Africa's response to childhood infection

The AfSPID BULLETIN

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EDITOR'S COMMENT

Dear Colleagues

I welcome you to this 12th edition of the AfSPID Bulletin.

COVID-19 continues to take the centre stage of healthcare discussion, having swept through the world with first and second waves. A recent prospective systematic postmortem surveillance study from Zambia had tried to debunk the "Africa paradox" by giving some evidence on possible under-reporting of SARS-COV-2 in the setting.[1] Thus, Africa has not been spared in the widespread community transmission of the virus. The case of Africa and COVID-19 is peculiar in that most of its countries are limited by less robust health systems with suboptimal testing, reporting and surveillance for the virus.

The pandemic has shaped not only the health but economic and social landscapes either directly or indirectly. The light at the end of the tunnel of this enigma is the emergency authorisation granted for the use of the SARS-CoV-2 vaccines. Governments in many countries of the world have put plans in place to immunise their citizenry. In the African continent, South Africa flagged off its immunisation exercise a couple of weeks ago while countries such as Ghana, Ivory Coast and Nigeria follow closely behind in the vaccine roll out.

The breakthrough with COVID-19 vaccines is more than welcome. In terms of vaccine administration and priorities, most countries are prioritising frontline health workers and the elderly as expected. It is important that vaccine hesitancy is tackled to ensure optimal uptake to achieve the much-desired herd immunity. Immunising healthcare workers will not only reduce morbidity and mortality among them, it will also demonstrate acceptance by example. Added to this, communication campaigns must be carried out to facilitate buy-in by the community. Research and surveillance are recommended to further address much of the issues that are still unclear concerning the SARS-CoV-2. One such unanswered question is whether the new variants of the virus will be covered by the immunity elicited by current vaccines.

In this issue of the bulletin, Ombeva Malande examines the bottlenecks and opportunities for COVID-19 vaccines in Africa. The World Health Organization (WHO) and other international organisations, through the United Nations backed Covid-19 vaccine Global Access (COVAX) facility are working to reduce the inequality in vaccine procurement and distribution to less developed countries.

COVID-19 may have joined the league of vaccine preventable diseases (VPDs); but how are the other VPDs faring in the continent? Malande reports on yellow fever in Uganda which continues to experience repeated outbreaks. Tunde Ogunbosi and colleagues reflect on the lingering problem of diphtheria with its diagnostic and therapeutic challenges in Nigeria.

Indirectly, the virus is shaping the landscape of various other health programmes. For instance, in the face of the pandemic, how has the HIV programme in children fared? A commentary from Jocyelyn Dame examines this issue in Ghana. Continuing with Paediatric HIV, Damalie Nalwanga and Victor Musiime will take us through recent advances in paediatric HIV research with emphasis on the implications for clinical practice.

I hope you will find these reports interesting. Enjoy!

Regina Oladokun
Deputy Editor

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SOCIETY NEWS

12TH WSPID CONFERENCE

Development of the programme for the 12th WSPID conference is in full swing. The International Scientific Committee is currently holding regular conference calls to build the scientific programme. The conference dates have been changed to 22 – 24 February 2022. The conference format is still under discussion.

APPOINTMENT OF SIX ASSOCIATE EDITORS

To strengthen the newsletter six associate editors have been appointed. They will support the editor in managing the new case reports & medical images section of the newsletter, and assist the editor & deputy-editor in sourcing commentaries/reviews and research articles from their respective regions.

Figure 1: New associate editors: Dr Harsha Lochan (top left), Associate Professor Heloise Buys (top centre), Dr Babatunde Ogunbosi (top right), Dr Olubukola Idoko (bottom left), Dr Tinsae Alemayehu (bottom centre) and Dr Oliver Ombeva Malande (bottom right)

TWITTER ACCOUNT

To increase the visibility of the AfSPID Bulletin a twitter account was opened for AfSPID by Tinsae Alemayehu and Olubukola (Bukky) Idoko in December 2020, twitter address: @afspid

NEWSLETTER CIRCULATION

One of the decisions taken at the editorial board meeting in November 2020 was to estimate the circulation of the AfSPID Bulletin. Thus, a survey of the members of the AfSPID EXCO and editorial board of the AfSPID Bulletin was recently undertaken. As of 2 March 2021, between 2400 and 2450 individuals in 27 African and 8 non-African countries receive the newsletter. Nigeria, Kenya, Uganda, Tanzania, Ghana, the Gambia, Ethiopia and South Africa are the countries most represented in the current distribution list.

These initial estimates provide a reference for future circulation surveys. It should also assist us to rebalance the composition of the editorial board of the AfSPID Bulletin by actively recruiting members from under-represented countries.

COMMENTARIES & REVIEWS

COVID-19 – WHICH WAY AFRICA?

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Background

COVID-19 a novel viral disease caused by Sars-COV-2 virus is arguably the worst pandemic of the 21st century with over 116 million people so far infected, over 2.5 million deaths and over 21 million currently active cases worldwide.[1] Africa currently has over 3.9 million confirmed cases and over 105,000 deaths, with the highest percentage occurring in South Africa.[1] The emergence of a new variant in South Africa, that is thought to be more infectious than the original strain has increased concern that new surges of the disease may occur across Africa from this strain. The strict lockdowns associated with COVID-19 had a negative effect on routine childhood immunisation globally with more than half (53% of 129) of reporting countries experiencing moderate-to-severe disruptions, or a total vaccine service disruption in March-April 2020.[2] There are concerns regarding resurgence of measles, possible reversal of gains in polio control, and halting or delay in introduction of new vaccines. These concerns resulted in the call to action by the World Health Organization (WHO) for all countries to make a joint effort to deliver routine immunisations as an essential service during the COVID-19 pandemic, and for countries to plan

and develop strategies to increase acceptance and demand for vaccination.[2]

COVID-19 Vaccine for Africa – Bottlenecks and opportunities

Considerable effort has been made to ensure success of containment measures and production of effective COVID-19 vaccines. Five main COVID-19 vaccines are now approved and in use, including one produced by a collaboration between Pfizer and BioNTech; one by Moderna, a third through a collaboration between University of Oxford and the British-Swedish company AstraZeneca, and two inactivated vaccines by Sinopharm and Sinovac.[3] Furthermore, 89 preclinical vaccines are under investigation in animals, a further 84 vaccine candidates are in human clinical trials (37 in Phase 1, 27 in phase 2, 20 in Phase 3), 6 are authorised in early or limited use, 5 have full approval and 4 had the clinical trials abandoned.[4] The excitement and celebrations that greeted the discovery of COVID-19 vaccines have been tempered to a large part by very high demand that far outweighs supply, high cost of vaccines, a disease that rapidly spreads faster than the rate of vaccine manufacture, emergence of new strains of the virus and vaccine hesitancy.

The World Health Organization (WHO) defines vaccine hesitancy as "a delay in the acceptance of or the refusal of vaccines by communities despite the availability of vaccination services".[5] The WHO's Strategic Advisory Group of Experts (SAGE) has a working group on vaccine hesitancy that identified 3 main factors thought to underly vaccine hesitancy. These factors are included in the 3C's model described as: 1. Confidence (where there is no trust in vaccines and in healthcare providers of vaccines); 2. Complacency (where target groups do not perceive the need for vaccination or they do not value vaccination) and 3. Convenience (deals with access to vaccines and access to vaccination services).[5] Vaccine hesitancy ranges from delaying vaccination to refusing vaccination - a complex and context-specific, varying across time, place and vaccines and can be expressed by anybody, including scientists, religious leaders and healthcare workers.[6]

The COVID-19 pandemic has contributed to rising vaccine hesitancy due to misinformation that has been spread on social media, leading to mistrust, to complacency and to a decrease in vaccine confidence.[7] Recent reports indicate that anti-vaxxer groups have increased their social media presence and are followed by more than 7.8 million people since 2019.[8] Social media is extremely damaging, since most subscribers tend to indiscriminately share every message they receive, without first checking if it is true or false. More recently, many social media platforms are beginning to take steps to remove or block or ban misleading content, and its promoters, much as anti-vaxxers still find other ways to share or distribute misinformation. COVID-19 presents a unique opportunity to develop and test innovative context-specific communication interventions that incorporate the latest behavioural change methodologies. These include better tailoring of pro-vaccine messages, social mobilisation, enhanced outreach programmes and catch-up immunisation campaigns.[9]

Africa risks being left behind in the race to roll out COVID-19 vaccines, yet more than 226 million doses of COVID-19 vaccines have already been administered in 121 countries. Guinea was the first poor African country that rolled out the vaccine to about 25 people and Seychelles, a higher income country has rolled out a national COVID-19 vaccination campaign.[10] The Seychelles, Morocco and Egypt are administering the Chinese-made Sinopharm vaccine and Guinea, the Russian Sputnik V. The COVAX facility refers to a global initiative that is working to provide COVID-19 vaccines to 92 low and middle-income countries; that was formed by the Coalition for Epidemic Preparedness Innovations (CEPI), the GAVI alliance and the WHO.[3] This initiative has secured about 2 billion doses of COVID-19 vaccine from five vaccine producers, with the option for more than 1 billion additional doses; through donations and deals with manufacturers that have brought us to almost 2 billion doses secured. The coalition has committed to providing vaccines for at least 20% of the population per country by the end of 2021 through provision of 600 million doses in phases. On the other hand, a coalition of organisations and activists referred to as "The People's Vaccine Alliance" found that "rich nations representing just 14% of the world's population had bought up more than half (53%) of all the most promising vaccines." Canada for example was reported by data company Infinity, to have secured "enough doses to vaccinate each Canadian five times". This finding has shown just how hard it will be for most poor African countries to secure anywhere near enough vaccines for its citizens.

