# The AfSPID BULLETIN

Volume 7 (3) Newsletter of the African Society for Paediatric Infectious Diseases December 2020


## TABLE OF CONTENTS



## EDITOR'S COMMENT

Dear Colleagues

Welcome to the eleventh edition of the AfSPID newsletter.

I hope that you enjoy the festive period and have a very successful 2021.

The COVID-19 pandemic remains uppermost in our daily experience and discussion. Recent developments suggest that widespread administration of effective vaccines could commence shortly and should hopefully disrupt the course of the pandemic in 2021. COVID-19 is an important focus of this newsletter. Declining childhood immunisation coverage is discussed by Mulugeta Gebremicael a paediatric infectious diseases fellow and James Nuttall, the impact of COVID-19 on health services in Nigeria by Olushola Olibamoyo and Oghenebrume Wariri, the results of a survey of paediatricians on access to COVID-19 testing in Ethiopia are described and discussed by Tinsae Alemayehu, and in the journal watch section, Brian Eley summarises the results of two landmark studies that investigated inborn errors of immunity in patients with COVID-19. This edition also contains a comprehensive review on the treatment of drug resistant tuberculosis by Harsha Lochan, a commentary on vancomycin therapeutic drug monitoring by Leonore Greybe, another paediatric infectious diseases fellow, a systematic review of the prevalence of PCR-confirmed pertussis in Africa by Rudzani Muloiwa and in the new section on case reports & medical images the first medical image to appear in the newsletter was contributed by Heloise Buys.

To further strengthen the newsletter enabling its growth and sustainability several changes are being implemented over the next 1-2 years. Six additional editorial board members are introduced today, refer to the section entitled society news. The first editorial board meeting was recently held at which consensus was reached on changes to the structure and function of the newsletter, refer to the meeting summary in the section entitled society news. Important changes include, the creation of a section entitled society news, the grouping of reviews and commentaries into a discrete section, the start of a new section on case reports and medical images, and the commencement of a section on research articles. The author guidelines have also been changed to support these structural changes, refer page 60. Until October 2020 the newsletter was archived on the FIDSSA website. From November 2020 it will also be archived on the WSPID website at https://wspid.org/member-societies/. Discussion at the recent editorial board meeting resolved that the newsletter should also be placed on a social media platform. This consideration is now being actively pursued. In the next two years the editorial board will be further expanded, and several associate editors appointed to support the development of the new case report & medical image section as well as other sections.

I'm very happy with these developments as well as the spectrum of topics addressed in this newsletter. I hope that you enjoy this edition and are encouraged to contribute to future editions.

Kind regards, Brian Eley

## 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 is scheduled to take place in Mexico in December 2021, however, a final decision on the meeting format (physical, fully virtual or partially virtual) has still to be taken.

### FORMATION OF YOUNG WSPID

Young World Society of Pediatric Infectious Diseases (young WSPID) was formed in March 2020 to increase the involvement of younger members in the training and educational activities of WSPID. Young WSPID currently has two streams, the online educational taskforce and the mentorship taskforce. Currently 12 health professionals from Africa are participating in Young WSPID. In future editions of the newsletter, members of the editorial board of the AfSPID bulletin affiliated to Young WSPID will update us on this exciting initiative.

### NEW MEMEBERS OF THE EDITORIAL BOARD OF THE AfSPID BULLETIN

Towards strengthening the AfSPID newsletter six new editorial board members are introduced to the readership today, Dr Harsha Lochan (South Africa), Dr Joycelyn Assimeng Dame (Ghana), Dr Babatunde Ogunbosi (Nigeria), Professor Rudzani Muloiwa (South Africa), Dr Victor Musiime (Uganda) and Associate Professor Heloise Buys (South Africa).

***Figure 1: New members of the editorial board: Dr Harsha Lochan (top left), Dr Joycelyn Assimeng Dame (top centre), Dr Babatunde Ogunbosi (top right), Professor Rudzani Muloiwa (bottom left), Dr Victor Musiime (bottom centre) and Associate Professor Heloise Buys (bottom right)***

**Harsha Lochan** is a paediatric infectious diseases sub-specialist. She trained in paediatric infectious diseases at Red Cross War Memorial Children's Hospital and the University of Cape Town (UCT) between November 2012 and December 2014. She works in the Department of Paediatrics and Child Health, Frere hospital, East London, South Africa and the Walter Sisulu University, Mthatha, Eastern Cape, South Africa. She heads HIV and TB services and general paediatrics at Frere hospital. Her current research interests include blood culture trends, UVC light in infection control and neurocysticercosis. She is a member of Young WSPID.

**Joycelyn Assimeng Dame** a paediatric infectious diseases subspecialist, trained in paediatric infectious diseases at Red Cross War Memorial Children's Hospital and UCT between August 2017 and March 2019. She works as a consultant paediatrician and paediatric infectious diseases specialist at Korle Bu Teaching Hospital, Accra, Ghana. She is a part-time lecturer at the University of Ghana, School of Medicine and Dentistry. She is experienced in the evaluation & management of complicated or atypical infections including HIV, complicated drug-susceptible & resistant TB, vaccine adverse events, and evaluation of primary immune deficiencies in children, and the treatment of drug-resistant infections. She is the current chairman of the Infection Prevention and Control Committee and a member of sentinel Site Surveillance Committee for antibiotic resistance at Korle Bu Teaching Hospital. Her associations include the Paediatric Society of Ghana, African Society of Paediatric Infectious Diseases and Young WSPID. Her research interests are in paediatric HIV/TB, drug resistant infections, hospital antimicrobial and infection control and antimicrobial stewardship.

**Babatunde Ogunbosi** is a senior lecturer/consultant in the Paediatric Infectious Diseases Unit, Department of Paediatrics, College of Medicine, University of Ibadan/University College Hospital, Ibadan (UCH). He is a graduate of the Ahmadu Bello University, Zaria (MBBS,1998) and a Fellow of the National Postgraduate Medical College of Nigeria, Faculty of Paediatrics, 2008. During his residency at the UCH he received many awards and was at different times; the best junior resident, best senior resident and the best resident at the UCH 50th anniversary. In 2012, as a Fogarty Fellow under the NU-AITRP programme, he completed a Master of Science in Clinical Investigation at the Northwestern University, Chicago. He completed a clinical fellowship in paediatric infectious disease at Red War Memorial Cross Children Hospital and UCT and is a certified paediatric infectious diseases sub-specialist of the Colleges of Medicine of South Africa. He plays an active role in the National HIV, TB and Malaria programmes. He is a keen advocate of child health and champion of antimicrobial stewardship with research interest in antimicrobial resistance and other ID issues. He is the current General Secretary of the Nigerian Society for Paediatric Infectious Diseases (NISPID).

After doing his undergraduate degree at the University of (KwaZulu) Natal, **Rudzani Muloiwa** trained as a paediatrician at the Red Cross War Memorial Children's Hospital and UCT, obtaining a Fellowship in Paediatrics with the Colleges of Medicines of South Africa (CMSA) in 2004. After this he completed an M.Sc. (Public Health Developing Countries) at the London School of Hygiene & Tropical Medicine. Although Rudzani is a general paediatrician, he has an interest in infectious diseases

with a special emphasis on vaccine preventable diseases and has consequently spent a one-year fellowship in paediatric infectious diseases at Red Cross War Memorial Children's Hospital. He also runs the paediatric and adolescent HIV clinical services at Groote Schuur Hospital. For most of the last three years he has served as both Assistant Dean for Undergraduate Student Affairs and recently as Acting Deputy Dean of the Faculty of Health Sciences at UCT. He is a current member of the Vaccines for Africa Initiative (VACFA) which is located within the School of Public Health & Family Medicine at UCT. Since 2017 Rudzani serves as a member of the South Africa NITAG (NAGI) and a steering committee member of the Global Pertussis Initiative (GPI). He is a member of the current UCT Council. He was appointed the Head of Paediatrics and Child Health, Faculty of Health Sciences, UCT in November 2020. Rudzani's research interests lie in the area of evidence-based vaccinology. His PhD, which is currently under examination addresses the topic of resurgent pertussis in an African setting.

**Victor Musiime,** MBChB, MMed (Paed), PhD is a senior lecturer in the Department of Paediatrics and Child Health at Makerere University College of Health Sciences, Uganda and an investigator at Joint Clinical Research Centre (JCRC), Uganda. He completed his PhD (medical sciences) at the University of Antwerp Belgium in 2013. This was built on a career majoring in paediatric HIV and other infectious diseases since he became a paediatrician in 2004. His work has mainly been in HIV research, clinical care and treatment. He played a key role in the setting up the Paediatrics department at JCRC and was part of / led a team of personnel that initiated and followed up a cohort of over 2000 HIV-infected children and adolescents on antiretroviral therapy, provided treatment for opportunistic infections including tuberculosis, psychosocial support, as well as other forms of comprehensive paediatric HIV care and treatment. He is and has been an investigator on studies at JCRC in collaboration with sites in other African countries and other parts of the world, including clinical trials, such as ARROW, CHAPAS 2, CHAPAS 3, CHAPAS 4, ODYSSEY, SMILE, BREATHER, LIVING, LOLIPOP, EMPIRICAL and PediCAP. As a senior lecturer at Makerere University, he supervises doctoral and master's student research projects, conducts clinical and didactic teaching sessions for undergraduate and post graduate courses and plays the lead role in the coordination of the Master of Medicine course, in the Department of Paediatrics and Child Health.

**Heloise Buys** is the Head of Clinical Unit Ambulatory and Emergency Paediatrics at Red Cross War Memorial Children's hospital (RCWMCH). She is a senior clinician in general and emergency paediatrics and a senior lecturer and sub-programme convenor for the MBChB Programme in the Faculty of Health Sciences at the University of Cape Town. She is also an examiner and moderator for the Fellowship of the College of Paediatricians, Colleges of Medicine of South Africa. She has an interest in clinical paediatric HIV management and previously worked in the paediatric infectious diseases clinic, RCWMCH for 15 years spanning the pre- and post- ARV therapy era, gaining experience in inpatient and outpatient patient management, commencing at a time when South Africa went through its worst phase of the disease - she reminisces, 'as a clinician it was heart-breaking to see so many children die.'

## SUMMARY OF 1ST EDITORIAL BOARD MEETING

The first meeting of the editorial board of the AfSPID Bulletin was held on 27 November 2020.

