had no sick contacts and was fully immunized for his age. On examination, he was acutely sick looking. He had a temperature record of 40.1^{o}C, pulse rate of 112 beats per minute, respiratory rate of 28 per minute and saturation of oxygen in room air of 92%. He had no rash and was fully conscious with no focal neurologic deficits and negative meningeal signs.

His complete blood count showed 9960 white blood cells/mm^3 with 69% neutrophils and 24% lymphocytes, platelets 290,000 cells/mm^3 and haemoglobin 15.1 g/dL. His blood film was negative for haemoparasites and his serum C-reactive protein was 0.9 mg/l. Despite a working diagnosis of meningitis his parents did not give consent for a lumbar puncture. Magnetic resonance imaging of the brain was done (see images below) which showed temporal lobe oedema and enhancement with effaced gyri suggesting HSV encephalitis.





The child was treated with 14 days of parenteral acyclovir and paracetamol suppositories as needed. His seizures decreased in frequency until the 2nd day of admission following which they disappeared. He also became afebrile after 2 days of admission. Upon discharge, he was feeding well, afebrile and playful.

Primary herpes simplex virus (HSV) infection enters the body via skin and mucosa, moving on to sensory ganglia and proceeding to skin and mucosa and in the case of disseminated disease, to viscera.[1] Eliciting a contact history in post-neonatal HSV encephalitis is often unsuccessful with usual presenting signs being fever, altered sensorium, focal seizures and vomiting.[2] Meningoencephalitis due to HSV can be a result of primary or recurrent HSV infection and has a predilection for the temporal lobes (better exhibited by MRI) in relation to its mechanism of entry.[3,4]

The most sensitive test for HSV encephalitis is cerebrospinal fluid (CSF) PCR.[1] Analysis of CSF often shows a lymphocyte predominant pleocytosis while late presentations are accompanied by a raised number of red blood cells in CSF due to necrotizing meningoencephalitis.[1] Treatment requires 14 – 21 days of parenteral acyclovir.[5] Late diagnosis, age of patient younger than 3 years and a Glasgow comma scale (GCS) score of 10 and below confer poor prognosis.[6]

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MISSED DIAGNOSIS OF RABIES IN A 4-YEAR-OLD BOY

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Abstract

Rabies is a fatal but preventable viral disease that spreads to people and pets if they are bitten or scratched by rabid animals. In many developing countries such as Nigeria, dogs still carry rabies. The case reported is that of a 4-year-old boy who presented with loose stools, drooling of saliva but no hydrophobia, hence the initial misdiagnosis. After much probing, the parents admitted that he had experienced a minor scratch from a stray dog three months prior to presentation which had been forgotten. His condition ran a very turbulent course necessitating intensive care, but he died 4 days after admission. Reverse-transcriptase PCR screening for rabies virus RNA was positive on serum and saliva.

Introduction

Rabies is a fatal disease in all mammals including humans. It is caused by rabies virus, a single-stranded RNA virus that belongs to the Lyssavirus genus of the Rhabdoviridae family of bullet-shaped viruses, which has a single–stranded RNA genome. Domestic dogs, cats, and rabbits, and wild animals, such as skunks, raccoons, and bats all have the potential to transfer the virus to humans via bites and scratches. According to the WHO, about 99% of deaths from rabies are caused by bites by rabid dogs.[1] Rabies is one of the oldest diseases known in medical science. Endemic rabies was confirmed in South Africa as far back as 18th century.[2]

In low- and middle-income countries (LMIC), up to 59,000 people die annually from rabies and bites from rabid dogs account for most of these deaths.[1] In countries like the United States, rabies is mostly found in wild animals such as bats, raccoons, skunks, and foxes. However, in many other countries including Nigeria, dogs still carry rabies. Human rabies cases result from viral introduction through broken skin or mucosa due to encounters with rabid animals, particularly bites as well as scratches and nicks. Aerosolised transmission and human to human transmission have also been documented.[2] Most rabies deaths in children are caused by dog bites.[3]

The rabies virus infects the central nervous system. From the site of entry, the virus is transported along afferent axons to the central nervous system where proliferation is followed by widespread distribution throughout the brain and spinal cord. Infection of the brain commonly leads to behavioural changes.

Rabies is one of the top 10 global infectious causes of mortality and one of the most amenable to available preventive measures. After a potential rabies exposure, the vaccine should be given as prophylaxis to avert the catastrophic manifestations of the disease which ultimately results in death. Rabies can be prevented by vaccinating pets, staying away from wildlife, and seeking medical care after potential exposures.[4] The death of a human from rabies is a missed opportunity to avert a catastrophe and should be viewed as a health system failure.