With their wide experience in procuring vaccines for over 100 countries, UNICEF has started supporting coordination, procurement, international freight and the delivery of COVID-19 vaccines under the COVAX Facility. Already UNICEF is building stocks for one billion syringes and the purchase of about 10 million safety boxes to ensure needles and syringes are disposed safely immediately after use. It is encouraging that all the 54 countries in Africa have expressed interest to be involved in the COVAX Facility. In the arrangement, 8 countries classified as higher and middle-income will self-finance their participation in the facility, whereas the low and lower-middle income countries will be able to access the COVID-19 vaccines for free. To speed up the process, the COVAX vaccines have been granted WHO Emergency Use Listing authorisation and undergone strict safety and effectiveness validation. To finance these vaccines, the COVAX facility has raised about US $6 billion from pledges, but requires a further US $2.8 billion to achieve the 2021 targets.

The COVAX facility is based on the plan that each vaccine recipient will have to receive two doses of vaccine disbursed in phases, with the initial 30 million vaccine doses expected to begin reaching counties by March. These vaccines will mainly target about 3% of the general population, with priority being given to healthcare workers first, then expanded to the elderly and people with pre-existing conditions. While these plans offer hope, the timelines could change depending on how fast the manufacturers produce the required vaccines to meet the demand. Besides, transport and cold chain capacity remains a big challenge in many African countries. The WHO, UNICEF and GAVI alliance are already working with and providing technical support for countries to make sure they are ready to receive, store, distribute and administer the vaccines. The WHO has an introduction readiness assessment tool, which benchmarks countries at an 80% target. Most African countries are at 42% average readiness for campaigns for mass vaccination, an improvement on 33% seen about two months ago.

Another opportunity for Africa to get vaccines is through the Africa Union's vaccine acquisition task force, which has secured 270 million COVID-19 vaccines for African nations.[12] These vaccines will be supplied by Pfizer/BionTech, Johnson & Johnson and AstraZeneca - through an independent license with the Serum Institute of India. John Nkengasong, the director of Africa Centres for Disease Control and Prevention, described this initiative as a significant achievement. This facility, unlike the COVAX arrangement is strictly for African nations. The

purchases of the vaccines will be made through the Africa Medical Supplies Platform, together with the African Export-Import Bank which will help countries to secure financing for the vaccines by providing advance commitment guarantees of up to $2 billion to the manufacturers.[12] After delivery of vaccines, countries will either pay for the vaccines using domestic resources or could opt for a five-year instalment payment plan arranged through the bank. The challenge is that even with both COVAX and this AU initiative that raises available doses to 870 million, the combined efforts still fall short of the overall African Union's target of vaccinating over 60% of the continent's total population, to approach the threshold that can provide herd immunity and normalise lives for people across Africa.

There is need to employ a full array of different role players and financers when it comes to mobilisation for COVID-19 vaccination for Africa.[9] All countries will need to pull together their full capacity of government infrastructure to establish plans and structures across government departments for financing and vaccine roll out.[9] Non-governmental organisations will have to play their role to reach communities, taking advantage of their existing networks and the high levels of trust that some enjoy, and leverage this while functioning as advocates for and networks for COVID-19 vaccine uptake.[9] The civil society, especially community-based organisations, religious groups, community volunteers, and cultural institutions will need to be used to promote and embrace the new vaccines. The use of private-public partnerships may help to strengthen the weak and strained health systems across Africa, as well as help build partnerships with industry that can co-fund the purchase of the vaccines and cold chain infrastructure in African countries.[9] The WHO recommends a pre-emptive pro-vaccination strategy to deal with hesitancy to COVID-19 vaccines. This approach psychologically immunises the public and communities against misinformation by proactively reporting trusted vaccine information,[5] and corrects information from reputable sources while encouraging others to share correct information to drown out all the misinformation while desisting from sharing fake news or misinformation, especially on social media.

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CONTROL OF OUTBREAKS CAUSED BY DRUG RESISTANT BACTERIA IN A NEONATAL UNIT: A REVIEW

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Background

Globally, over two million neonatal deaths (deaths in the first 28 days of life) occur annually.[1,2] About a third of these are of infectious origin and commonly occur in sub-Saharan Africa, a region characterised by weak health systems and constrained resources.[3] The existence of bacterial organisms that have become resistant to existing antimicrobials is an emerging public health problem.[4] Antibiotic-resistant bacteria survive despite being exposed to an adequate concentration of an antimicrobial compound for a duration that was previously known to be lethal to them. Antibiotic resistance may be as a result of inherent characteristics or through the acquisition of adaptive mechanisms and can be considered as being mono (resistant to a single antimicrobial drug), multi (resistant to at least one agent in three or more classes of antimicrobial drugs), pan (resistant to all classes of antimicrobial drugs) or extensive (susceptible to only two or fewer classes of drugs).[5] Resistant bacterial infection can occur as an outbreak in the neonatal intensive care unit (NICU). In the context of a NICU, "an outbreak occurs when two or more sterile site isolates of the same species, with the same antibiogram, from different babies (not twins) are obtained within the space of two weeks".[6]This review appraises the evidence on how outbreaks in a NICU caused by resistant bacteria can be controlled in resource constrained African settings.

Literature search strategy

We searched the university of Oxford library, using its search engine SOLO (Search Oxford Libraries Online)

which contains Pubmed, Cochrane Library and Medline using search terms “newborn” OR “neonate”, AND “sub-Saharan Africa” AND “outbreak” OR “health-care associated infection” AND “antibiotic-resistant” OR “multidrug -resistant” for papers published in English text from 2004 to 2021. We also searched reference lists of articles and selected relevant articles. Additional articles were provided by co-authors.

Epidemiology of outbreaks caused by resistant bacterial infections

Resistant strains of bacteria have been implicated in more than 15.0% of NICU outbreaks worldwide.[7] Multiple studies have identified antibiotic-resistant Gram negative organisms as major isolates in NICU outbreaks.[8-10] For example, a review of 276 NICU outbreaks affecting 5,718 patients reported extended spectrum beta-lactamase (ESBL) producing *Klebsiella pneumoniae* as the most common aetiologic agent.[11] Likewise, a retrospective review of 284 laboratory confirmed bloodstream neonatal infections in two large NICUs located in sub-Saharan Africa found the dominant pathogen to be *Klebsiella pneumoniae* of which 60.7% were ESBL producers.[3] In contrast, an 8 year review found Gram-positive antibiotic-resistant isolates such as Methicillin Resistant *Staphylococcus aureus* (MRSA) and Vancomycin Resistant *Enterococci* (VRE) to be more common than Gram-negative organisms.[12]

Dissimilarities in isolates obtained in resource-constraint settings and resource-rich countries have been observed and may be attributed to recognised differences in the age of viability (ability of the foetus to survive outside the uterus). Thus, in the latter, the tendency for prolonged hospital stay, parenteral nutrition, use of invasive devices including ventilators and catheters may result in the increased isolation of Gram-positive organisms such as coagulase positive *Staphylococcus aureus*. On the other hand, it may also be that in sub-Saharan Africa, existing peculiarities such as predominance of home deliveries, lack of skilled birth attendance with limitations in laboratory and clinical surveillance have led to an under-reporting of cases of Gram-positive antibiotic-resistant organisms.[13] Thus, it may be that differences in the epidemiology of antibiotic-resistant pathogens depends on the strength of health systems and can change with time.

Risk factors for outbreaks

Neonates, on account of their relative immune deficiency serve as vulnerable hosts to bacterial infections. This vulnerability is mainly found among neonates that are considered high-risk; that is they are either small for gestational age and/or have a low birth weight in addition to other co-morbidities.[14] Such neonates tend to have a prolonged hospital stay, with the attendant risk of being exposed to resistant pathogens.

A non-exhaustive overview of some of these pathogens and their mechanism of drug resistance based on a review of literature is shown in Table 1.