Attendees: Brian Eley (chair), Regina Oladokun, Adegoke Falade, Mark Cotton, Olukukola Idoko, Ombeva Malande, Tinsae Alemayehu, Rudzani Muloiwa, Joycelyn Dame

Apologies: Harsha Lochan, Babatunde Ogunbosi & Heloise Buys

Meeting summary:

1. Review of milestones
    a. Between April 2013 and June 2020: 10 editions of the newsletter were published. The next edition will be circulated in December 2020. For 2021 the aim is to publish three editions, in March/April, July/August and November/December
    b. Author instructions were published in the newsletter from January 2015 onwards
    c. Archiving on the FIDSSA website from the inception of the newsletter, https://www.fidssa.co.za/SASPID and from November 2020 on the WSPID website at https://wspid.org/member-societies/
    d. Appointment of a deputy editor in January 2019
    e. Expansion of editorial board commenced in January 2020 and will continue for the next few years
2. Roles & responsibilities
    a. The roles & responsibilities of the editor were defined. The deputy editor has started to fill some of the editor's roles. During the next 6-12 months the editor and deputy editor will meet to review & clarify their roles.
    b. Ordinary editorial board members currently have two responsibilities, namely (1) to advise the editor on matters concerning the newsletter - in future at least one meeting of the editorial board will be convened per annum for the editor to consult with board members, and (2) to write or commission from one of their students / registrars / research associates / colleagues a minimum of one article per year – the meeting re-affirmed the importance of this role, to ensure the sustainability of the newsletter.
3. Structure of newsletter: The current structure includes contents, the editor's commentary, received articles without a clear structure, the journal watch section, conference news, information on how to join AfSPID and on the final page the editorial policy, author guidelines and archiving information.

    From December 2020 onwards the main structural changes are (1) society news will be taken out of the editor's commentary and placed in a separate section entitled society news – this section may include news on WSPID, Young WSPID, AfSPID including meeting minutes, the AfSPID newsletter, and other ID societies e.g. SASPID and NISPID, (2) the received articles are mainly reviews and commentaries thus a section entitled reviews & commentaries will be created for these article, (3) a new section entitled case reports & medical images was

proposed. After enthusiastic discussion, this proposal was accepted and was linked to a discussion on the appointment of deputy editors to manage this new section (refer below) and (4) the creation of a section for research articles, in the event that African researchers would like to publish their research findings in the newsletter. If this section is well supported peer-review of research articles will be introduced.

4. Appointment of deputy editors: The chair proposed the appointment of one or a group of associate editors to take responsibility for an entire section of the newsletter, commission and write articles for this section, edit all received articles, check received articles for plagiarism and ensure that at least one article be published in this section per newsletter. After discussion, strong support emerged for the appointment of a group of associate editors to manage and develop the new section on case reports & medical images, to ensure that at least one case report and one medical image is published per newsletter. The first group of associate editors will be appointed within the next few months. Ombeva Malande offered to develop a check list for assessing submitted case reports.
5. Changes to author guidelines: To support the changes to the newsletter, the author guidelines will be revised. Revisions include the addition of guidelines for medical images, research articles and contributions to the journal watch section
6. Circulation of newsletter: It is not clear how widely in Africa the newsletter is circulated. Approximately 50 individuals receive it through Mark Cotton's secretary. Furthermore, some editorial board and EXCO members circulate it to their own networks. To estimate the current circulation editorial board and EXCO members will be approached during the next few months. Furthermore, it was proposed that social media be used to advertise the newsletter. Bukky Idoko and Tinsae Alemayehu volunteered to create and manage a twitter account for posting the newsletter and other AfSPID communications.
7. Further expansion of the editorial board: Expansion of the editorial board to include representatives from sub-regions and countries not represented was discussed. Mark Cotton offered to enquire about North African representation. The ideal number of board members was discussed but no consensus was reached. One proposal was that the editorial board should be limited to 25 members, another suggestion was to keep the membership open-ended but to review the number of editorial members on a regular basis. The search for new members will continue.

## REVIEWS & COMMENTARIES

# THE TREATMENT OF DRUG RESISTANT TUBERCULOSIS IN CHILDREN

Harsha Lochan, Department of Paediatrics and Child Health, Frere Hospital, East London and Walter Sisulu University, Mthatha, South Africa

Corresponding author: harshalochan@gmail.com

**Introduction**

Tuberculosis is one of the top 10 causes of death worldwide and a source of major ill health. The United Nations has dedicated Goal 3.3 of the sustainable development goals (SDG) to ending global communicable epidemics. In line with the SDG, the World Health Organization (WHO) End TB strategy has outlined targets to be achieved by the year 2030[1]. The goals include a 90% reduction in TB-related deaths, an overall 80% reduction in TB incidence and the percentage of TB-affected households experiencing catastrophic costs to be zero. In addition, the United Nations General Assembly high level meeting on TB held in 2018, re-emphasising the commitment to achieving the above goals[2]. The target was to diagnose and treat 40 million people with TB overall and 1.5 million people with drug resistant TB (DR-TB) between 2018 and 2022. The targets for children were 3.5 million and 115 000, respectively. There were also further pledges from member countries for funding into ongoing TB research, widespread access to diagnosis, treatment, care and TB prevention measures. The ultimate vision is a world free of TB. Drug resistant TB, as an important public health threat is integral to this vision. The treatment of TB with drug resistant strains is not only more challenging than drug susceptible strains but also more costly. This past year due to the COVID-19 pandemic and disruptions in health services, the progress in achieving the goals to reduce the burden of TB disease, may be under threat[3]. The past few years has seen major advancements in the diagnosis and the treatment of DR-TB.

**The burden of drug resistant TB disease**

Rifampicin resistant TB (RR-TB) is defined as TB caused by *Mycobacterium tuberculosis* strains resistant to rifampicin. This includes strains that may still be susceptible to isoniazid. Multi-drug resistant TB (MDR-TB) refers to strains that are resistance to isoniazid and rifampicin without resistance to other first-line antituberculosis drugs. If in addition there is resistance to any fluoroquinolone and one of the three second line injectable agents (capreomycin, amikacin or kanamycin), then it refers to extensively drug resistant TB (XDR-TB). There may also be strains of MDR-TB with additional resistance to the fluroquinolones.

There are 30 high TB burden countries in the world, half of which are in Africa (Angola, Central African Republic, Congo, Democratic Republic of Congo, Ethiopia, Kenya, Lesotho, Liberia, Mozambique, Namibia, Nigeria, Sierra Leone, South Africa, Tanzania, Zambia and Zimbabwe). Worldwide, RR-TB was present in 3.3% of the estimated 10 million new TB cases and in 18% of re-treatment cases during 2019. Of the almost 465 000 people estimated to be infected with RR-TB worldwide, 78% were MDR-TB cases. India (27%), China (14%) and the Russian Federation (8%) constituted the bulk of the incident cases. According to country case notifications received, 333 304 people were identified and provided with treatment for RR-TB in 2018-2019 and this included only 8986 children (0-14 years), which is only 8 % of the target of 115 000 cases set for the years 2018-2022[3]. The African region had an estimated 77 000 cases (uncertainty interval 64-90 0000) of RR-TB[3].

**Diagnosis of drug-resistant TB disease in children**

The diagnosis of DR-TB disease in children can be quite challenging. Microbiological confirmation of DR-TB may not always be possible and feasible in children. This could be due to the pacibaciliary nature of the disease, difficulty

in obtaining specimens (induced sputum, gastric aspirates) from children or even limited availability of laboratory services with rapid diagnostic tests, culture and drug susceptibility testing (DST) especially in low-middle income countries (LMIC). Children, with a household contact of a RR-TB source case, have an increased risk of developing active TB disease (4% (95% CI, 1.5-6.5%)) with more than 50% of cases being detected within 2 years of initial exposure[4]. This emphasises the need for active contact investigation especially in children. Children under 5 years of age are a high-risk group for the development of TB disease. Marais and colleagues demonstrated that up to 20% develop disease following infection with infants showing up to 50% disease progression and with more severe forms of TB disease[5]. Extra-pulmonary TB disease can be quite severe and devastating especially TB meningitis. Therefore, the diagnosis of RR-TB in children may in many instances be based on a combination of a history of symptoms (cough, growth faltering, risk due to underlying immunosuppressive diseases), failure of previous treatment for TB, known close contacts with RR-TB, clinical signs, tuberculin skin test, and/or radiological suspicion for TB. Children with probable RR-TB (signs, symptoms and radiology consistent with TB disease without bacteriological confirmation and exposed to an infectious case of RR-TB) and those with possible RR-TB (signs, symptoms and radiology consistent with TB disease without bacteriological confirmation, not improving on first-line TB therapy) should be commenced on appropriate treatment as children can deteriorate rapidly if left untreated. If no microbiological confirmation and DST is obtainable for the index case, then treatment regimen is based on the DST of the contact with RR-TB. It is therefore important to have all results available. Children may be considered to have non-severe RR-TB disease if they are clinically diagnosed with no microbiological confirmation, unilateral pulmonary disease, non-cavitating pulmonary disease and isolated peripheral node disease.

**Microbiological diagnosis of RR-TB**

As previously mentioned, the paucibaciliary nature of TB disease in children can make it challenging to confirm DR-TB in this population. The difficulty and expertise in obtaining respiratory samples may also be a barrier. The WHO recommended rapid tests for TB diagnosis include the Xpert MTB/RIF and the Xpert MTB/RIF Ultra assays (Cepheid, Sunnyvale, USA). These tests detect the presence of the *Mycobacterium tuberculosis* complex as well as resistance to rifampicin. The Xpert MTB/RIF Ultra detects more mutations in the *rpoB* gene that confers rifampicin resistance and with the introduction of its use; should hopefully increase the detection of RR-TB incident cases. From previous studies, it is known that the diagnostic accuracy of Xpert MTB/RIF in respiratory samples from children is significantly lower than in adults[6]. In recent studies, the sensitivity of Xpert MTB/RIF Ultra in detecting culture-confirmed TB in children ranged from 64 to 74% an increase from original Xpert MTB/RIF assay[7,8]. More than one respiratory specimen has been proven to significantly increase the sensitivity of the test in detecting *M. tuberculosis* compared to culture up to 80% from induced sputum and nasopharyngeal samples[9]. The Xpert MTB/RIF and Xpert MTB/RIF Ultra assay are used for diagnostic purposes and not for ongoing monitoring of TB disease. These tests do not replace the need for smear with microscopy for acid-fast bacilli, culture for mycobacteria, and growth-based drug susceptibility testing (DST).

After detecting rifampicin resistance on Xpert MTB/RIF, additional specimens should be sent for smear microscopy, culture and DST. First and second- line, line probe assays are carried out to identify resistance to additional anti-tuberculous drugs. Figure 1 shows the algorithm used to identify further drug susceptibility for isolates[10].