Most of the human rabies deaths occur in developing countries. Poor disease notification, limited awareness, false beliefs, poor access to healthcare and the prohibitive cost of pet vaccination and post-exposure vaccine and immunoglobulin all contribute to the high rate of the disease in LMIC.[2]

This report describes a boy with atypical features of rabies resulting in an initial diagnosis of organophosphate poisoning.

Case Presentation

Our patient was a 4-year-old boy who had been well until 4 days before presentation at the University College Hospital (UCH) Ibadan, when he developed nasal discharge with frequent sneezing. A day later, he started vomiting and experienced loose stools, high grade fever and insomnia.

At the onset of symptoms, the mother administered paracetamol, cough syrup and vitamin C. He was subsequently taken to a private hospital where IV quinine, IV augmentin, IM metoclopramide, IV frusemide and IV fluids were given with no significant improvement. He was considered to have severe sepsis with severe malaria. He was transferred to the UCH when his clinical condition deteriorated. He developed difficulty with breathing a few hours before admission in our hospital and later drooling of saliva, restlessness and confusion.

He presented to our facility in shock, was febrile and in severe respiratory distress. There was no hydrophobia, barking sounds or diaphoresis. There were no signs of meningeal irritation. On the third day of admission, he developed refractory seizures. His blood glucose level remained normal, a rapid malaria test was positive, and he had leukocytosis, neutrophilia and hypokalaemia. Urinalysis and liver function tests were normal. On echocardiography he had mild tricuspid regurgitation, pericardial effusion and poor systolic function (ejection fraction=47% and fractional shortening=23%). Blood and cerebrospinal fluid cultures were sterile.

The initial working diagnosis was severe sepsis with multiple organ dysfunction. Additionally, organophosphate poisoning was suspected on account of the excessive drooling, vomiting and diarrhoea. However, there was no pupillary constriction, neither could a history of organophosphate ingestion be substantiated. Before becoming sick he had visited a neighbour's house to play with his friend and for a while both were left unsupervised. Thus, it was not clear whether the patient had accidentally ingested a poison. Rabies was considered when after much probing, the parents reported that the patient had sustained a minor scratch on his leg from a stray dog in the neighbourhood 3 months earlier. At the time that it occurred, the scratch was thought to be inconsequential. With this history, the case was reported to the public health unit who visited the settlement. The dog owners claimed that the dog was alive, but they were unable to produce it for examination.

At admission, he was promptly resuscitated with appropriate fluids and the electrolyte imbalance was corrected. He received IV ceftriaxone. As per protocol for severe malaria, IV artesunate was administered. IV atropine was administered on account of the suspected organophosphate poisoning. He was admitted into the ICU and was mechanically ventilated. He also received dopamine, an adrenaline infusion and IV hydrocortisone. He was given IV phenobarbitone, IV diazepam, and IV phenytoin for refractory seizures as well as IM paraldehyde for breakthrough seizures. However, he succumbed to the illness 4 days after admission. Serum and saliva specimens obtained on the third day of admission were positive for rabies virus RNA by reverse-transcriptase polymerase chain reaction (RT-PCR). The confirmation of the positive rabies RT-PCR result was received 2 days after his demise. The parents declined post-mortem examination and no additional specimens could be collected.

Discussion

Our patient presented 3 months after a forgotten dog scratch. The omission of immediate administration of post exposure immunization was because it was thought to be seemingly innocuous. The child was bitten by a dog which had not been receiving appropriate care. The availability of vaccines for both animals and humans has led to a steep decline in rabies cases.[1] This case illustrates that in any scratch or bite from a stray dog where the vaccination history is unknown, extra caution is warranted and prophylaxis should be provided to prevent rabies. After exposure, where indicated, it is important to administer post exposure vaccination; the key to fighting the virus being a quick response.[5]

Post exposure prophylaxis (PEP) consists of a dose of human rabies immune globulin (HRIG) and rabies vaccine given on the day of the rabies exposure, and then a dose of vaccine given again on days 3, 7, and 14. For people who have never been vaccinated against rabies, post exposure prophylaxis (PEP) should always include administration of both HRIG and rabies vaccine. The combination of HRIG and vaccine is recommended for both bite and non-bite exposures, regardless of the interval between exposure and initiation of treatment. People who have been previously vaccinated or are receiving pre-exposure vaccination for rabies should only receive vaccine.[6]