These resistant strains may develop due to an over-prescription of antibiotics (especially broad-spectrum antibiotics given for long duration) and ineffective or non-existent infection control programmes in NICUs.[6]

Multicentre studies have recognised the NICU environment as a reservoir of infections.[3,24] To comprehend why this is so, consider that a NICU is an area designated to provide special care to high-risk neonates and often carries out this function with the aid of invasive devices and the healthcare workers (HCW) who operate them. In this review, the NICU environment will be considered as a tripartite made up of the structures, devices, and HCW/visitors which can all serve as a niche for antibiotic-resistant bacteria to thrive. Invasive devices such as suction machines, catheters (peripheral and central) and endotracheal tubes may become coated with biofilms formed by MRSA, *Pseudomonas aureginosa* and *ESBL Escherichia coli*.[15,21,25] Outbreak occurrence have been found to be increased with prolonged use of such devices.[15] For example, a systemic review of 23 studies found 15.0% of device derived isolates in neonatal units to be MRSA.[26] Additionally, vancomycin resistant *Enterococcus* (VRE) have also been isolated on hospital surfaces due to their inherent ability to remain viable on inanimate objects as fomites.[27] In various reviews, neonatal unit design frameworks that failed to consider appropriate: sink to bed ratios, spacing between cots, waste disposal siting, a centralised feed preparation area and single family rooms, environmental screening of such poorly designed NICUs increased the risk of common source outbreaks.[6,28-30]

Table 1: Major antimicrobial resistant organisms in NICUs

Major neonatal bacterial pathogens	Drug resistant variants	Mechanism of resistance	Drug of choice
Gram-positive organisms			
Staphylococcus aureus[15,16]	MRSA	Alteration of binding site	Vancomycin, Ortavancin or Linezolid
	VRSA	Enzymatic inactivation	Oritavancin
Enterococcus species[17]	VRE	Plasmid encoded beta-lactamase mutation	Linezolid or Ortavancin
Streptococcus agalactiae (GBS)	Clindamycin-resistance		Vancomycin
Gram-negative organisms			
Escherichia coli[18]	ESBL-producing organisms	Transferable plasmid mediated resistance genes	Meropenem or Aztreonam
Klebsiella pneumoniae[19]			
Serratia marcescens[20]			
Pseudomonas aeruginosa[21,22]	Carbapenem-resistant strains	Efflux pumps, horizontal resistant gene transfer or mutations	Doripenem, Plazomicin or POL700
Acinetobacter baumannii[23]		Plasmid or chromosomal encoded carbapenemases	Limited

MRSA=Methicillin-resistant *Staphylococcus aureus, VRSA*=Vancomycin resistant *Staphylococcus aureus, VRE*=Vancomycin resistant *Enterococcus, ESBL=extended spectrum beta-lactamase*

Transmissible antibiotic-resistant organisms derived from personal belongings of HCW/visitors, door knobs, walls of hospital settings, faecal contaminants for example, multi-drug resistant (MDR) *Escherichia coli* acquired during bathing/nappy change and invasive procedures may colonise HCW/visitors and subsequently result in outbreaks within NICUs.[31-33] Such transmission is commonly encountered in sub-Saharan Africa due to understaffed and overcrowded neonatal units that are characterised by long shifts.[3,23]

Outbreak control processes

Multifaceted interventions aimed at reducing outbreak risk factors in NICUs have been studied.[6] These include personal protective equipment (PPE), hand hygiene

interventions, antimicrobial stewardship, active surveillance, care bundles and antimicrobial locks.[15]

Grading of evidence

In 2019, The Centre for Disease Control (CDC) and Healthcare Infection Control Practice (HICPAC) revised its grading scheme for categorising infection control and prevention strategies. The updated recommendation categorisation scheme includes (1) recommendation categories, (2) guidelines for justifying the choice of recommendation strength and (3) guidelines for classifying the level of confidence in the evidence on which the recommendation is based.[34] There exists no such grading for use in Africa, as such this review will use the CDC/HIPAC grading to assess infection prevention and control strategies.

Personal protective equipment

Limited evidence from outcome studies have resulted in classifying PPE such as gloves, goggles and gowns as a conditional recommendation.[34]

Single use devices are recommended, but where this is not feasible disinfectants should be used to clean equipment. For example, hydrogen peroxide vapour as a disinfectant has been used to control outbreaks of multi-drug resistant environmental organisms such as *Serratia spp.* and *Pseudomonas spp*.[64]

Hand Hygiene

Hand hygiene as described by the World Health Organisation (WHO) involves hand washing and drying, avoidance of artificial nails and rings, and disinfection with alcohol-based rub.[35] Non-adherence to hand hygiene practices led to an outbreak of ESBL-producing *Klebsiella pneumoniae* caused by transient carriage of the bacterium on artificial nails.[36,37] Similarly, another study described an outbreak of MDR *Serratia marcescens* among 15 neonates attributed to HCW non-adherence to hand hygiene.[10] In a bid to control such outbreaks, the effect of hand hygiene as an outbreak control strategy has been studied by Pessoa-Silva *et al.* These researchers evaluated the WHO five moments of hand hygiene strategy in a quasi-experimental study and demonstrated a 60.0% risk reduction in bacterial infection acquisition among a high-risk population of neonates.[38] Similarly, Pittet *et al*. implemented a series of hand hygiene campaigns and observed a significant decrease in MRSA transmission rates from 2.16 to 0.93 episodes per 10,000 patient-days.[39] These findings have helped shaped a consensus view that was used by the CDC and HIPAC to recommend hand hygiene (grade IB evidence) for preventing and controlling of outbreaks in NICUs.

Care bundles

Hand hygiene as a stand-alone preventive strategy may often not eliminate bacterial contamination.[21,40] For this reason the concept of "care bundles" has been introduced. These are evidence based infection control protocols that include combinations of interventions, designed to complement each other.[41] Care bundles have been found to effectively reduce the risk of emergence and transmission of resistant pathogens in ventilator–associated pneumonia (VAP), central line-associated blood stream infection (CLABSI) and antibiotic stewardship programmes (ASP).[41-43]

Because of the recognised risk of bacterial contamination of central lines (higher risk with umbilical catheters), care bundles that are concerned with the insertion, maintenance, and removal of percutaneous intravascular devices serve as the cornerstone of CLABSI prevention, Table 2.

Table 2: Grading of components of central-line bundle

Bundles	**Components**	**CDC / HICPAC grade**
Insertion	Hand hygiene Maximal sterile barrier Skin disinfection Sterile gauze dressing Use of checklist	Recommended
Maintenance	Hand hygiene Daily inspection Disinfection Aseptic techniques	Recommended
Removal	Hand hygiene Maximal sterile barrier Skin disinfection Minimise duration of use	Recommended

Adapted from references 34 and 44.

Central-line antimicrobial locks

A prospective randomised trial found that using antimicrobial locks that contained heparinised saline and vancomycin served as prophylaxis against CLABSI.[45] The use of antimicrobial locks as a component of central-line care is graded as II evidence.[46]

Ventilator associated pneumonia care bundles

After 2 days on a ventilator, biofilm containing resistant organisms like MRSA derived from the oral cavity can migrate down an endotracheal or tracheostomy tube connected to the ventilator and result in VAP.[47] In affected neonates, VAP is associated with increased morbidity and mortality. VAP bundle elements and their corresponding CDC evidence grading in parenthesis include: hand hygiene (IA), barrier nursing (IA), elevation of the head of the bed (II), oral hygiene (II), regular closed suctioning, cleaning of the ventilator circuit, and assessment for prompt extubation (IB) have been implemented to prevent VAP.[48,49] A prospective cohort study reported a 63.0% reduction in VAP after initiation of care bundles. Although this reduction was not statistically significant, the study's findings were consistent with findings of a systemic review that included eight non-randomized interventional studies.[50,51]

Antibiotic stewardship programmes

The subtle presentation and devastating effects of neonatal blood stream infections often necessitate the commencement of antibiotic therapy despite pending blood cultures.[52] As a consequence of this unavoidable empiric treatment, inappropriate use of antibiotics that can deplete normal bacterial flora of neonates occurs, this leads to uninhibited proliferation of emergent resistant strains.[53,54] Though antibiotics like vancomycin can be used to treat antibiotic-resistant organisms like MRSA, adverse effects such as kidney failure following its use and the inherent risk of the organism evolving to become vancomycin resistant and cause more devastating outbreaks necessitates rational use of the drug.[16,55,56] To curtail this, ASP have been developed, they aim to ensure "appropriate selection, dosing, route of administration and duration of antimicrobial treatment that would result in the best clinical outcome for the treatment or prevention of infection with minimal toxicity to patient and minimal

impact on the emergence of resistance".[57] A systematic review, that comprised 14 observational (10 cohort and 4 case control) studies demonstrated the negative effects of inappropriate antibiotic use and the importance of ASP as a strategy for outbreak prevention and control. In terms of evidence based hierarchy, the observational "*low quality*" methodologies used in the studies for the review would lead to classification of ASP as a CDC/HIPAC grade II level evidence.[58] An appraisal and grading of each individual component of the ASP strategy though difficult to undertake, may reveal the relative effectiveness of each component.[43] For example, accumulating evidence suggests the importance of feedback mechanisms in behavioural change. Such change has effectively improved adherence to guidelines and reduced numbers of cases of inappropriate antibiotic use. Figure 1 outlines the basic mechanisms of ASP.[4]

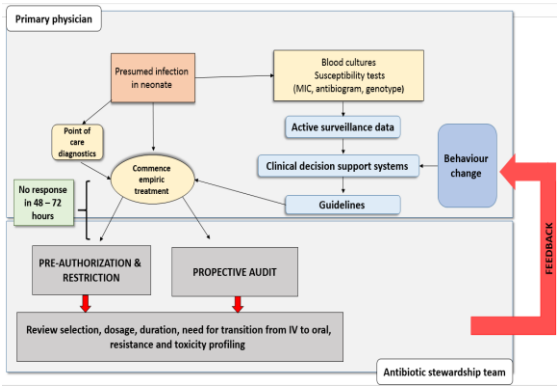

Figure 1: Basic mechanisms of antibiotic stewardship programmes. Yellow boxes depict clinical actions to be taken, blue boxes show non-clinical activities and grey boxes signify actions taken by antimicrobial stewardship teams. Adapted from reference 4.