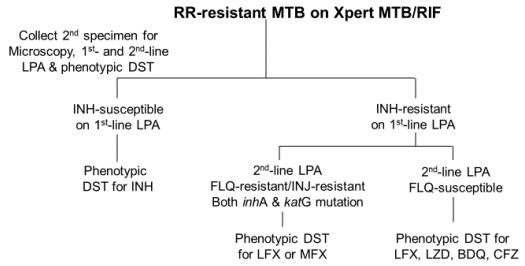



***Figure 1: Laboratory reflex testing for RR-TB (BDQ = bedaquiline, CFZ = clofazimine, DST = drug susceptibility testing, FLQ = fluoroquinolone, INH = isoniazid, INJ = injectable, LPA = line probe assay, LFX = levofloxacin, LZD = linezolid, MFX = moxifloxacin, first line LPA = MTBDRplus, second line LPA = MTBDRsl)***

**New developments in DR-TB disease treatment**

The injectable agents, kanamycin and amikacin, were part of the intensive phase backbone in the treatment of RR-TB for many years. Patients with RR-TB had to endure up to six months of receiving intramuscular injections of either of the drugs in addition to the prolonged treatment durations of 18-24 months. Aminoglycoside induced ototoxity was a well-documented co-morbidity[11]. Children being treated for DR-TB were often hospitalised and separated from families for the duration of their treatment. In 2016, the WHO approved a short course regimen of 9-12 months still using an injectable agent in the intensive phase of the disease treatment. In 2018, an injectable-free, all oral regimen was approved for use with the drug bedaquiline (BDQ) in adult patients with RR-TB. Later that year, bedaquiline was approved for use for adolescents older than 12 years and the drug delaminid for use in children 6 years and older. A year later, the all oral short course regimen was approved for use in children from 6 years of age. The use of the newer TB drugs in children are extrapolated from adult studies and have only recently included adolescents and younger children.

Two new drugs have been developed for the treatment of DR-TB. Bedaquiline is a diarylquinolone that interferes with mycobacterial ATP synthase. It has been shown to have early bactericidal activity. Compared to placebo, when added to a standard MDR-TB regimen for 24 weeks, bedaquiline showed a faster time to culture conversion by 40 days and a 20% increase in culture conversion[12]. The WHO currently recommends the use of bedaquiline from 6 years of age and > 15kg. The drug is currently available in a 100mg tablet that can be crushed or swallowed whole. Safety concerns for the drug were that of raised transaminases that could lead to hepatic toxicity and QTc prolongation (>450 ms) in adult studies. Other side effects included nausea, peripheral neuropathy and otovestibular toxicity[13]. Drug interactions between antiretroviral agents and bedaquiline have been observed. Co-administration with efavirenz can lower bedaquiline levels while lopinavir/ritonavir causes increased levels of the drug[14]. Access to bedaquiline is improving and at the end of 2019 it was being used in 109 countries with India, South Africa, the Russian Federation and Ukraine accounting for 68% of patients being treated.

Delamanid is a nitroimidazole agent that inhibits the synthesis of mycolic acids, a component of the *Mycobacterium* cell wall. It has bactericidal activity against replicating *M. tuberculosis*. A phase 3 randomised control study showed that the reduction in time to culture conversion was only 6 days[15]. The WHO has recommended its use in children from 3 years of age and this would serve as a replacement for an injectable agent in young children[16]. Delaminid is an expensive drug and has been available to use via the Delamanid compassionate use program[17].

**Drug regimens**

The treatment of children with DR-TB disease can be complicated and therefore treatment by an experienced clinician and linkage to the overall TB control program would be ideal. In most under-resourced settings, this is not always feasible. Medication recommended may not be readily available at the treating centre. Child-friendly drug formulations are still a problem and caregivers are educated on crushing and dissolving adult dose medication. There is a high pill burden especially if the child suffers from other co-morbidities. There is a lack of paediatric data on the safety and efficacy for newer drugs. Nevertheless, children with DR-TB need to be managed. The following are the recommended treatment regimens.

1. Short Course Regimen for MDR-TB/RR-TB

The all oral short course regimen for the treatment of MDR-TB has been used since 2018 in adults and since 2019 for children > 6 years of age. The recommendation for this was from the results of the Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with Multidrug-Resistant Tuberculosis (STREAM) trial which suggested that a shortened 9 month regimen containing bedaquiline was comparable with the standard approved 18-24 month regimen[18,19]. The new shorter regimen is recommended as a standard package. South Africa was one of the first countries to roll-out this regimen.

People (≥ 6 years and ≥ 15 kg) diagnosed with MDR-TB/RR-TB are eligible to receive the shorter course regimen of 9-11 months if: they have no prior history of treatment with second-line TB drugs (>1 month), there is no evidence of resistance to fluroquinolones, injectable agents, bedaquiline (BDQ), clofazimine (CFZ) or linezolid (LZD) (follow up the LPA and DST results), there is only one isoniazid (INH) mutation (*inhA* or *katG*) or no mutation causing resistance, they have no close contact with the above characteristics, there is no evidence of extra-pulmonary TB disease (meningitis, pericarditis, osteoarticular, abdominal disease) or extensive, bilateral cavitatory pulmonary MDR-TB/RR-TB disease[10,18]. HIV infection is not an exclusion criterion to the shorter course regimen provided the above criteria are met. The regimen recommended is as follows:

**4 – 6 months (Intensive Phase)**

Lzd (2 months) + Bdq (6 months) + high dose INH (4 - 6 months)
+ Lfx + Cfz + PZA + EMB

**5 months (Continuation phase)**
Lfx + Cfz + PZA + EMB

* Lfx = levofloxacin, PZA = pyrazinamide, EMB = ethambutol

2. Longer course regimen for MDR-TB/RR-TB

All persons who do not qualify for the shorter course regimen will receive a longer regimen as treatment therefore all children less than 6 years of age, persons more than 6 years of age with fluoroquinolone resistance (on LPA or DST), with extra-pulmonary TB disease (meningitis, pericarditis, osteoarticular, abdominal disease) will be treated for 18-20 months (15-17 months after culture conversion). A longer individualised treatment course would also be utilised for those who have not responding to treatment or have failed a previous RR-TB treatment regimen[10,18]. Table 1 lists the medications that are used to build a treatment regimen of 4-5 susceptible drugs based on DST results of the child or the infectious contact. This should include all 3 medicines from group A (if feasible), one from group B and using group C to complete the 4th or 5th drug when drugs from either group A or B cannot be used. Weight-banded dosing charts are available with most guidelines on DR-TB[10].

***Table 1: WHO drug groupings recommended for treatment MDR-TB/RR-TB in the longer regimen (page 96 of guideline)***

| Groups | Medicine | Doses (daily dosing per os) | CNS disease |
|---|---|---|---|
| **Group A** | Levofloxacin or Moxifloxacin | 15 -20 mg/kg | Yes |
| | Bedaquiline | 6 mg/kg for 14 days then 3-4 mg/kg 3 times per week | Yes |
| | Linezolid | 10–12 mg/kg > 16kg, 15 mg/kg < 16kg | |
| **Group B** | Clofazimine | 2–5 mg/kg | Yes |
| | Terizidone/ Cycloserine | 15-20 mg/kg | |
| **Group C** | Ethambutol | 15-25 mg/kg | |
| | Delaminid | 50mg tablet | Yes |
| | Pyrazinamide | 30–40 mg/kg | Yes |
| | Meropenem*^ | 20-40 mg/kg IV 8 hourly | |
| | Amikacin | 15-25 mg/kg IV/IM | Yes |
| | Ethionamide | 15-20 mg/kg | |
| | Para-amino-salicylic acid | 200-300 mg/kg | |
| **Other** | High Dose Isoniazid | 15-20 mg/kg | Yes |

*Imipenem-cilastin not used in children less than 15 years old, ^Must be used in combination with amoxicillin / clavulanic acid

Table 2 outlines the possible longer regimens that can be built using the drug groupings from Table 1. The use of delamanid under 3 years of age, while not currently approved, may be beneficial to the outcomes of the child in certain circumstances. This should be discussed with an expert or the local advisory board for DR-TB. Isoniazid could also be considered for inclusion in the regimen at a higher dose of 15-20 mg/kg if the *inhA* mutation conferring resistance is present. Should the *katG* mutation be detected, then ethionamide could be considered as the add-on drug.

***Table 2: Possible longer regimens for RR-/MDR-TB with or without fluoroquinolone resistance and disease affecting the central nervous system***

| Age group | Regimen | |
|---|---|---|
| | **Fluoroquinolone susceptible** | **Fluoroquinolone resistant** |
| < 3 years | Lfx + Lzd + Cfz + Trd + (Dlm or PAS) | Lzd + Cfz + Trd + (Dlm/ PAS and/or high dose INH/Eto*) |
| 3 – 6 years | Lfx + Lzd + Cfz + Trd + (Dlm or PAS) | Lzd + Cfz + Trd + Dlm +(PAS or Eto) |
| ≥ 6 years | Bdq + Lfx + Lzd + Cfz + Trd (Bdq & Lzd for 6 months) | Bdq + Lzd + Cfz + Trd +Dlm (Bdq & Lzd for 6 months) |
| | | |
| | **Central nervous system disease** | |
| < 6 years | Lfx + Lzd + Trd + Dlm + (Eto/ high dose INH) + (PZA) | |
| ≥ 6 years | Bdq + Lzd + Dlm + Lfx + Cfz + Trd + PZA + (high dose INH/Eto) (Bdq, Lzd, Dlm for 12 months) | |

* Depending on INH mutation. Bdq = Bedaquiline, Cfz = Clofazimine, Dlm = Delamanid, EMB = ethambutol Eto = Ethionamide, INH = Isoniazid, Lfx = levofloxacin, Lzd = Linezolid, PAS = Para-amino salyclic acid, PZA = pyrazinamide, Trd =Terizidone

3. Isoniazid mono-resistance TB

Isoniazid mono-resistance TB in children accounts for 2% of all cases. The diagnosis can be made using the first-line LPA and DST on culture results. Therefore, recommendations are extrapolated from adult studies. Often patients are already on a first-line TB regimen comprising isoniazid (INH), rifampicin (Rif), pyrazinamide (PZA) with or without ethambutol (EMB) depending on the severity of disease. Recommended regimen would be high dose INH + Rif + PZA + EMB + Levofloxacin for a duration of 6 months[10,18].

**Monitoring children on treatment**

Patients receiving anti-tuberculous medication for MDR-TB/RR-TB can experience side effects relating to the drugs or co-morbidities that the child may have. The response to treatment also requires monitoring. In order to manage and pre-empt adverse events, regular visits and investigations are needed throughout treatment. Table 3 lists the investigations at initiation and during the course of treatment[10,17]. HIV status, growth parameters, radiological evidence and specimens for Xpert MTB/RIF and culture are important initial assessments. The management of adverse events is beyond the scope of this document (see relevant guidelines).