His presentation was deemed atypical in that he did not present initially with classical symptoms such as hydrophobia, agitation, aerophobia, hallucinations, dysphagia, confusion, and aggressive behaviour until later during the admission. However, the case met the WHO case definition of human rabies which is "a subject presenting with an acute neurological syndrome (encephalitis) dominated by forms of hyperactivity (furious rabies) or paralytic signs (paralytic rabies) progressing to coma and death, usually by cardiac or respiratory failure, typically within 7–10 days after the first sign".[5] Furthermore, as a result of his age, it might have been difficult to establish the presence of other well-established signs and symptoms of rabies including paraesthesia or localised pain or dysphagia. One lesson here is that when children present with unusual behavioural manifestations with diagnostic dilemma, rabies should be suspected.[7] The incubation period of 3 months in our patient was somewhat long and was thought to explain the atypical manifestation without hydrophobia.[8] The majority of rabies cases present after an incubation period of one to 3 months.[5] A shorter incubation period is reported to be related to bite sites more proximal to the head, and deep or very severe wounds associated with the introduction of higher concentrations of the virus with a greater probability of disease development. Longer incubation periods have been documented.[1,8]

The dilemma in the diagnosis was further compounded by the delay in confirming the diagnosis in the laboratory. Laboratory support for molecular diagnosis of viral diseases is lacking in most LMIC as PCR is not available for routine care. In this patient, the analysis was carried out as part of a research collaboration with the investigating laboratory.

The child eventually succumbed to the illness four days after the onset of manifestation of the disease. Rabies has the highest case fatality of any known infection with a greater than 99% fatality rate if there is no intervention with prophylactic measures.[2] This case suggests awareness of rabies should be increased among the lay public and health professionals. Community engagement and education on responsible pet ownership, how to prevent dog bites and immediate care measures after a bite are important. It has also been advocated that a comprehensive, strategic, and targeted control and prevention approach be implemented with collaboration from human, animal, and environmental health disciplines at local, national, and global levels.[9,10]

Conclusion

This case report of rabies in a child emphasizes the importance of public awareness about transmission and prevention as there is no established specific therapy for rabies. Furthermore, when children present with unusual behavioural manifestations rabies should be suspected.

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AN ISOLATED INTRACRANIAL HYDATID CYST

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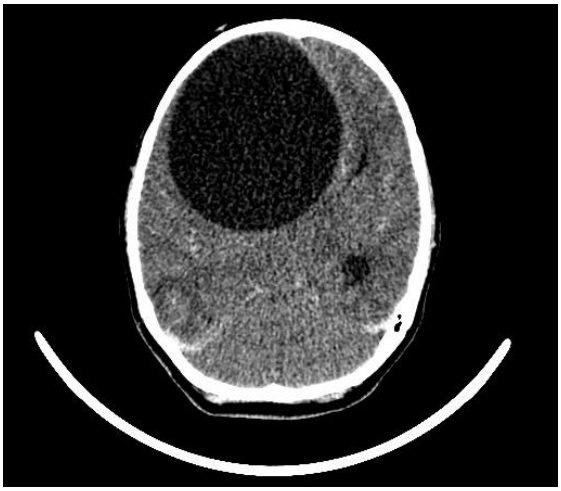
A previously well, 12-year-old boy who is HIV negative, presented with a seven-month history of progressively worsening headaches and new-onset generalized tonic-clonic seizures. His general practitioner initiated anti-epileptics after his second episode of seizures. In the 72 hours before the current presentation, the patient had several episodes of staring blankly, vomiting and an altered level of consciousness. Notably, on history he acknowledged spending holidays with his grandparents in a rural area, with free-roaming farm animals. On examination, he was alert and orientated, afebrile with normal vital signs. The neurological examination was mostly unremarkable. Uncontrasted computed tomography of the brain showed a large cystic lesion occupying most of the frontal lobe with marked midline shift and effacement of basal cisterns. Further radiological investigations ruled out other cystic lesions in the chest and abdomen. Differential diagnoses included an arachnoid cyst, cystic tumour, porencephalic cyst, neurocysticercosis and a hydatid cyst. A tentative diagnosis of an isolated intracranial hydatid cyst was made. Albendazole was commenced, and he underwent surgery. A large, unruptured hydatid cyst was removed, confirming the diagnosis of hydatid disease.



PUBLICATION WATCH

IMMUNOLOGICAL INSIGHTS DURING THE FIRST 12 MONTHS OF COVID-19

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The paper by Carvalho, Kramer and Iwasaki reviews important immunological discoveries during the first year of the COVID-19 pandemic, culminating in the development of efficacious vaccines against SARS-CoV-2.[1] This "Publication Watch" review highlights a few of many immunological advances that are discussed in this paper.