In the event of an outbreak a multidisciplinary response team (microbiologist, epidemiologist, infectious disease clinician) should be established with terms of reference and standard operating procedures to confirm the existence of the outbreak and implement control.[59] Outbreak confirmation is mainly achieved using surveillance and audit data. Clinical and laboratory surveillance ensures continuous scrutiny of risk factors, pathogens and antimicrobials in NICUs.[60] Analysed data from surveillance reports help determine if the number of cases with antimicrobial-resistant infections has exceeded the norm and aids in line-listing.[6] Mathematical models may aid in delineating likely causes and progression of such outbreaks.[61,62] On the other hand, audits help ensure that best practices are adhered to, by comparing current practices with evidence-based recommendations and giving room for educative feedbacks. [4]

In verifying the existence of an outbreak specimens for blood culture, susceptibility tests and molecular techniques such as polymerase chain reaction (PCR) or whole genomic sequencing are recommended to confirm an outbreak. Such tests help rule out sample contamination and detect the source of isolates.[63] Following verification outbreaks are classified as confirmed, probable or possible. Once cases have been confirmed, appropriate infection control measures can be implemented.

Therapeutic drug failures caused by resistant organisms' calls for the discovery and targeted design of novel antimicrobials.[22] This would help in curtail the devastating effects of outbreaks caused by pan-drug resistant organisms. Similarly, vaccines against resistant pathogens may induce herd immunity and serve as an outbreak preventive strategy.[65]

In designing NICUs, the multidimensional needs of infection control should be considered to ensure effective outbreak response. Designs should consider the role of water as a medium for the transfer of resistant organisms like *P. aeruginosa*.[21] NICUs should be equipped with a disinfection station, isolation unit and waste disposal area as depicted in Figure 2.

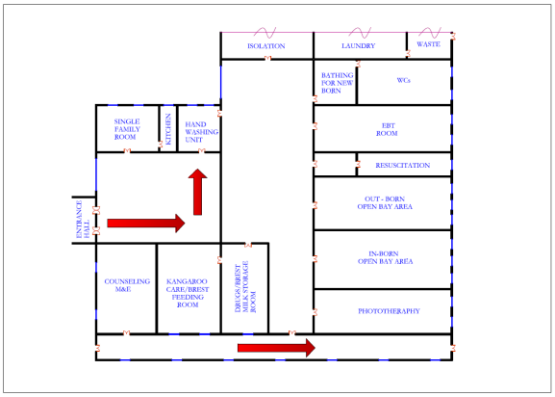

Figure 2: Floor plan of a model NICU design that considers findings from published research

There needs to be adequate beds and staffing. In resource constraint settings, cohort isolation has been shown to result in a decline in MRSA associated infections.[66]

Though, its effectiveness is not clearly established in the literature, which has led to a no recommendation by CDC/HIPAC, the occurrence of drug resistant bacterial outbreaks has often led to the closure of NICUs to prevent spread.[34,67] In resource constraint settings, the feasibility of this strategy might be low, owing to high burden of patients and weak health systems.

Conclusion

In conclusion, evidence-based measures for controlling resistant bacterial infections, though still evolving, have improved neonatal outcomes in recent times. More efforts should be placed at strengthening weak health systems and conducting collaborative research on infection control in NICUs in order to determine and reduce the global burden of resistant bacterial infections.

Only studies that were published in English were reviewed as such language restriction serves as a limitation of this review. However, it does give a brief overview of the problem and suggests ways to curtail the occurrence of drug-resistant infections in NICUs located in sub-Saharan Africa.

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YELLOW FEVER – A CONTINUING THREAT IN UGANDA

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Background

Yellow fever refers to a mosquito-borne viral disease that is prone to epidemics and is vaccine preventable. It is caused by yellow fever virus, an arbovirus that is transmitted through a bite of Aedes and Haemagogus mosquitoes.[1,2] These mosquitoes bite during the day, and while domestic mosquitoes breed around houses, wild variants breed in forests and jungles. There is a semi-domestic mosquito that breeds in both habitats. The international spread potential makes yellow fever a potential global health threat.[1,3] The virus has a 3-6-day incubation period, and many infected people are asymptomatic. Those who do get symptoms often experience fever, muscle/joint pain with backache, headache, loss of appetite, or nausea or vomiting - symptoms that often disappear after 3 to 4 days.

A few patients progress to the second phase about 24 hours after resolution of the initial symptoms – with recurrence of high fever, occurrence of jaundice, dark urine, abdominal pain - often with vomiting. It may worsen, resulting in bleeding from the mouth, nose, eyes or stomach.[2] More than 50% of individuals affected by this toxic phase die within 7 - 10 days.[4,5]

Three types of transmission cycles have been described: (1) the sylvatic, whose primary reservoir is monkeys after they are bitten by infected mosquitoes, (2) the intermediate type where semi-domestic mosquitoes often infect both monkeys and humans – common in African outbreaks and (3) the urban type where infected humans introduce the virus into heavily populated urban centres with little immunity causing large epidemics.[1,4,5] In these conditions, infected mosquitoes transmit the virus from person to person.

Africa continues to experience yellow fever outbreaks, Figure 1.[6]

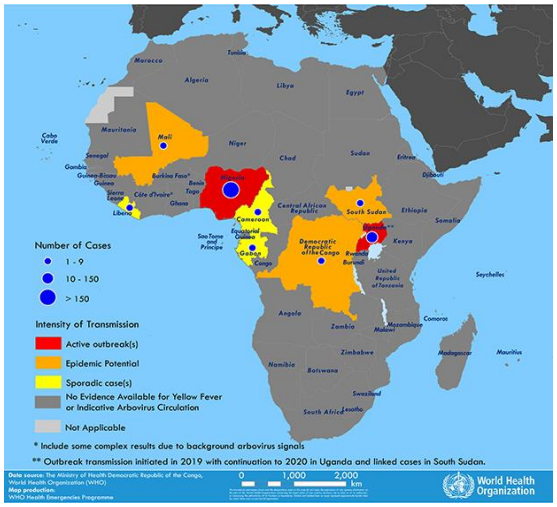

Figure 1: Distribution of yellow fever cases in Africa in 2020

Source: WHO, Source link: https://www.who.int/images/default-source/health-topics/yellow-fever/fig-1-weekly-epi-record---yf-cases---africa-2020-v29b19d140d5a04dbbbe8c6f9950306cf9.tmb-768v.png?sfvrsn=21b99c02_1

Uganda country review

In East Africa, Uganda is the country that experiences frequent yellow fever outbreaks, with recent outbreaks reported in 2019, 2018, 2016 and 2011.[5,7] Uganda has a very low estimated overall population immunity against yellow fever of 4.2%.[5] Most districts affected by these outbreaks border the heavily forested Democratic Republic of Congo (DRC) and South Sudan and are characterised by frequent population movements across international borders as well as high interconnectivity.[3] The 2019-2020 outbreak was the most recent in Uganda.[8] These cases were identified through the national surveillance system during the period 4th November 2019 to 14th February 2020, during which eight, laboratory confirmed, PCR-positive cases of yellow fever were reported: 3 in Buliisa, 1 in Maracha and 4 in Moyo, with a 50% case fatality rate.[8,9] The index case for this outbreak was a 37-year-old male cattle farmer, who transported and sold milk in several districts and in the DRC and who was found to have viral haemorrhagic fever (VHF). He reported to hospital on 30th October 2019 with fever and headache for five days with worsening symptoms of vomiting, abdominal pain and epistaxis leading to his death on 4th November 2019. Tests were subsequently done on 8 close family contacts, from whom the second case was diagnosed, while the other 7 tested negative.[8,9]

In Moyo district, which borders South Sudan, a further two RT-PCR confirmed cases were reported.[8] These involved 18- and 21-year-old timber traders who often trade between Uganda and South Sudan. They experienced symptoms from 3rd January 2020 onwards and were admitted to a nearby health centre, and subsequently refereed to a nearby General Hospital with fever, fatigue, vomiting, diarrhoea, headache, abdominal and joint pains, that progressed to confusion and bleeding. They deteriorated and died on 5th and 6th January 2020. The same district later notified a second cluster of a PCR-confirmed yellow fever case from a different village - a 59-year-old patient who presented with unexplained bleeding and fever on the 22nd of January 2020 and died on the 23rd of January 2020. Two of this patient's family members had died in the preceding two weeks with similar symptoms. There were three additional cases of PCR-positive cases confirmed, one each in Buliisa, Moyo and Maracha districts.[8]

In 2020, following these outbreaks, the Uganda ministry of health rolled out a yellow fever vaccination drive in the north-western Nile region with the aim of vaccinating up to 1.6 million citizens.[9] The yellow fever vaccination campaign, launched on 20th August 2020 by the Uganda Ministry of Health, was supported by the Global Alliance on Vaccines (GAVI), the World Health Organization (WHO), and the United Nations Children's Fund (UNICEF).[8,9] This campaign targeted the districts of Koboko, Maracha, Moyo, Obongi and Yumbe. Frequent outbreaks are the reason why Uganda is considered a high-risk country for yellow fever in the global strategy, Eliminate Yellow fever Epidemics (EYE).[10] The global EYE strategy was developed by a coalition of partners (the GAVI Alliance, UNICEF and the WHO) to face yellow fever's ever-changing epidemiology, the resurgence of mosquitoes and related transmission, and the increased risk of yellow fever urban outbreaks and international yellow fever spread.[5] The EYE strategy is a global, comprehensive and long-term strategy (run from 2017 to 2026) that targets the most vulnerable countries, while similarly addressing the global risk, through building resilience in urban centres against yellow fever spread, and preparedness in areas that have potential for outbreaks while also ensuring reliable vaccine supply is sustained.