***Table 3: Treatment monitoring schedule (adapted from the Sentinel Handbook, 2019)***

| | **Baseline** | **Month** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 9 | 12 | 15 |
| HIV status∞ | √ | | | | | | | | | |
| Growth – height and weight | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Clinical assessment | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Toxicity symptoms | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Chest radiographs | √ | | | | | | √ | | | |
| TB culture | √ | √ | √ | √ | | | √ | | √ | |
| Thyroid function tests (TSH, T4)^ | √ | Repeat 3 monthly | | | | | | | | |
| Full blood count + differential* | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Liver function tests (ALT) | √ | Repeat if vomiting or if symptoms of liver impairment | | | | | | | | |
| ECG for QTc interval | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Visual acuity§ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |

^ At baseline and 3-monthly if on PAS/Eto/Trd, * Week 2 and 4 when commenced on linezolid, ∞ If HIV infected, then for CD4 count and with HIV viral load monitoring at month 6, § For Linezolid toxicity.

Audiology assessments should be carried out if injectable agents are used during treatment and colour vision testing when ethambutol is used.

Adherence counselling is so important at the outset. The treatment duration for most children will be at least 18 months. Offering support for the caregivers, the child in the form of group support, nutritional, financial (if feasible) will be ongoing throughout the treatment process.

**Prophylaxis after exposure to DR-TB**

Due to higher risk of TB disease progression in younger children, children under 5 years with a household MDR-TB/RR-TB contact should be offered preventative therapy once TB disease is excluded. Children with HIV infection of any age should also be offered preventive therapy. Preventative therapy following exposure and infection with MDR-TB/RR-TB has been shown to be effective in preventing progression to TB disease[20]. Current recommended regimens include a 3-drug regimen or 2-drug regimen depending on the DST of the contact. Fluoroquinolones are used with the addition of ethambutol and or high-dose isoniazid.

**Conclusion**

DR-TB in children is challenging to diagnose and treat with less than half of cases having a definitive microbiological diagnosis. There are ongoing studies to evaluate the safety and efficacy of newer anti-tuberculosis drugs, but major strides have already been made towards improving the safety and efficacy of treatment regimens used in children.

## References

1. The End TB strategy (https://www.who.int/tb/strategy/end-tb/en/, accessed 13 February 2020)
2. United Nations General Assembly Resolution 73/3: Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis. United Nations 2018 (https://www.un.org/en/ga/73/resolutions.shtml, accessed 20 October 2020)
3. Global tuberculosis report 2020. Geneva: World Health Organization; 2020. (https://www.who.int/tb/publications/global_report/en/, accessed 25 October 2020)
4. Shah NS, Yuen CM, Heo M, Tolman AW, Becerra MC. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. Clin Infect Dis 2014; 58: 381-391
5. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004; 8:392–402
6. Zar HJ, Workman L, Isaacs W, Dheda K, Zemanay W, Nicol MP. Rapid diagnosis of pulmonary tuberculosis in African children in a primary care setting by use of Xpert MTB/RIF on respiratory specimens: a prospective study. Lancet Glob Health 2013;1:e97–e104.
7. Nicol MP, Workman L, Prins M, et al. Accuracy of xpert MTB/RIF ultra for the diagnosis of pulmonary tuberculosis in children. Pediatr Infect Dis J. 2018; 37:e261–3.
8. Sabi I, Rachow A, Mapamba D, et al. . Xpert MTB/RIF Ultra assay for the diagnosis of pulmonary tuberculosis in children: a multicentre comparative accuracy study. J Infect. 2018; 77:321–7.
9. Zar HJ, Workman L, Prins M, et al. Tuberculosis Diagnosis in Children Using Xpert Ultra on Different Respiratory Specimens. Am J Respir Crit Care Med. 2019; 200:1531–1538
10. Management of Rifampicin-resistant tuberculosis: A Clinical reference guide. National department of Health, South Africa, November 2019
11. Seddon JA, Godfrey-Faussett P, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in patients on treatment for drug-resistant tuberculosis**.** Eur Respir J. 2012; 40: 1277-1286
12. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014;371: 723–732
13. Borisov SE, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J 2017; 49.
14. Huynh J, Marais B. Multidrug-resistant tuberculosis infection and disease in children: a review of new and repurposed drugs. Ther Adv Infectious Dis 2019;6:1-16
15. World Health Organisation. The use of delamanid in the treatment of multidrug resistant tuberculosis in children and adolescents: interim policy guidance, http://apps.who.int/iris/bitstream (Accessed 8 February 2020)
16. Seddon JA, Schaaf HS, Marais BJ, et al. Time to act on injectable-free regimens for children with multidrug-resistant tuberculosis. Lancet Respir Med 2018; 6: 662–664
17. The Sentinel Project for Pediatric Drug-Resistant Tuberculosis. Management of multidrug-resistant tuberculosis in children: a field guide, http://sentinel-project.org/wp-content/uploads/2019/02/Updated_DRTB-Field-Guide-2019-V3.pdf
18. World Health Organisation, WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020, http://apps.who.int/iris (Accessed 31 October 2020).
19. Nunn AJ, Phillips PP, Meredith SK, Chiang C-Y, Conradie F, Dalai D, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med. 2019;380(13):1201–13.
20. Seddon JA, Hesseling AC, Finlayson H*, et al*. Preventive therapy for child contacts of multidrugr resistant tuberculosis: a prospective cohort study. *Clin Infect Dis* 2013; 57: 1676–1684.


# DECLINING IMMUNISATION COVERAGE DURING COVID-19 AND THE NEED FOR CATCH-UP


Mulugeta Naizgi Gebremicael and James Nuttall, Paediatric Infectious Diseases Unit, Red Cross War Memorial Children's Hospital and the Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa.

Corresponding author: naizgimulugeta@gmail.comm>


## Introduction

Immunisation is a cost-effective public health intervention, averting around 2 to 3 million deaths each year [1]. As a result of continuous progress in vaccination, the world is closer to the eradication of polio. As of August 25, 2020, the Africa Regional Certification Commission certified the WHO African Region as wild polio-free [2]. After this historic milestone, five of the six WHO regions are now free of the wild poliovirus, representing over 90% of the world's population [2]. In the last two decades, deaths from measles also declined by 73 percent worldwide, saving an estimated 23.2 million children's lives [3]. In addition to the role of vaccination in disease prevention, it also decreases antibiotic use and reduces antimicrobial resistance (AMR) [4]. This role is starting to become well recognised after the introduction of both pneumococcal conjugate vaccines & *Haemophilus influenzae* type B (Hib). Before the introduction of effective conjugate vaccines, the incidence of Hib disease in many countries ranged from 3.5 to 601 per 100,000 in children of under five years of age [5]. Since the early 1970s, there has been a steady increase in Hib beta-lactam resistance, mediated by bacterial expression of beta-lactamases and to a lesser extent, modified penicillin-binding proteins [6]. This picture changed after the introduction of Hib conjugate vaccine with a significant drop in disease cases and beta-lactamase positive strains [7.8]**.** Viral vaccines like influenza are also very effective in reducing antibacterial resistance by decreasing the likelihood of secondary bacterial infections and inappropriate antibiotic prescriptions for viral respiratory tract infections.

## Global & African trend in immunisation coverage before the COVID-19 pandemic

Knowing the immunisation coverage before the COVID-19 pandemic enables a better understanding of the potential negative consequences of interruption of the immunisation service as a result of the pandemic. The global trends of immunisation coverage from 1980 to 1990 showed a rapid escalation followed by a slower rate over the next two decades until 2010 and then a gradual plateauing in progress through 2019 (Figure 1) [9]. Coverage of the third dose of Diptheria, Tetanus, and Pertussis (DTP3) is often used as an indicator of how well countries are performing in routine immunisation services. In 2019, global coverage rates for DTP3 reached 85 percent, up from 72 percent in 2000 and 20 percent in 1980 [9]. Over the last decade, there has not been much progress, and only 85 countries are expected to reach the DTP3 coverage target of 90 percent or above as per the Global Vaccine Action Plan (GVAP) by the end of 2020 [10].

The progress made in DTP3 coverage also had considerable unevenness, and disparity among regions with the Central and West Africa UNICEF region lagging much further behind other areas [9]**.** This trend shows as the progress was not a linear trajectory, and gains achieved can be lost at any time when there is an emergency. Similarly, newer vaccine introductions, such as pneumococcal conjugate vaccine (PCV), rotavirus (ROTAC), and measles second dose (MCV2), show a similar pattern of rapid increment in coverage upon initial introduction [9]. Still, none have reached the current average global coverage levels of more established vaccines, even ten years after implementation. Due to the worldwide stagnation of immunisation coverage over the last decade, in 2019 19.7 million children under one year of age did not complete DTP3, and almost half them were in Africa [9]. The number of children who did not benefit from any vaccination, zero-dose children, was estimated at 13.8 million in the same year. Most of the zero dose children live in Africa and countries affected by conflict [9].

Even in the pre-COVID-19 era, the performance of immunisation programmes in Africa was mostly sub-optimal compared with the other WHO regions [9, 11]. DTP3 coverage stagnated at 76% in 2019, a level it attained in 2016 [11]. Nigeria and South Africa are among the countries that have the highest numbers of COVID-19 cases in Africa. DTP3 coverage before the pandemic in these countries was reported as 57% and 77%, respectively [11]. Similarly, single-dose measles-containing vaccine (MCV1) coverage for the continent is at 74%. Only eight countries have attained the recommended 95% MCV1 coverage level. At this rate, most countries are unlikely to meet the Global Vaccine Action Plan (GVAP) targets for DTP3 or measles elimination even without COVID-19 [11]. Globally there were concerns on how to tackle this stagnation in immunisation coverage over the last decade, even before the pandemic, to scale up & achieve the Sustainable development Goal 3.b.1 target of universal vaccination coverage [12].