One of the early findings was that SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) as a receptor to gain entry to host cells. The interaction between SARS-CoV-2 and ACE2 is mediated by the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. Subsequent studies have shown that the RBD is the target of many neutralising antibodies induced by SARS-CoV-2 infection and that these neutralising antibodies prevent the virus from interacting with the human ACE2. Thus, the spike protein of SARS-CoV-2 became the prime target for vaccine development. Vaccine development proceeded with alacrity. The first clinical studies with a vaccine targeting the spike protein, an mRNA vaccine, commenced in March 2020, approximately 2 months after the genomic sequencing of SARS-CoV-2 was completed.

The pathogenesis of severe COVID-19 was another important research area. Transcriptional profiling showed that when the host response fails to initiate strong early type I and type III interferon responses sustained viral replication occurs leading to serious SARS-CoV-2 infection. The pivotal role played by type I interferon induction was confirmed in two seminal studies that showed that either inborn errors in interferon signaling or the induction of neutralising antibodies to type I interferons predispose SARS-CoV-2-infected patients to life-threatening COVID-19. These two papers were discussed in a previous edition of Publication Watch.[2] Similarities

between severe COVID-19 and the systemic inflammatory syndromes of haemophagocytic lymphohistiocytosis and cytokine release syndrome made the IL-6 pathway a focus for intervention studies involving monoclonal antibodies that target the IL-6 receptor such as tocilizumab.

Initially children were thought to experience only mild or asymptomatic infections. However, in April and May 2020 the first descriptions of multisystem inflammatory syndrome in children (MIS-C) started to appear in the peer-review literature, in a subset of children and adolescents with current or previous SARS-CoV-2 infection. This new syndrome to some extent overlaps with the manifestations and inflammatory response of Kawasaki disease (KD). However, studies revealed differences in the immunopathogenesis of MIS-C and KD, notably, IL-17A drives the cytokine storm of KD but not MIS-C, while patients with MIS-C develop a distinct pattern of autoantibodies suggesting the involvement of autoimmunity in the immunopathology of MIS-C.

The emergence of virus variants in November and December 2020 started another line of research and discoveries. The South African-origin variant, B.1.351 has mutations at positions 501, 417 and 484 in the RBD of the gene encoding the spike protein which results in reduced neutralisation by antibodies induced by certain vaccines.

From November 2020 onwards, phase III trials showed that several vaccines were highly efficacious against symptomatic SARS-CoV-2 infection.

Clinicians, including ID fellows interested in the immunology of COVID-19 should find this paper interesting.

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POLIO ERADICATION STRATEGY 2022-2026

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A recent publication describes the strategy of the Global Polio Eradication Initiative (GPEI) for the next five years. This strategy includes two goals for stopping the circulation of polioviruses, the steps for realising these goals and the anticipated timelines.[1]

The first goal is to permanently interrupt all poliovirus transmission in the two remaining endemic countries, Afghanistan and Pakistan, by the end of 2023. These are the only two countries where wild poliovirus type 1 (WPV1) has not been interrupted. Additionally, vaccine-derived polio virus type 2 (cVDPV2) now co-circulates with WPV1 in both countries. In 2020, these two countries experienced 140 and 443 cases of polio caused by WPV1 and cVDPV2, respectively.

The second goal is to stop cVDPV transmission and prevent outbreaks in non-endemic countries, by the end of 2023 and 2028 for cVDPV2 and cVDPV1 & 3, respectively. cVDPV2 is the main cause of cVDPV transmission. In 2020, 1059 cases of paralytic polio caused by cVDPV2 were reported from endemic and non-endemic countries, of which 614 (58%) cases occurred in African countries. The planned steps to achieve this goal include (1) the deployment of novel oral poliovirus vaccine type 2 (nOPV2) designed to be more genetically stable than the existing OPV2 vaccine and thus less inclined to regain neurovirulence and seed new outbreaks of cVDPV2, and (2) the development and utilisation of novel OPV vaccines directed against type 1 and type 3 polio viruses.

The timelines of the new strategy appear ambitious given that previous polio strategies have not achieved global eradication, and the social, political and community challenges that have undermined previous eradication strategies persist. Experts have recently argued for a change in the overall global strategy, citing several cogent reasons why a strategy focussing on eradicating the virus has not worked. Instead, they propose that the focus should be on eliminating the disease (paralytic poliomyelitis) by maintaining the highest possible rates of population immunity through comprehensive immunisation.[2]

The progress of implementing the 2022-2026 strategy and its impact will be watched with interest.

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