Recommendations

There is need for efforts to control the yellow fever virus spread. Uganda plans to introduce yellow fever vaccination into its routine national immunisation programme and organise preventive mass vaccination activities in selected areas to rapidly boost population immunity. Targeted vector control efforts may be helpful in at risk urban settings to interrupt transmission. The country requires strong case-based surveillance for yellow fever to help detect outbreaks early and halt spread to new areas. Travellers and citizens should be educated on mosquito biting habits and how to protect themselves including sleeping under insecticide treated mosquito nets. Occasionally, infected travellers have exported cases to countries that are free of yellow fever.

To prevent international spread of yellow fever, the International Health Regulations (2005) should be applied and all travellers to high-risk areas must present valid yellow fever vaccination certificates. All international travellers must receive yellow fever vaccination due to persistent or periodic transmission of yellow fever virus. In areas experiencing high transmission rates, vaccination (though not generally recommended) for infants aged 6 to 8 months, pregnant or breastfeeding women should be considered carefully and weighed against risks and benefits. Before country entry, all visitors aged one year and older must have a valid yellow fever vaccination certificate. The international certificate of vaccination against yellow fever is valid from 10 days after vaccination and throughout the life of the person vaccinated. A single dose of WHO approved yellow fever vaccine is sufficient to confer sustained immunity and life-long protection against yellow fever disease. A booster dose of the vaccine is not needed and is not required of international travellers as a condition of entry.

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MANAGING HIV-INFECTED CHILDREN DURING THE CORONAVIRUS DISEASE 2019 PANDEMIC IN RESOURCE CONSTRAINED COUNTRIES

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Introduction

Coronavirus disease 2019 (COVID-19) is a rapidly evolving pandemic, with huge social and economic consequence across all nations.[1,2] It presents with less severe disease in children than adults, even though children under 1 year of age and those with underlying comorbidities may be at increased risk for more severe illness.[3-5]

Data from South Africa and Italy shows that people living with HIV, especially those with comorbidities, have elevated risk of poor COVID-19 outcomes, irrespective of viral suppression, and the degree of immunosuppression may affect disease severity.[6,7] Contrary to this, another study suggested that immunosuppression and low CD4 cell counts might protect HIV-infected individuals from developing the cytokine storm associated with severe disease in COVID-19.[8] Not much information is known about the impact of COVID-19 in HIV-infected children. In a surveillance report on 60 children aged ≤18 years with COVID-19, who died in South Africa between 1 March and 18 September 2020, 2 of the 16 underlying comorbidities reported was HIV.[9]

Antiretroviral drugs

The challenges of paediatric HIV are not over, as nearly 110,000 children died of AIDS in 2019, according to the 2019 UNICEF global data on the HIV epidemic in children.[10] According to that report, in 2019, a person under the age of 20 was newly infected with HIV every 110 seconds, bringing the total number of children living with HIV to 2.8 million. Sub- Saharan Africa bears the brunt of HIV infections where 88% of children under the age of 15 are found.[10] UNICEF executive director, Henrietta Fore noted that: “Even as the world struggles in the midst of an ongoing global pandemic, hundreds of thousands of children continue to suffer the ravages of the HIV epidemic”.

In 2019, under half of HIV-infected children worldwide did not have access to life-saving treatment, significantly lagging coverage for both mothers, 85%, and all adults living with HIV, 62%.[10] There are concerns that in resource constrained countries, as more government spending is directed towards the fight against COVID-19, less funding will be made available for antiretroviral (ARV) drugs. This would be a great disadvantage to children whose HIV treatment coverage lags that of adults and are not the face of the current pandemic. Interruption of their ARVs could reverse any gains made in paediatric HIV. In Zimbabwe, a rapid survey assessment done in April 2020, showed that 19% of HIV patients had not been able to get a refill of antiretroviral drugs, or were only able to get a partial refill.[11]

Supply of HIV medications for longer periods than needed, as part of the mitigation strategies to prevent exposure to COVID-19 in the healthcare facility, could ultimately affect the supply chain and lead to stockouts, especially in countries that rely wholly or partly on donor funding for their ARVs.

Thus, ministries of health, non-governmental agencies and global health partners which support HIV programs, must work together to develop, and adapt guidelines for healthcare systems and in particular the supply chain, to avoid stockouts of ARVs.

Prevention of mother to child transmission of HIV

Maternal testing for HIV during antenatal visits and subsequent initiation of ARVs, is key to prevention of mother to child transmission (PMTCT) of HIV. Mitigation strategies and travel restrictions during the pandemic that disrupt HIV testing in antenatal and child health services, could exacerbate the high rates of maternal and infant mortality from undetected HIV infection. New-born testing and early initiation of ARV prophylaxis must not be disrupted, if elimination of mother to child transmission of HIV is to be achieved by 2030. Currently in Ghana, there is an unacceptable delay time of 2 months and beyond, in receiving the results of HIV DNA-PCR for HIV-exposed infants.

In communities with high transmission of COVID-19, virtual follow up services can be offered for mothers who are stable on treatment and have access to internet services, and or mobile phones. For others, follow up services can be done by community health workers who can use dried blood smears for early infant diagnosis, and initiate ARV prophylaxis for HIV-exposed infants. When it is impractical to do so, PMTCT services must continue at designated healthcare centres with all

COVID-19 protocols in place such as wearing of face masks, frequent hand hygiene and social distancing. Healthcare workforces and communities must work together to reduce the risk of exposure to COVID-19, while avoiding interruptions to essential HIV services such as prevention of mother to child transmission of HIV.

Immunisation

A decrease in childhood immunisation coverage rates could be a devastating indirect effect of the pandemic, with an increase in morbidity and mortality in children from vaccine preventable diseases. A decrease in paediatric immunisation coverage rates was seen in a referral health centre in Sierra Leone where a 52–83% decrease was seen in 2020, compared with the previous year.[12] The benefits of immunisation has been shown to outweigh the risk of spreading COVID-19 at immunisation sites in a benefit-risk analysis.[13] Children with HIV are more susceptible to vaccine-preventable illnesses and immunisation is a key preventive strategy in preventing morbidity and mortality among this vulnerable group. If national immunisation programs are suspended or caregivers fail to attend scheduled visits due to their fear of contracting COVID-19, unimmunised HIV-infected or -exposed children could develop vaccine preventable diseases with severe consequence. When herd immunity is lost in any community due to a decrease in immunisation coverage rates, disease outbreaks occur and cause severe disease among children and the immunocompromised.[14] In the Western Cape province of South Africa, a significant increase in the number of children with tuberculosis meningitis and tuberculomas at a large academic referral hospital in 2017, was related to disruptions in the supply of the BCG vaccine in 2015.[15] This is a stark reminder of the role of vaccines in disease control.

Routine and supplemental immunisation programs must continue during the pandemic, and public education on the benefits of national immunisation programs must be intensified. Consequently, healthcare centres that provide immunisation services must ensure that all the COVID-19 safety protocols are in place to reassure parents or caregivers. Telephone calls and other reminders like short message services should be used to remind parents and caregivers of their appointments. Governments and their health ministries must prioritise their national immunisation programs during this pandemic and ensure that strategies are put in place to avoid stockouts even as they prepare to procure the COVID-19 vaccine.

It is unclear which antibody responses HIV-infected children mount to COVID-19 vaccines as low vaccine responses have been observed in them.[16] However, since they may be at higher risk of severe disease, HIV-infected children could be prioritised for the COVID-19 vaccine. Ongoing COVID-19 vaccine trials in children 12-16 years have commenced, and it is expected that children younger than 12 years would be included in subsequent trials so that children and in particular HIV-infected children will receive the COVID-19 vaccine.

Adherence to antiretroviral treatment

Children living with chronic diseases such as HIV, experience more stress than healthy children due to the need to adhere to medication daily, scheduled hospital visits, school disruption, being thought of as different from their peers, and thoughts of death.[17] During the pandemic they may experience more stress from the stay home orders, closure of schools and lack of interaction with their peers, or they may experience fear when they see family members succumb to COVID-19. This chronic stress may impact on their health behaviour and lead to decreased adherence to their ARVs.[18]

Patients who are retained in care are more likely to adhere to ARVs and experience improved health outcomes.[19] Older children and adolescents with adherence issues require frequent monitoring of their viral load, periodic review of their clinical status, intensified adherence counselling and medication switch when necessary. Thus, when medical appointments are suspended due to the risk of exposure to COVID-19 at the healthcare facility or from lockdowns, HIV-infected children and adolescents with adherence issues may develop treatment failure. Missed medical appointments are independently associated with increased risk of AIDS-defining illnesses and death[20], and sexually active adolescents with high viral loads could transmit HIV infection to their partners.

Every effort must be made to ensure the continuity of care of HIV-infected children and adolescents, either by scheduled in person visits to the treatment centres, or by home visits of community care workers. Those with adherence challenges must be given all the assistance they need, and support groups should be encouraged to meet on virtual platforms.