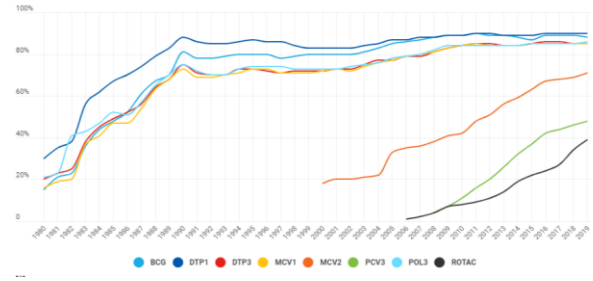



***Figure 1. Global immunisation coverage, selected antigens, 1980–2019. Figure taken from "WHO and UNICEF report on warn of a decline in vaccinations during COVID-19. GENEVA/NEW YORK, 15 July 2020" [https://www.who.int/news-room/detail/15-07-2020-who-and-unicef-warn-of-a-decline-in-vaccinations-during-covid-19](https://www.who.int/news-room/detail/15-07-2020-who-and-unicef-warn-of-a-decline-in-vaccinations-during-covid-19)***

**Impact of COVID-19 on routine immunisation**

When immunisation services are interrupted during emergencies, the risk of vaccine-preventable disease (VPD) outbreaks is high. Since the start of 2019, around 310 000 suspected measles cases have been reported in the Democratic Republic of the Congo (DRC), with measles-related mortality exceeding 6000 following the Ebola outbreak [13]. Similarly, historical evidence from previous epidemics like the Ebola outbreak in West Africa has shown that such events indirectly exacerbate morbidity and mortality related to a decrease in immunisation coverage [14]. On 15 July 2020, the WHO and UNICEF reported a significant decline in the number of children receiving routine vaccines worldwide due to gaps in the delivery and uptake of immunisation services caused by the COVID-19 pandemic [15]. These disruptions further reduce vaccine coverage, which has already been hampered by a decade of stalling coverage. According to the report, this is the first time in 28 years that a substantial drop in the number of children completing three DTP doses has occurred (Figure2) [15]. Besides, a minimum of 30 measles vaccination campaigns have been at risk of being cancelled.

An online immunisation pulse survey was done in May 2020 on the impact of COVID-19 on immunisation by the WHO, UNICEF, the Vaccine Alliance Gavi, and the Sabin Vaccine Institute involving 260 immunisation experts, including academia, representatives of Ministries of Health and global health organisations, across 82 countries [15,16]. According to the report, three-quarters of the 82 countries that responded reported COVID-19 related disruptions in their immunisation programmes as of May 2020 [15,16]. A previous pulse poll, conducted in April also showed that routine immunisations had been disrupted or even suspended in many countries [16]. This impact puts approximately 80 million children under the age of one year at an increased risk of contracting VPDs [16]. The main reported reasons for disruption to immunisation services were low availability of personal protective equipment (PPE) for healthcare workers (HCW), travel restrictions, and low availability of HCWs. National responders from 73% of countries indicated that they had seen disruptions in demand, with these percentages being highest for respondents from countries in the WHO African region (89%) [15,16]**.** The main reported reasons for disruptions in demand were: concern related to exposure to COVID-19, limited public transport, lockdown, and physical distancing policies [15,16]. In South Africa, a country with the highest burden of COVID-19 in Africa, the disruption to the immunisation programme is significant. According to a report from the South African National Department of Health, the national immunisation coverage in April during the lockdown dropped to 61% from 82% in April last year [17]. Similarly, the second dose measles (MCV2) dropped from 77% last year to 55% in April this year. Therefore, with further scale down of the lockdown and opening of schools, there will be a very high risk of outbreaks, particularly in Africa [17].

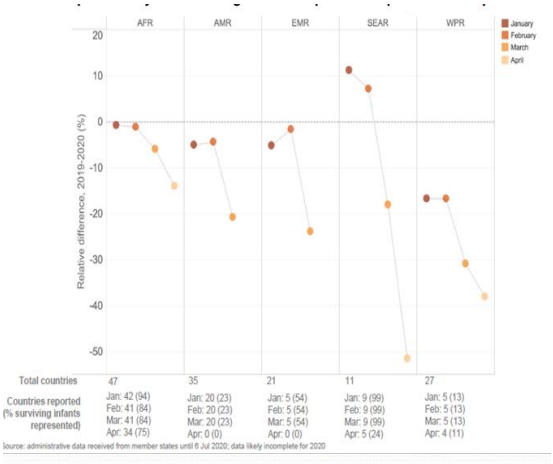



***Figure 2. Immunisation across the world by the COVID-19 pandemic 2020. Preliminary DTP coverage***

***data compared to equivalent 2019 period. Figure taken from "WHO and UNICEF report on warn of a decline in vaccinations during COVID-19. GENEVA/NEW YORK, 15 July 2020" https://www.who.int/news-room/detail/15-07-2020-who-and-unicef-warn-of-a-decline-in-vaccinations-during-covid-19***

**Maintaining immunisation during COVID-19**

According to data that we have so far, children's COVID-19 mortality rate is meagre compared to adults [18]. The same is not true for infections we vaccinate against like pneumonia, meningitis, diarrhoea, and measles. If we do not maintain the regular vaccination schedule, we will risk the lives of many children and disease outbreaks that could overwhelm the already overburdened healthcare system in Africa. A recent study by Abbas et al. showed that the benefit of sustaining routine immunisation in Africa is greater than the risk of COVID-19 deaths resulting from visiting health services for vaccination [19]. Maintaining essential health services, such as immunisation in times of emergency, is very important. New WHO guidelines on immunization and COVID-19 also recommend that countries act now to protect immunization services in order to further minimise disease outbreaks, and loss of life while continuing the response to COVID-19 [20]. To maintain vaccination, we should facilitate the introduction of catch-up programmes and encourage caregivers to continue vaccinating their children. In addition to this, ensuring strong supply chains, training of HCWs and disease surveillance is very important [20]. However, preventive immunisation campaigns are not recommended by WHO in a place where there is no active outbreak.

To maintain immunisation coverage during COVID-19, countries that faced significant disruption in their immunisation service should apply catch-up immunisation. Sustaining vaccination will be essential, especially in Africa, as the impact of COVID-19 on the immunisation service is higher than any other region in the world. Catch-up vaccination aims to provide optimal protection against disease as quickly as possible by completing a child's recommended vaccination schedule in the shortest but most effective time frame based on the general principles for catch-up vaccination. Experts advise the introduction of patient reminder and recall interventions to improve immunisation rates: appointment systems, sending reminder SMS messages, telephone calls to recall children, arranging catch-up outreach activities as well as media campaigns to encourage families and the community to vaccinate their children [21].

**Conclusion:** Immunisation is a cost-effective public health intervention, averting around 2 to 3 million deaths each year. Disease prevention by vaccination also decreases antibiotic use and reduces AMR. However, the progress in vaccination coverage was stagnant in the last decade. The onset of the COVID-19 pandemic has further disrupted the immunisation service due to gaps in the delivery and demand-side, putting millions of children at increased risk of contracting VPDs. The impact will be more significant in Africa as the continent is home to most unvaccinated children. So, there is a need to maintain vaccination during COVID-19 by implementing catch-up to save the lives of many children and prevent overwhelming the already overburdened healthcare system in Africa.

**References**


1. Immunization. Geneva: World Health Organization. https://www.who.int/news-room/facts-in-pictures/detail/immunization Date accessed: September 10, 2020.
2. The Africa Regional Commission for the Certification of Poliomyelitis Eradication. Certifying the interruption of wild poliovirus transmission in the WHO African region on the turbulent journey to a poliofree world. Lancet Glob Health 8, 2020 https://doi.org/10.1016/S2214-109X(20)30382-X.
3. Measles. Geneva: World Health Organization. https://www.who.int/news-room/fact-sheets/detail/measles.
4. Kathrin U. Jansen & Annaliesa S. Anderson (2018) The role of vaccines in fighting antimicrobial resistance (AMR), Human Vaccines & Immuno therapeutics, 14:9, 2142-2149, DOI: 10.1080/21645515.2018.1476814
5. Peltola H, Rod TO, Jonsdottir K, Bottiger M, Coolidge JA. Life-threatening Haemophilus influenzae infections in Scandinavia: a five-country analysis of the incidence and the main clinical and bacteriologic characteristics. Rev Infect Dis. 1990; 12:708–15. doi:10.1093/clinids/ 12.4.708. PMID: 2385772.
6. Tristram S, Jacobs MR, Appelbaum PC. Antimicrobial resistance in Haemophilus influenzae. Clin Microbiol Rev. 2007; 20:368–89. doi:10.1128/CMR.00040-06. PMID: 17428889.
7. Adam HJ, Richardson SE, Jamieson FB, Rawte P, Low DE, Fisman DN. Changing epidemiology of invasive Haemophilus influenzae in Ontario, Canada: evidence for herd effects and strain replacement due to Hib vaccination. Vaccine. 2010; 28:4073–8. doi:10.1016/j. vaccine.2010.03.075. PMID: 20398617.
8. Heilmann KP, Rice CL, Miller AL, Miller NJ, Beekmann SE, Pfaller MA, Richter SS, Doern GV. Decreasing prevalence of beta-lactamase production among respiratory tract isolates of Haemophilus influenzae in the United States. Antimicrob Agents Chemother 2005; 49:2561–4. doi:10.1128/AAC.49.6.2561-2564.2005. PMID: 15917574.
9. WHO/UNICEF. Progress and Challenges with Achieving Universal Immunization Coverage. 2019 Estimates of Immunization Coverage. ( data as of 15 July,2020) https://www.who.int/immunization/monitoring_surveillance/who-immuniz.pdf
10. WHO. Global vaccine action plan 2011-2020. https://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/
11. World Health Organization. Global Vaccine Action Plan: 2019 regional reports on progress towards to the GVAP-RVAP goals [Internet]. [cited 2020 May 19]. Available from:. World Health Organization; 2019. https://www.who.int/immunization/global_vaccine_action_plan/GVAP2019-RegionalReports-web.pdf?ua=1
12. UNICEF. SDG global indicators related to children https://data.unicef.org/wp-content/uploads/2018/05/SDG-Briefing-Notes-web.pdf
13. WHO. Deaths from Democratic Republic of the Congo measles outbreak of 2019. https://www.afro.who.int/news/deaths-democratic-republic-congo-measles-outbreak-top-6000
14. Elston JWT, Cartwright C, Ndumbi P, Wright J. The health impact of the 2014–15 Ebola outbreaks. Public Health 2017; 143:60–70.
15. WHO and UNICEF. Warn of a decline in vaccinations during COVID-19. https://www.who.int/news-room/detail/15-07-2020-who-and-unicef-warn-of-a-decline-in-vaccinations-during-covid-19. Date accessed: September 10, 2020.
16. WHO, UNICEF, Gavi, and the Sabin Vaccine Institute. An online immunization pulse survey was done in May 2020 on the impact of COVID-19 on immunization https://www.who.int/news-room/detail/22-05-2020-at-least-80-million-children-under-one-at-risk-of-diseases-such-as-diphtheria-measles-and-polio-as-covid-19-disrupts-routine-vaccination-efforts-warn-gavi-who-and-unicef
17. South Africa National Department of Health. Impact of COVID-19 on immunization. https://www.news24.com/citypress/news/dramatic-drop-in-sas-immunisation-rates-since-covid-19-lockdown-2020062
18. Bhopa S et al. Children's mortality from COVID-19 compared with all-deaths and other relevant causes of death: epidemiological information for decision-making by parents, teachers, clinicians and policymakers. Public Health 185 (2020) 19e20
19. Abbas K et.al. Routine childhood immunisation during the COVID-19 pandemic in Africa: a benefit–risk analysis of health benefits versus excess risk of SARS-CoV-2 infection. Lancet Glob Health. (20)30308-9
20. WHO. Guiding principles for immunization activities during the COVID-19 pandemic. Interim guidance 26 March 2020. https://apps.who.int/iris/handle/10665/331590
21. Yann J et al. Patient reminder and recall interventions to improve immunization rates. January 2018. Cochrane

database of systematic reviews (Online) 1(6).
DOI: 10.1002/14651858.CD003941.pub3

# PAEDIATRIC VANCOMYCIN THERAPEUTIC DRUG MONITORING IN AFRICA – CURRENT EVIDENCE AND CHALLENGES

Leonore Greybe, Paediatric Infectious Diseases Unit, Red Cross War Memorial Children's Hospital and the Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa.