Conclusion

The COVID-19 pandemic presents several barriers and challenges to the HIV care continuum of children in resource constrained settings. HIV services such as early infant diagnosis, viral load monitoring, adolescent services, continuity of case identification and life-long antiretroviral therapy should remain a national health priority. Healthcare services must be creative and adapt to support the physical and mental health of HIV-infected children.

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RESEARCH

PAEDIATRIC HIV RESEARCH: RECENT ADVANCES AND THEIR IMPLICATIONS FOR CLINICAL PRACTICE

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Introduction

Globally, an estimated 38 million people are living with HIV according to UNAIDS 2020 data. Of these, 1.8 million are children under 15 years. In 2019, an estimated 1.7 million new infections were reported globally, with children accounting for nine percent of these. Eighty four percent of these new infections in children occur in sub-Saharan Africa. While Eastern and Southern countries African countries have made tremendous progress over the last ten years with 38% reduction in new infections and 49% reduction in AIDS-related deaths, West and Central African countries are falling behind, registering only 25% and 37% reductions, respectively. Eastern and Southern African countries like Uganda, Rwanda, Botswana, Zambia, Zimbabwe among others have reached the fast track 90-90-90 HIV testing and treatment targets with counterparts like Kenya, Malawi and Tanzania following closely. However, Western and Central African countries are still far from achieving the targets. This has been attributed to less domestic and international focus on HIV in the Western and Central African region.[1]

Great strides have been made in paediatric HIV research, especially in the era of antiretroviral therapy (ART) with development of safer and more user-friendly drug formulations; timing of initiation of ART; and prevention of new infections. Significant gaps remain in the care for children with advanced disease and adolescents. This review highlights the recent advances in antiretroviral drug development for children and takes into consideration the gaps that remain for future research.

ODYSSEY and P1093 trials

Dolutegravir (DTG) is a highly effective integrase inhibitor with a low propensity for developing resistance. It has been recommended and rolled out for use as a first line drug among adults and children as first line treatment combined with two nucleoside reverse transcriptase inhibitors.[2] However, the tablets with the recommended doses for children were initially not readily available in resource limited settings. The ODYSSEY trial in Uganda, Zimbabwe and South Africa investigated the pharmacokinetics related to using the 50mg film-coated adult tablet in children weighing 20kg and above compared to the recommended lower dose film coated and dispersible tablets. The study found that the 50mg once daily film coated tablets when used in children above 20kg resulted in C_{trough} (Coefficient of variation) closer to that of fasted adults taking the same dose, compared to the then recommended lower dose formulations for children. Additionally, the 50mg film-coated tablet given once daily was safe in these children.[3] This allows for harmonization of adult and paediatric dolutegravir dosing and improves children's access to dolutegravir. These findings informed the 2019 WHO paediatric dosing guidelines and led to the US Food and Drug Administration approval of adult dosing down to 20kg. The final results of the ODYSSEY trial will be presented at CROI 2021 (https://www.croiconference.org).

The IMPAACT P1093 study reported about the safety and efficacy of a dolutegravir based ART regimen among twenty-three treatment-experienced adolescents through a median 153 weeks of follow-up. Dolutegravir was well tolerated and safe, with no discontinuation due to adverse events. The adolescents who reported over 95% adherence on 3-day recall had virological success (□50 copies/mL) during follow up.[4] These findings suggest that not only is dolutegravir safe for ART experienced adolescents in the long term, but also highly efficacious. Coupled with adherence monitoring and counselling, dolutegravir can be effectively used in the adolescent population.

The LOLIPOP study

The WHO recommends use of lopinavir/ritonavir as part of first line treatment regimens in situations where children are intolerant to dolutegravir, it is contra-indicated, or appropriate formulations are not available.[2] The formulations of lopinavir/ritonavir that are currently in use include syrups, pellets, and tablets. Lopinavir/ritonavir has a bitter taste which affects adherence in children. Syrups

require refrigeration and tablets are difficult to administer in younger children. There is ongoing research into more acceptable and tolerable formulations of lopinavir/ritonavir for children including fixed dose combination granules of abacavir, lamivudine and Lopinavir/ritonavir (4-in-1 formulation called quadrimmune). The LOLIPOP study is a phase I/II, open label, randomized cross over pharmacokinetic, safety and acceptability study in Uganda. Preliminary findings showed the 4-in-1 formulation was safe and effective in achieving or maintaining viral suppression. Furthermore, the 4-in-1 formulation provided comparable drug exposures with the abacavir/lamivudine 60/30 mg) dispersible tablets plus lopinavir/ritonavir 40 10mg pellets in majority of the participating children abacavir/lamivudine 60/30 mg.[5] A qualitative study nested within the LOLIPOP study assessed caregivers' acceptability of the 4 in 1 formulation in comparison to lopinavir/ritonavir 40/10 mg) pellets plus dual. The study found that caregivers found the 4 in 1 formulation more acceptable than LPV/r pellets or other previous formulations, partly due to its palatability (strawberry flavoured), easy storage and administration, and packaging.[6] This is an important finding in as far as improving adherence to ART and treatment outcomes among younger children.

Gilead study; GS-US-292-0106

While adults have access to fixed dose combinations, which improve treatment adherence, no single dose, once daily tablets are approved for use in children under 12 years. The GS-US-292-0106 is an open label single arm study being done in Uganda, the USA, and Thailand. Part A of this study which assessed pharmacokinetics of a once daily single tablet coformulation of 150 mg elvitegravir, 150 mg cobicistat, 200 mg, emtricitabine, and 10 mg tenofovir alafenamide among 23 virologically suppressed children aged 6-11 years is complete. During the 24-week follow-up period, participants reported only mild and moderate adverse events, and maintained viral suppression (HIV-1 RNA <50 copies/mL). The tablet caused modest increases in the Area Under the Curve (AUC) for the different tablet components compared to adult data; tenofovir alafenamide (71%), tenofovir (52%), elvitegravir (34%), cobicistat (58%), and emtricitabine (75%).[7] A lower dose of this combination in being tested in children ≥ two years and interim analyses show high acceptability and sustained virological suppression.[8] The bictegravir, emtricitabine, and tenofovir alafenamide single tablet fixed-dose combination was also safe, efficacious and no clinically relevant exposures in 100 adolescents and children aged 6 to 18 years compared with adults.[9] These findings suggest that there is hope for a safe efficacious once daily single dose tablet for children. When rolled out for clinical use, this tablet will significantly improve treatment adherence in older children (6-11 years) and adolescents.

Ongoing challenges in care for children living with HIV

Management of advanced HIV

Despite the widespread availability of effective ART, over 690,000 people died from AIDS-related deaths worldwide in 2019. Of these, 95,000 were children less than 15 years.[1] Management of advanced disease in children is still very challenging. Patients at high risk of mortality are often either newly diagnosed with HIV or failing in their ART regimens at presentation. They present with severe immunosuppression evidenced by severe opportunistic infections and features of malnutrition.

The REALITY Trial

"The Reduction of EArly mortaLITY in HIV-infected Adults and Children Starting Antiretroviral Therapy (REALITY)" trial tried to address this problem. It was an open label, randomised controlled trial, among adults and children 5 years. The REALITY trial randomised participants to standard of care (co-trimoxazole) according to national guidelines or an enhanced prophylaxis package (12 weeks of fluconazole 100mg daily, 12 weeks of fixed-dose combination of co-trimoxazole, isoniazid, and pyridoxine as a once daily tablet, 5 days of azithromycin and a single dose of albendazole. All the drugs were started simultaneously on the same day as ART. The enhanced prophylaxis package was reported to reduce mortality by 27% over 24 weeks.[10] The study also investigated the effect of ready-to-use supplementary food on mortality among these patients. The control group received nutritional supplementation when recommended by the current guidelines. This ready-to-use supplementary food did not reduce early mortality in this population.[11]

The WHO defines advanced disease as; all children younger than 5 years with HIV, and those older than 5 years with CD4 cell count <200 cells/mm^3 or WHO stage 3 or 4 event. WHO, taking the REALITY trial results into consideration, recommends that a package of interventions including: screening for tuberculosis and cryptococcal antigen (in adolescents), treatment and prophylaxis with co-trimoxazole, TB preventive treatment, fluconazole (among cryptococcal antigen positive adolescents with no evidence of meningitis), rapid initiation of ART (same day) unless clinical symptoms suggest TB or cryptococcal meningitis, and intensified adherence support interventions be offered to everyone with advanced HIV disease.[12]

The EMPIRICAL Trial

An ongoing trial, the Empirical trial (NCT03915366), is aiming at reducing mortality among HIV infected infants. It is a randomised factorial clinical trial, which is being conducted in Uganda, Zimbabwe, Zambia, Mozambique, Ivory Coast and Malawi. The objective of the study is to evaluate the safety and efficacy of empirical treatment against cytomegalovirus and tuberculosis in HIV-infected infants hospitalised for severe pneumonia. This study will provide insights into whether additional interventions are warranted for HIV-infected infants with advanced disease.