Corresponding author: leonore.greybe@gmail.com>

**Abstract**

Antimicrobial resistance in Africa is on the rise and *Methicillin-Resistant Staphylococcus Aureus* (MRSA) is a priority pathogen. Despite challenges in dosing and monitoring of vancomycin in paediatric patients, it remains the antibiotic of choice for the treatment of severe MRSA infections. The current vancomycin therapeutic drug monitoring guidelines from the American Society of Health-System Pharmacists, Infectious Diseases Society of America (IDSA), and Society of Infectious Diseases Pharmacists currently recommended individualised targeting of the AUC:MIC ratio of 400–600, regardless of MIC. The use of innovative methods to monitor vancomycin levels may limit toxicity, but the additional resource requirement may limit the usefulness of therapeutic drug monitoring (TDM). Research on emerging resistant pathogens is imperative to inform future antibiotic guideline implementation in Africa.

**Commentary**

*Staphylococcus Aureus (S. aureus)* is a gram-positive commensal bacterium found colonizing the anterior nares and skin of up to 50% of children with skin disorders, burns and regular needle use.[1] Although *S. aureus* is the leading cause of skin, soft tissue and musculoskeletal infections in healthy children, it can cause a variety of localized and invasive infections, including healthcare associated infections (HAI) due to the organism's unique ability to adhere to foreign materials.[1] First described in the UK in the early 1960's, the adaptive power of *S. aureus* to evade antibiotics led to the emergence of *Methicillin-Resistant S. aureus* (MRSA), later found throughout the world.[2] MRSA is currently classified as a high priority pathogen on the World Health Organization (WHO) list of antibiotic resistant bacteria, which guide research and discovery of new antibiotics in accordance with global public health priorities.[3] The risk factors for antimicrobial resistance (AMR) in children include infancy, malnutrition, duration of hospital admission, previous exposure to antimicrobials and infection with human immunodeficiency virus (HIV).[4]

Globally, MRSA is found in the community and associated with HAI in almost every country. According to data from 85 (44%) member states of the WHO in 2014, national reported MRSA proportions exceed 20% in all regions, with 5/6 (83%) regions reporting resistance of 50% and more. African region countries reported resistant *S. aureus* in 12 - 80% of isolates from national data sources, and in 52% of invasive isolates from a single member state. The resistant proportion of invasive isolates as further reported in publications (n=27), ranged from 33-95%.[5] *Figure 1* shows the sources of MRSA resistance data and the major knowledge gaps, based on the data available for the *WHO antimicrobial resistance; global report on surveillance*.[5]

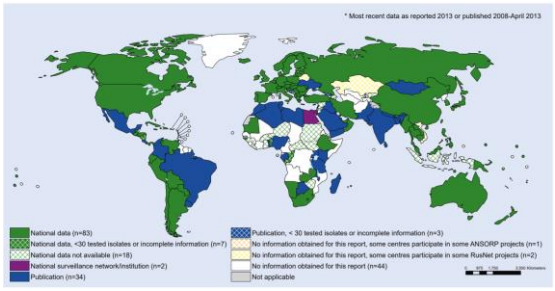



***Figure 1: Sources of data on MRSA courtesy of the WHO antimicrobial resistance; global report on surveillance.[5] National data does not imply that the data collected are representative for that country as a whole because information gaps are likely.***

A global surveillance study of AMR among blood-borne pathogens published in 2018 found that AMR was predominantly found in isolates from Africa, Latin America, and Asia. Extended spectrum beta-lactamase-producing Enterobacteriaceae and other gram-negatives resistant to carbapenems and tigecycline were the most common isolates, followed by gram-positive cocci, which included staphylococci and enterococci. The proportion of MRSA isolates from Africa (32.6%) in this study, was comparable with the proportion of MRSA isolates globally (33%).[6] Resistant bacteria have also been documented elsewhere in studies from Africa. A systematic review of AMR by Tadesse et al. only found MRSA reported in 8.9% of studies reviewed. The median prevalence of MRSA was 10.4% (interquartile range 12.6 – 33.8%), but as cefoxitin is typically used to screen for MRSA, the rate is likely underestimated. Less than two thirds of African countries contributed to AMR surveillance data.[7] A systematic review of HAI in Africa, with more than half of the publications from East Africa, found higher rates of MRSA (3.9% - 56.8%) in *S. aureus* isolates. This review also highlighted the paucity of HAI surveillance data in Africa, the variability between regions due to differences in geography, climate, and resources, and the emergence of MRSA as a priority pathogen.[8]

A meta-analysis on the aetiology of serious bacterial infections in neonates indicated that AMR is a major concern with *S. aureus* identified as the most common gram-positive organism causing infection.[9] Another specific review of the aetiology and resistance patterns of community-acquired bloodstream infections (BSI) in African children in studies published between 1990 and 2019 found that 29.5% of *S. aureus* BSI were caused by MRSA.[10] Reporting on the aetiology and resistance patterns of HAI BSI in African children have been published from cohorts in South Africa, Tanzania, and Kenya. In a prospective cohort from Kenya, the risk of HAI BSI was 5.9/1000 admissions and *S. aureus* was identified as the causative organism in 16%, but no susceptibility results were reported.[11] In a Tanzanian cohort, *S. aureus* was the most common gram-positive organism causing HAI and 12% were resistant to cloxacillin. All MRSA isolates were noted to be sensitive to vancomycin.[12] The prevalence of MRSA in all public and private hospitalised patients as reported from 4 regions in South Africa, showed a decrease in MRSA prevalence from 53% in 2010 to 40% in 2012 with MRSA present in 30-20% of isolates from the 0-9 year age group.[13] Children less than 5years old, were associated with a statistically significant risk to acquire MRSA.[13]

Vancomycin is a glycopeptide antibiotic active against gram-positive bacteria by inhibiting bacterial cell wall synthesis. The intravenous preparation is reserved for the treatment of infections due to resistant staphylococci and enterococci.[14] Despite challenges in dosing and monitoring of vancomycin, it remains the antibiotic of choice for the treatment of severe MRSA infections.[15] Vancomycin has a narrow therapeutic index and adequate concentrations are essential for clinical response. Inappropriate dosing is associated with treatment failure, antimicrobial resistance, and toxicity.[16] The efficacy of vancomycin is associated with the area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0-24}$) over minimum inhibitory concentration (MIC). For MRSA with an MIC of 1mg/L and AUC/MIC ratio >400 is recommended.[17]

Increased vancomycin dosing and higher trough levels were associated with improved outcomes in adult MRSA bacteraemia.[18] The 2011 Clinical Practice Guidelines by the IDSA suggested that vancomycin trough levels at a target range of 15–20 mg/L in adults with severe bacterial infections could be used as a surrogate marker for AUC/MIC.[19] The efficacy and safety of targeting trough concentrations of 15–20 mg/L in children were not established at the time and a dose of 15 mg/kg 6 hourly was recommended.[19] One paediatric study supported a correlation between an increased dose of 15mg/kg 6 hourly, and increased first trough levels without a significant increase in nephrotoxicity, but the increased dose did not consistently achieve goal trough levels as suggested for adult patients.[20] Several small retrospective studies also failed to show a correlation between higher serum trough target attainment and improved clinical outcomes in the paediatric population.[21–23] One study reported that trough levels less than 10mg/L did not predict reoccurrence of infection, or affect the 30 day mortality rate.[22] Furthermore, simulation data of vancomycin pharmacokinetics in children subsequently showed that 90% of simulated children achieved AUC/MIC >400 at trough concentrations of 7 -10 mg/L.[24] Nephrotoxicity at vancomycin trough levels >15 mg/L occurs more commonly in the paediatric population, especially in critically ill children where hypovolaemia and the concurrent use of other nephrotoxic drugs may aggravate vancomycin's toxic effects.[25] Although trough monitoring is still used in clinical practice, the inter-patient variability between trough concentrations and the actual AUC in adults and paediatrics have now been established.[16] The absence of clear benefit in the pursuit of higher trough levels calls this practice into question.

Current IDSA guidelines no longer advise trough monitoring, but rather advocate for individualised targeting of the AUC:MIC ratio of 400–600, regardless of MIC, to achieve clinical efficacy while improving safety. In the absence of therapeutic drug monitoring (TDM), a paediatric dose of 15mg/kg 6hourly is still recommended.[15] $AUC_{0-24}$ can be calculated by the use of one of two innovative methods. Bayesian model software can be used to accurately estimate AUC by incorporating population modelling with limited pharmacokinetic (PK) sampling. The program's knowledge of the way the drug has behaved in prior patients, combined with the specific dose and drug concentrations and individual patient variables, can provide real time AUC-guided dose adjustment. An alternative method as shown in *figure 2*, calculates the individual's concentration-time profile by collecting peak and trough samples and applying log-linear equations to calculate the AUC. This method slightly underestimates the $AUC_{0-24}$. The calculations are based on kinetics from the measured levels and not age-related PK parameters, which makes this approach potentially accessible to paediatric practice.[16]

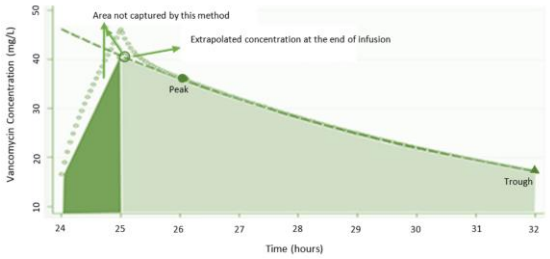



***Figure 2: Expected area under the curve vancomycin concentration time profile, adapted from Pai et al.[16]***

A recent retrospective review of vancomycin TDM at a children's hospital found that 75% of children with normal renal function attained $AUC_{0-24}$>400 with recommended dosing, but children in the 1-3 year age group (51%) were less likely to attain target AUC due to increased renal clearance of vancomycin. The use of TDM only after 72hours of vancomycin administration, in all children except for those in critical care, led to fewer dose adjustments and a 30% relative reduction in likelihood of AKI per year.[26] After a 3-month audit, a study in Cape Town used a Bayesian TDM model to improve the monitoring of vancomycin levels in hospitalised patients. The audit found that >60% of trough concentration samples of both paediatric and adult patients were outside of the therapeutic range.[27] After implementation of the computerised system, 71% of serum vancomycin concentrations included in the study, irrespective of dosing method, achieved an $AUC_{0-24}$/MIC > 400.[27]

**Conclusion**

Information concerning the true extent of AMR in the African Region is limited due to a lack of representative surveillance data.[5,7] High rates of MRSA imply that treatment for suspected or verified resistant *S. aureus* infections will require second line antibiotics which is more costly, have serious side effects and require additional monitoring.[15] The use of innovative methods to monitor vancomycin levels require additional technical and human resources, but may limit toxicity especially in critically ill adults and children.[16] In order to limit expenditure, some authors suggest limiting monitoring to only include patients on vancomycin >72hours and those in critical care.[26] Unfortunately, the additional resource requirements as well as the lack of evidence of clear benefit in paediatric practice, may well keep TDM out of reach for many resource restricted settings. Future research of emerging resistant pathogens in Africa and the implementation of technology to assist in the identification and management of these pathogens are imperative to inform future antibiotic guideline implementation on the continent.

**References**


1. DW AA of PP infections. IK, Brady MT, Jackson MA LS. Red Book: 2018 Report of the Committee on Infectious Diseases. *Am Acad Pediatr*. Published online 2018.
2. Deurenberg RH, Stobberingh EE. The evolution of Staphylococcus aureus. *Infect Genet Evol*. Published online 2008. doi:10.1016/j.meegid.2008.07.007
3. WHO. Global priority list of antibiotic-resistant batceria to guide research, discovery, and development of new antibiotics. *Who*. Published online 2017.
4. Dramowski A, Whitelaw A, Cotton MF. Burden, spectrum, and impact of healthcare-associated infection at a South African children's hospital. *J Hosp Infect*. 2016;94(4):364-372. doi:10.1016/j.jhin.2016.08.022
5. WHO. Antimicrobial resistance. Global report on

surveillance. *World Heal Organ*. Published online 2014. doi:10.1007/s13312-014-0374-3
6. Zhang Z, Chen M, Yu Y, Pan S, Liu Y. Antimicrobial susceptibility among gram-positive and gram-negative blood-borne pathogens collected between 2012-2016 as part of the Tigecycline Evaluation and Surveillance Trial. *Antimicrob Resist Infect Control*. 2018;7(1):1-13. doi:10.1186/s13756-018-0441-y
7. Tadesse BT, Ashley EA, Ongarello S, et al. Antimicrobial resistance in Africa: A systematic review. *BMC Infect Dis*. 2017;17(1):1-17. doi:10.1186/s12879-017-2713-1
8. Irek EO, Amupitan AA, Obadare TO, Aboderin AO. A systematic review of healthcare-associated infections in Africa: An antimicrobial resistance perspective. *Afr J Lab Med*. Published online 2018. doi:10.4102/ajlm.v7i2.796
9. Okomo U, Akpalu ENK, Le Doare K, et al. Aetiology of invasive bacterial infection and antimicrobial resistance in neonates in sub-Saharan Africa: a systematic review and meta-analysis in line with the STROBE-NI reporting guidelines. *Lancet Infect Dis*. 2019;19(11):1219-1234. doi:10.1016/S1473-3099(19)30414-1
10. Droz N, Hsia Y, Ellis S, Dramowski A, Sharland M, Basmaci R. Bacterial pathogens and resistance causing community acquired paediatric bloodstream infections in low- And middle-income countries: A systematic review and meta-analysis. *Antimicrob Resist Infect Control*. 2019;8(1):1-12. doi:10.1186/s13756-019-0673-5
11. Aiken AM, Mturi N, Njuguna P, et al. Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: A prospective cohort study. *Lancet*. Published online 2011. doi:10.1016/S0140-6736(11)61622-X
12. Blomberg B, Manji KP, Urassa WK, et al. Antimicrobial resistance predicts death in Tanzanian children with bloodstream infections: a prospective cohort study. *BMC Infect Dis*. 2007;7(1):1-14. doi:10.1186/1471-2334-7-43
13. Perovic O, Iyaloo S, Kularatne R, et al. Prevalence and trends of staphylococcus aureus bacteraemia in hospitalized patients in South Africa, 2010 to 2012: Laboratory-based surveillance mapping of antimicrobial resistance and molecular epidemiology. *PLoS One*. Published online 2015. doi:10.1371/journal.pone.0145429
14. Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town, and the Health and Medical Publishing Group publishers for the SAMA. *The South African Medicines Formulary*.
15. Rybak MJ, Le J, Lodise TP, et al. Executive Summary: Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant Staphylococcus aureus Infections: A Revised Consensus Guideline and Review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of A. *Pharmacotherapy*. 2020;40(4):363-367. doi:10.1002/phar.2376
16. Pai MP, Neely M, Rodvold KA, Lodise TP. Innovative approaches to optimizing the delivery of vancomycin in individual patients. *Adv Drug Deliv Rev*. Published online 2014. doi:10.1016/j.addr.2014.05.016
17. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. *Clin Pharmacokinet*. Published online 2004. doi:10.2165/00003088-200443130-00005
18. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant staphylococcus aureus bacteremia: Support for consensus guidelines suggested targets. *Clin Infect Dis*. Published online 2011. doi:10.1093/cid/cir124
19. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis*. 2011;52(3). doi:10.1093/cid/ciq146
20. Frymoyer A, Guglielmo BJ, Wilson SD, Scarpace SB, Benet LZ, Hersh AL. Impact of a hospitalwide increase in empiric pediatric vancomycin dosing on initial trough concentrations. *Pharmacotherapy*. Published online 2011. doi:10.1592/phco.31.9.871
21. McNeil JC, Kok EY, Forbes AR, et al. Healthcare-associated Staphylococcus aureus bacteremia in children: Evidence for reverse vancomycin creep and impact of vancomycin trough values on outcome. *Pediatr Infect Dis J*. Published online 2016. doi:10.1097/INF.0000000000000991
22. Yoo RN, Kim SH, Lee J. Impact of initial vancomycin trough concentration on clinical and microbiological outcomes of methicillin-resistant Staphylococcus aureus bacteremia in children. *J Korean Med Sci*. Published online 2017. doi:10.3346/jkms.2017.32.1.22
23. Regen RB, Schuman SS, Chhim RF, Arnold SR, Lee KR. Vancomycin treatment failure in children with methicillin-resistant Staphylococcus aureus Bacteremia. *J Pediatr Pharmacol Ther*. Published online 2019. doi:10.5863/1551-6776-24.4.312
24. Frymoyer A, Guglielmo BJ, Hersh AL. Desired vancomycin trough serum concentration for treating invasive methicillin-resistant staphylococcal infections. *Pediatr Infect Dis J*. 2013;32(10):1077-1079. doi:10.1097/INF.0b013e318299f75c
25. Fiorito TM, Luther MK, Dennehy PH, LaPlante KL, Matson KL. Nephrotoxicity With Vancomycin in the Pediatric Population: A Systematic Review and Meta-Analysis. *Pediatr Infect Dis J*. 2018;37(7):654-661. doi:10.1097/INF.0000000000001882
26. Olson J, Hersh AL, Sorensen J, Zobell J, Anderson C, Thorell EA. Intravenous Vancomycin Therapeutic Drug Monitoring in Children: Evaluation of a Pharmacy-Driven Protocol and Collaborative Practice Agreement. *J Pediatric Infect Dis Soc*. Published online 2020. doi:10.1093/jpids/piz036
27. Abulfathi AA, Chirehwa M, Rosenkranz B, Decloedt EH. Evaluation of the Effectiveness of Dose Individualization to Achieve Therapeutic Vancomycin Concentrations. *J Clin Pharmacol*. 2018;58(9):1134-1139. doi:10.1002/jcph.1254

## THE IMPACT OF THE ONGOING COVID-19 PANDEMIC ON THE DELIVERY OF ROUTINE HEALTH SERVICES IN NIGERIA

Olushola Olibamoyo, Department of Behavioural Medicine, Faculty of Clinical Sciences, Lagos State University College of Medicine, Ikeja, Lagos State, Nigeria

Oghenebrume Wariri, Vaccines and Immunity Theme, Medical Research Council Unit, The Gambia at the London School of Hygiene and Tropical Medicine (MRCG at LSHTM), Atlantic Boulevard, Fajara, The Gambia

Corresponding author: Oghenebrume.Wariri@lshtm.ac.uk

**Background**

Coronavirus Disease-2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) in March 2020[1] and has spread to six continents, with more than 45 million cases and about 1 million deaths registered as of the end of October 2020[1]. Compared to the rest of the world, the pandemic has evolved differently in sub-Saharan Africa[2]. The outbreak started slowly and later than it did in Europe and the Americas, probably due to the low intensity of international air traffic and the swift closure of national borders in many sub-Saharan African countries following the first few confirmed cases. In Nigeria, significant progress has been made in the pandemic response, backed by international, regional, and national alliances in comparison to previous epidemics. There is evidence to suggest that the Nigerian health system, whose capacities to deal with COVID-19 pandemic is comparatively lower than in many high-income countries (HIC) settings, have not been overwhelmed, even at the peak of the pandemic. However, the potential indirect consequences on other co-morbidities, endemic public health challenges, and emergency preparedness for other diseases due to disruptions to routine healthcare and reduced access to essential health services must be explored. In a commentary in the *Proceedings of the Nigerian Academy of Science*, Bolanle A. Ola and colleagues explored the impact and implications of the COVID-19 pandemic on

background co-morbidities and the major prevalent public health challenges, including mental health, in Nigeria[3]. Their commentary also discussed the need to build clinical research capacity to design and conduct clinical trials in Nigeria. We summarise the key issues raised in their commentary below and extend the position taken in their article by pushing the argument on vaccine development further.