Management of Adolescents

Thanks to increasing availability of ART worldwide, more children are surviving infancy. As such, the adolescent population is growing. Management of adolescents presents unique challenges. One of the main challenges highlighted is mental health disorders. Recent studies in Uganda and South Africa document a high prevalence of psychiatric and behavioural disorders in adolescents, particularly attention deficit hyperactivity disorder (ADHD).[13,14] These disorders, unless specifically screened for, could be missed during routine HIV care. This calls for closer attention to adolescents' mental health and specialist care to improve their quality of life. Other challenges of adolescents include chronic lung disease, particularly obliterative bronchiolitis following recurrent severe respiratory tract infections and tuberculosis, bronchiectasis, cardiovascular and renal complications, stunting, and pubertal delay.[15,16] According to Kranzer et al, adolescents 15-19 years also have a significantly higher rate of loss to follow-up compared to other children.[17] Adolescents who are lost to follow up are likely to miss their ART and develop severe life-threatening opportunistic infections. Management of HIV-infected adolescents therefore calls for extensive screening for

comorbid conditions with specialist care for identified conditions. Preventive measures include early initiation of ART, routine vaccination, prophylaxis against opportunistic infections as well as improving nutrition.

Resistance

Emerging resistance to antiretroviral drugs is a growing challenge to treatment of HIV. HIV drug resistance is usually a result of exposing the virus to suboptimal levels of a drug, incompletely suppressing the virus, and applying drug selective pressure. This largely occurs following poor treatment adherence. In children, HIV resistance can also be acquired from their ART exposed mothers. Resistance is less likely to develop when fixed dose combinations of ARVs with similar half-lives are used as selective drug pressure on the virus is less likely even with inadequate adherence.[18] Routine viral load monitoring can also help to reduce development of resistance. It results in early detection of virological failure, allowing adequate interventions including adherence counselling and treatment modification to be instigated in a timely manner.[15,19,20]

New models of care and antiretroviral drugs in the pipeline

Even in the face of many challenges, much can be done to consolidate the progress made in paediatric HIV. Current advances include:

1. Differentiated Service Delivery (DSD) Model

The DSD model is a client-centred approach where care is tailored to the patients' specific needs. This method simplifies HIV services for both the clients and the health system. The DSD model is especially beneficial in the face of the current "treat all" approach to HIV management.[21] The decentralised care allows clients in underserved populations to access care and improve their quality of life while reducing expenses that would have otherwise been incurred by the health system. DSDs should go beyond providing care to stable patients to providing care across all aspects of HIV care from prevention to management of advance disease.

2. New drugs

Recent studies are looking into use of neutralisng antibodies such as 3BNC117 and VRC01 to prevent replication of HIV and clear affected cells. Crowell et al investigated the ability of VRC01 to cause sustained viral control in the absence of ART among 19 virologically suppressed adults in Thailand. Although VRC01 was tolerated as monotherapy, it did not sustain viral suppression after 24 weeks of ART interruption.[22] VRC01 and other immunotherapies could be effective as combined regimens.

3. Use of long-acting injectable drugs

Although not yet widely available for clinical use, long-acting injectable drugs like cabotegravir, rilpivirine, leronlimab, islatravir, and albuvirtide among others show promise towards addressing the treatment adherence challenges among adolescents once readily available. Research into resistance associated with these drugs, as well as their effectiveness in various populations is warranted.[23]

4. Treatment simplification

Studies have investigated whether simplification to fewer and safer drugs among virologically suppressed individuals will reduce drug exposure and hence long-term toxicities and improve treatment adherence. The BREATHER trial showed that short cycle efavirenz based therapy (5 days on 2 days off) was non inferior to continuous therapy.[24] A follow-on study, the BREATHER Plus will investigate whether similar results will be obtained with DTG based treatment.

The SMILE trial (NCT02383108), whose final results are expected at IAS 2021 (https://www.ias2021.org), is investigating whether children with chronic HIV infection on ART with suppressed viral load will maintain similar levels of suppression with once daily integrase inhibitors plus darunavir/ritonavir when compared to standard of care triple ART.

Conclusion

Great strides have been made towards provision of efficacious and safe ART regimens to HIV-infected children. However, gaps remain particularly around managing advanced disease and care for adolescents. These need to be addressed if global, regional and national paediatric HIV targets are to be met. Further efforts will go a long way in ensuring that children living with HIV grow to disease-free adulthood, as we aim for elimination of mother to child transmission of the virus.

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CASE REPORTS & MEDICAL IMAGES

SPINAL TUBERCULOSIS WITH PARASPINAL ABSCESS FORMATION

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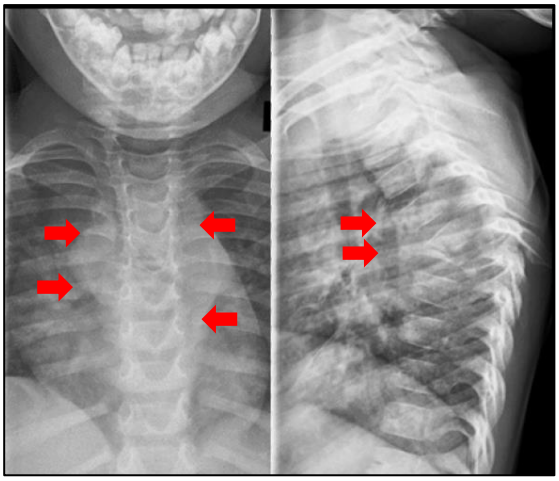
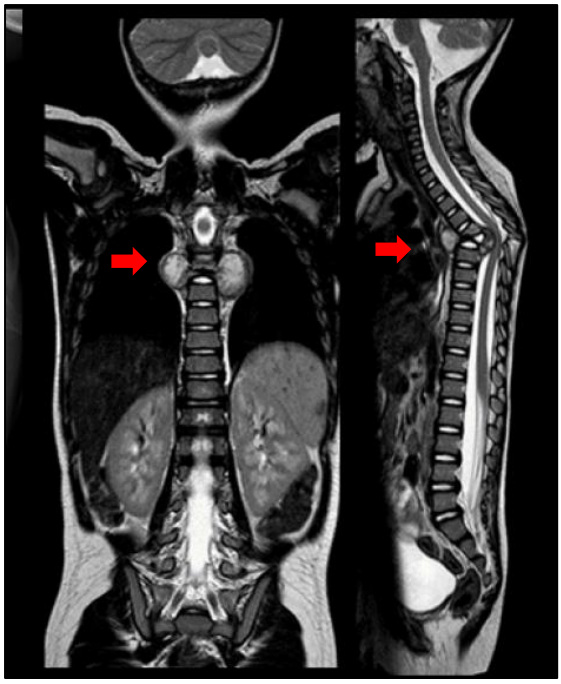
A 3-year old boy presented with painful swelling over his upper spine associated with loss of appetite and night sweats. At the time of presentation an adult household contact had culture-confirmed pulmonary tuberculosis (TB). On examination a gibbus was observed and the neurological examination was completely normal. His Mantoux was reactive. Imaging confirmed classical features of spinal TB.

The lateral chest radiograph showed destruction and collapse of two adjacent vertebral bodies (T5 and T6) with gibbus formation (kyphosis) and the anteroposterior view showed an associated paraspinal mass.



The magnetic resonance images confirmed the presence of a dumb-bell shaped rim-enhancing paraspinal abscess on the anteroposterior views; on the lateral views, collapse with anterior wedging of the T5 and T6 vertebral bodies, preservation but displacement of the intravertebral disc, compression of the spinal canal and spinal cord, but preservation of the spinal cord signal were evident.



Comment

In spinal TB *Mycobacterium tuberculosis* usually disseminates via the bloodstream, and frequently seeds to the metaphysis of adjacent vertebral bodies. With progression of the infection, destruction of the anterior segments of the vertebral bodies occurs resulting in the changes documented in our patient. Paraspinal abscess frequently develops as an extension of spinal TB.

The patient was treated with a standard anti-TB drug regimen for osteoarticular TB and surgical stabilisation of his vertebral column (instrumented autobone graft fusion) to protect his spinal cord from progression to myelopathy and paraplegia. He is being follow-up by the orthopedic service.

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REFLECTING ON DIPHTHERIA IN THE 21ST CENTUARY

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Abstract

The launch of the Expanded Programme on Immunisation in 1974 has seen a dramatic reduction in morbidity and mortality from vaccine preventable diseases. More than four decades later, diphtheria remains a significant cause of illness and death, especially in endemic regions. This has been worsened by poor immunisation coverage, lack of appropriate diagnostics and therapeutic options, especially diphtheria anti-toxin (DAT). We here discuss a suspected case of diphtheria in a thirteen-year-old boy and the associated management challenges which pervades most low- and middle-income countries like Nigeria. We also make a case for optimal immunisation coverage, improved diagnostics and stockpiling of DAT to reduce mortality from diphtheria.

Introduction

The introduction of the Expanded Programme on Immunisation (EPI) has led to significant reduction in vaccine preventable diseases (VPDs) globally.[1] However, in most low- and middle-income countries (LMICs), low vaccine coverage has meant a continued scourge by these largely preventable diseases with resultant mortality, especially in children. Diphtheria typifies one of these VPDs which continues to plague children, especially in endemic countries with low immunisation coverage.[2] This is often associated with poor diagnostic and management resources in the affected regions.[2-5]

Diphtheria is caused by an exotoxin producing gram positive bacilli, and thus referred to as a toxico-infection. The organism, *Corynebacterium diphtheriae*, has four biotypes: gravis, intermedius, mitis, and belfanti, causing indistinguishable respiratory diseases characterised by nasal, pharyngeal, or laryngeal involvement, or a combination of these. Less commonly, there may be cutaneous or systemic disease. The hallmark of respiratory disease being an adherent grey-white pseudomembrane in these areas. This is often associated with oedema of the affected region giving the characteristic “bull neck”, these manifestations may compromise the airway. The exotoxin may cause cardiac, neurological, or renal complications. Demonstration of toxin-producing strains of *C. diphtheria*e confirms the diagnosis. Management involves administration of penicillin or erythromycin, diphtheria anti-toxin (DAT) and airway management. The antibiotic kills the bacteria, stops toxin production, prevents colonisation and halts spread of the organism to close contacts. The antibiotic is readily available; unfortunately, the early administration of DAT and airway management, which account for most mortalities, are often lacking.[3]

Using a recent illustrative case of diphtheria, we discuss issues relating to diphtheria prevention and management in the 21st century in Nigeria; a reflection of the challenges encountered in most LMICs.

Case Presentation

A 13-year-old boy presented with neck swelling of 2 days, fever and pain on swallowing of a day’s duration. He had not received any childhood immunisations. At the onset of his illness, he was treated at home with paracetamol, vitamin C and massaging of the neck with a local balm. On examination, he was acutely ill, febrile (38^{o}C) and had halitosis and a thick purulent nasal discharge. There was diffuse swelling of both sides of the neck. He had a thick grey-white pseudomembrane on the soft palate and tonsillar region occluding the airway, Figure 1. His weight was 30kg, weight-for-age z-score was <2.0 and he was stunted (height, 150cm). He was tachpnoeic (respiratory rate of 32 cycles per minute) and dyspnoeic with mouth breathing and nasal flaring. He had tachycardia (heart rate of 120 beats per minute), normal blood pressure of 100/60 mmHg and normal neurological examination. On suspicion of diphtheria, he had a throat swab which grew a gram-positive bacillus. There was no facility for diphtheria

specific culture and toxin identification, either by serology or toxigenic gene identification. His full blood count showed leukocytosis with neutrophilia, and the blood culture was sterile.

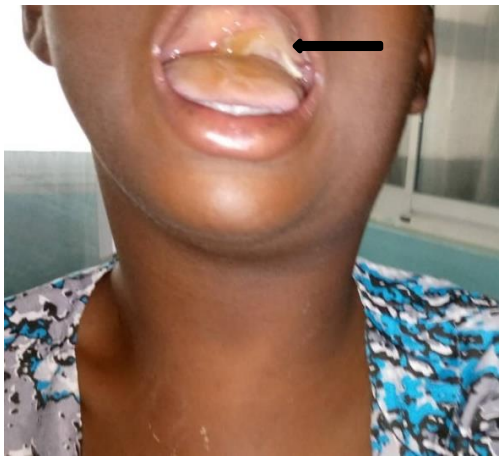

Figure 1: Grey-white membrane in the pharynx

He received intravenous penicillin and emergency tracheostomy on arrival at the emergency ward. Diphtheria anti-toxin was neither available in our facility, nor in-country. His airway obstruction having been sorted out, left him with a tracheostomy tube that got blocked repeatedly. He succumbed to the illness after seven days on admission following an episode of tracheostomy tube blockade.

Discussion

Notwithstanding the availability of a potent vaccine since 1923, cases of diphtheria are still being reported in some LMICs where the disease is endemic and immunisation coverage is low, or sporadically during outbreaks in advanced countries.[2] A recent epidemiological review showed that cases of diphtheria, which declined consistently since the widespread use of the vaccine with the introduction of the EPI in 70s, has increased in recent times.[2] Most of this increase has been in Southeast Asia; with India, Nepal and Indonesia responsible for 96%–99% of cases.[2] Africa is not left out, with most cases reported from Nigeria. This has been largely due to inadequate vaccine coverage which has plateaued globally at 84% to 85% in the last decade (6). The case in Nigeria is worthy of mention as DPT3 coverage remained unchanged between 2000 and 2017 at 42%.[6] The case illustrated in our report had not received any childhood immunisation at 13 years of age! Current immunisation data suggest that about 40% of children aged 12-24 months in Nigeria do not receive any immunisation from health facilities.[7] This reflects the challenging state of the immunisation programme in Nigeria and possibly other LMICs.

In countries with better childhood immunisation coverage, sporadic cases of diphtheria may occur in older adolescents possibly from a waning of immunity acquired from the primary immunisation series.[2] The WHO recommends boosters at 12-24 months, 4-7 years, and 10-25 years.[3] Combination of diphtheria-tetanus toxoid is recommended to address this waning immunity.[8] Most LMICs are yet to implement the booster vaccines as part of their routine immunisation programmes.

Facilities for the diagnosis of some of the infectious diseases are often lacking in LMICs. The confirmation of the diagnosis of diphtheria is a case in point, considering that the specific transport and culture media required were not available as discussed in this report. The capability to demonstrate toxin production using serology or potential for toxin production through the identification of toxigenic gene carriage by molecular methods was lacking. Surprisingly, the deficiency of diphtheria diagnostic facilities has also been reported in well-resourced countries in Europe.[9] When there is lack of appropriate diagnostic facilities for diphtheria, it negatively impacts on surveillance which should enhance policy recommendations and planning.

Though penicillin and erythromycin, the recommended antibiotics for treating diphtheria, are relatively cheap and readily available, some children may not receive the appropriate therapy when there is misdiagnosis or lack of access to these antibiotics.[5] The DAT, a main stay of treatment and is often not administered to cases of diphtheria in LMICs.[4,5] This is due to the reduced production by the manufacturer leading to global shortages.[3] Most western countries regularly stockpile DAT doses and similar has been advocated in countries where diphtheria remains endemic, including Nigeria.[4,9] Cardiac complications are a major contributor to diphtheria mortality, being responsible for approximately 20 to 60% of diphtheria deaths. Previous reports from Nigeria had documented the non-availability of DAT in the county and the *status quo* prevails till date.[4,5] The recommendation for a national or regional stockpile of DAT needs to be revisited.

Airway management is central to improved outcomes in patients with diphtheria.[3] The pathology produces an adherent membrane which may dislodge and cause suffocation. The associated oedema and attendant “bull neck” also worsen the narrowing of the airway and are more pronounced in young children. Airway support, including tracheostomy where necessary, should be provided expeditiously.[3] However, more importantly, is the management of such artificial airway support. This remains a challenge in children especially in LMICs. Tube blockage or removal may cause fatalities as was recorded in this case. Alternatives to this have included extracorporeal membrane oxygenation (ECMO) but challenges remain, as this requires advanced technology and is often not available in places where it is needed most.

Conclusion

As with most infectious diseases in LMICs countries such as Nigeria, diagnostic challenges for diphtheria remain a problem. On the issue of management, there is a need for a review of packages and approaches at the national or regional level to embark on certain “orphan” interventions that will ensure ready access to medicines in the essential medicines list and stockpiling of DAT. Vaccination, the age-long, cost-effective prevention for significant causes of childhood morbidity and mortality still experience sub-optimal uptake with consequent reversal of earlier gains in the control of VPDs. This life saving intervention should be accorded the priority it deserves.

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JOURNAL WATCH

MOTHER-TO-CHILD TRANSMISSION OF SARS-COV-2

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Less than 2% of neonates born to SARS-CoV-2-infected women test SARS-CoV-2 positive within 24 hours of birth. Postnatal transmission appears to be responsible for most of the SARS-CoV-2 infections documented in neonates.

Mother-to-fetus (*in utero* or transplacental) transmission is a rare event. It was first conclusively proven in a term infant who was born by caesarian section at 37 weeks gestation to a mother who had developed symptomatic SARS-CoV-2 infection a few days before delivery. Clear amniotic fluid collected before the rupture of membranes during caesarian section tested positive for both E and S genes of SARS-CoV-2. Furthermore, nasopharyngeal and rectal swabs collected from the baby at 1 hour of life and placental tissue tested positive by SARS-CoV-2 reverse transcriptase PCR. These and other virological and histological investigations confirmed that transplacental transmission of SARS-COV-2 had indeed occurred during late pregnancy.[1]

The World Health Organization recently convened an expert consultation at which consensus definitions were developed for *in utero* transmission, *in utero* transmission with fetal demise, intrapartum transmission and early postnatal (>48 hours to 28 days) transmission.[2] This is an important guide for neonatologists, paediatricians and paediatric infectious diseases sub-specialists as it should assist us in investigating and classifying neonatal SARS-CoV-2 infections that we encounter in clinical practice.

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FORTHCOMING EVENTS

7th African Society for Immunodeficiency (ASID) Congress takes place in Khartoum, Sudan in April 2021. For more information visit the ASID website: http://asid-africa.org/en/

3rd International meeting on childhood tuberculosis takes place from 23 to 25 September 2021 in Sofia, Bulgaria. For more information visit the meeting website: PTBnet Sofia 2020 | PTBnet Sofia 2020

12th World Society for Pediatric Infectious Diseases (WSPID) conference will take place from 22 to 24 February 2022. For information on the conference venue and dates visit the Paediatric Infectious Diseases Society website: http://www.pids.org/. AfSPID will once more host a dedicated symposium at this conference.

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