**COVID-19 and co-morbidities**

The COVID-19 presents largely with cough, dyspnoea, and constitutional symptoms [4], thus making clinical diagnosis difficult due to resemblance to common infectious diseases in Nigeria. The majority of confirmed cases to date have been asymptomatic. However, severe cases are more likely to occur in the elderly, in men, and/or in patients with underlying co-morbidities including diabetes mellitus, hypertension, and chronic pulmonary diseases[5]. The actual burden of the major non-communicable diseases (NCDs) in Nigeria is unknown but modelling studies suggest there have been steep increases in the last decade[6]. The situation might have been worsened by the pandemic due to disruption of health service delivery, with potential worsening of these conditions and increased risk of severe COVID-19 in Nigeria. Other factors, such as over-stretched routine public health service, insufficient financial and human resources, and incessant strike actions by health professionals, when combined with the afore-mentioned, can cause an unmitigated COVID-19 epidemic in Nigeria.

**COVID-19 and mental health**

COVID-19 pandemic has affected the fabric of society including mental health[7]. A recent online survey in three COVID-19 hotspots in Nigeria found a relative increase in depression, post-traumatic stress disorder, and emotional abuse among the general population[8]. The most vulnerable subpopulations include the elderly, children, those with chronic illnesses, those with pre-existing mental health problems, healthcare professionals, and patients with COVID-19. Spending time in quarantine, isolation, and social distancing have also been identified as risk factors for mental health issues, such as anxiety, depression, suicide, domestic violence, and alcohol and substance abuse[9].

Children and adolescents are not spared, especially those with special educational needs and children with pre-existing family dysfunctions as more than 90% of enrolled learners were out of school due to school closure during the peak of the pandemic in Nigeria[10]. Further research is needed to understand the long-term psychological and mental health outcomes due to the pandemic control policies as well as the effects of COVID-19 on the risk of anxiety, depression, and other outcomes such as rape, domestic violence, and suicide among Nigerians.

**COVID-19, tuberculosis and HIV**

Currently, Nigeria ranks among the high-burden countries for HIV and tuberculosis (TB), with approximately 40,000 new TB cases each month, and about two million people living with HIV (PLWH)[11]. A patient with cough, fever, or breathlessness could have COVID-19, background TB, or an opportunistic HIV-related respiratory disease.

During the ongoing pandemic, the social stigma of having a cough, reassignment of TB workforce, and diversion of TB-diagnostics tools such as GeneXpert machines to COVID-19 diagnosis may have further reduced access to these services for TB patients with consequent delays in diagnosis and treatment[12]. Equally, the lockdown may have led to an increase in household TB exposure and transmission especially among susceptible populations like children below five years and PLHW. Given the above, it might be reasonable to assume that the gains made against TB are at risk of being reversed by the impact of the ongoing COVID-19 epidemic in Nigeria.

HIV-infected individuals with co-morbidities, lower CD4 cell counts, or an unsuppressed viral load might be at an increased risk of severe COVID-19. Thus, caution is required when interpreting the incidence and clinical course of COVID-19 among PLWH compared with the HIV-negative population. Even amid the ongoing pandemic, it is critical to remember that TB and HIV have not disappeared from Nigeria. The pandemic offers an opportunity to assess the shared aspects of COVID-19, TB, and HIV, as well as the challenges and lessons learned from the control efforts of each of them that could be mutually beneficial.

**COVID-19 and maternal, newborn, child health and immunisation services**

This year, the world begins the final decade in the countdown to the end of the Sustainable Development Goals (SDGs). Also, it is a pivotal time in the history of global maternal, newborn, and child health which is linked with goal number three of the SGDs. However, maternal mortality, under-5 mortality, infant mortality, neonatal mortality, stillbirths' rates, and the number of unvaccinated children in Nigeria are among the highest in the world[13]. In this already bleak landscape, the ongoing COVID-19 pandemic has reduced access to essential maternal, child health, and immunisation services due to disruption of health systems, as well as the overall economic impact brought about by public health strategies aimed at flattening the rate of transmission.

The Strategic Advisory Group of Experts on Immunisation (SAGE) of WHO, in the early phase of the pandemic, recommended that all preventive mass vaccination campaigns be halted in 37 countries including Nigeria in a bid to prevent further spread of the SARS-CoV-2 virus[14]. There is evidence suggesting that this halt resulted in more than 117 million children in 37 countries being at risk of missing out on age-appropriate life-saving vaccines[14]. The halt to immunisation services during the COVID-19 pandemic, in addition to emerging issues of vaccine hesitancy being reported in sub-Saharan Africa and shut down of some health facilities during the lockdown could have further affected overall vaccination coverage rates in Nigeria which are generally suboptimal.

**COVID-19 candidate vaccine landscape and Nigeria**

Globally, vaccination has been recognized as the most potent tool for the control of infectious diseases. Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective coronavirus vaccine by the end of 2020. Currently, about 31 vaccines are undergoing clinical trials in humans, and at least 142 preclinical vaccines are under active investigation in animals[15]. As of 24th November 2020, preliminary analysis of phase-three trials of three candidate vaccines were made available. Pfizer® and BioNtech® were the first to make history on November 9 when they presented the preliminary data indicating that their mRNA-based coronavirus vaccine has 95%

protective efficacy against COVID-19 beginning 28 days after the first dose[16]. A week later, Moderna® reported efficacy of 94.5% with a similar vaccine based on their interim analysis. [17]. Lastly, the Oxford adenovirus-vectored coronavirus vaccine, developed with AstraZeneca, reported an average efficacy of 70%[18].

In making a choice on which of the soon to be licensed vaccines to be used in Nigeria or sub-Saharan Africa more generally, some trade-offs must be made. While efficacy and dosing regimen will be key, consideration must also be given to the unit cost and ease of storage of the vaccines which are key issues that Nigeria and other sub-Saharan African countries continue to grapple with. Vaccine 'nationalism' has emerged as a new phenomenon in the race to defeat COVID-19, with countries leading the vaccine development efforts prioritizing their citizens if the vaccine is proven efficacious, as opposed to vaccine 'diplomacy' expected from developing countries[19]. How countries in sub-Saharan Africa navigate this new trend and ensure that her citizens gain access to the vaccines being developed in a timely manner in order to halt the ongoing pandemic remains to be seen.

**Leveraging the pandemic to develop clinical/vaccine trial capacity in Nigeria**

Nigeria has a huge potential to become a leader in translational research on the continent due to its geography and population size. Its systemic and infrastructural challenges and the unacceptably high burden of diseases could serve as an impetus to foster the development of organized clinical/vaccine trial capacity that could entrench the research culture/integrity and scientific rigor required for credible research endeavours.

Leveraging on the ongoing collaborative COVID-19 research platforms and momentum generated by the ongoing pandemic would be critical for Nigeria to refocus its research culture and build capacity. To achieve this, political will/action, a commitment to in-country financing of research, and meaningful collaborations with established research platforms in sub-Saharan Africa and the global north would still be needed. Research collaborations could provide opportunities for research attachment programs while attracting competitive grants for translational research in Nigeria.

## Conclusion

Bolanle A. Ola and colleagues have highlighted the impact and implications of the COVID-19 pandemic on background co-morbidities and the major prevalent public health challenges in Nigeria. Their commentary adds another piece to the puzzle of the discussions around the impact of COVID-19 on routine health services in sub-Saharan Africa. The indirect public health and socio-economic impacts of COVID-19 in Nigeria is projected to be disproportionately worse among the poorest and most disadvantaged people in the population. In terms of research, large-scale population-based seroprevalence surveys should be part of the ongoing comprehensive response to COVID-19 to accurately determine the prevalence of SARS-CoV-2 in Nigeria. This could help establish a background surveillance system which could be a platform for generating reliable data on the epidemiology of both communicable and non-communicable diseases of public health importance. As a call to action, we encourage governments, international partners, researchers, and authors to consider the indirect impacts of the ongoing pandemic highlighted here in discussions about the response to the COVID-19 pandemic. We present additional challenges which should be considered, especially those related to the soon to be licensed COVID-19 vaccines and their use in Nigeria.

Amid the frenzied report about which COVID-19 vaccine will be most successful, there has been much less focus on a vital component of the process which is to ensure that the most vulnerable subpopulations in low- and middle-income countries receive the vaccine at the right time. Under the WHO ACT-Accelerator framework, countries will initially receive doses for 3%, then 20% of the population, ultimately scaling up to full coverage and it will be up to individual governments to work out who and where the health workers and key at-risk populations are[20]. The lack of a robust and comprehensive health information system in Nigeria will make it difficult to work out, in an equitable manner, those who need the limited doses which will be available initially. The national vaccination system, i.e. the Expanded Programme on Immunisation was primarily designed to ensure that children receive their life-saving vaccines and not for large-scale adult vaccination programs. Also, the cold chain, i.e. refrigerated storage required to preserve the vaccine may be different for the COVID-19 vaccine, making it more difficult for the vaccine to reach the most vulnerable in the rural areas in Nigeria where electricity is often limited. Additionally, a limited supply of the vaccine to about 3-20 % of the population initially may lead to an increased risk of counterfeiting of the vaccines by desperate individuals. This may give room for sceptics to further discredit vaccines in a landscape already characterised by growing scepticism due to dis- and misinformation at the peak of the pandemic.

**References**


1. World Health Organisation. *WHO Coronavirus Disease (COVID-19) Dashboard.* https://covid19.who.int/ (accessed 20 November 2020).
2. Kavanagh MM, Erondu NA, Tomori O, et al. Access to lifesaving medical resources for African countries: COVID-19 testing and response, ethics, and politics. *Lancet* 2020;395(10238):1735-8 DOI: 10.1016/S0140-6736(20)31093-X (accessed 20 November, 2020).
3. Ola BA, Nkereuwem E, Oriero EC et al. COVID-19 in Nigeria: Implications for Management of Related Co-morbidities, Prevalent Public Health Challenges, and Future Epidemic Preparedness. *Proc Niger Acad Sci*. 2020;13(1s). Available from: http://nasjournal.org.ng/index.php/pnas/article/view/209 (accessed 15 November 2020).
4. Di Gennaro F, Pizzol D, Marotta C, et al. Coronavirus Diseases (COVID-19) Current Status and Future Perspectives: A Narrative Review. *Int J Environ Res Public Health* 2020;17(8). DOI: 10.3390/ijerph17082690.
5. Hassan SA, Sheikh FN, Jamal S, Ezeh JK, Akhtar A. Coronavirus (COVID-19): A Review of Clinical Features, Diagnosis, and Treatment. *Cureus* 2020;12(3):e7355. DOI: 10.7759/cureus.7355.
6. Gouda HN, Charlson F, Sorsdahl K, et al. Burden of non-communicable diseases in sub-Saharan Africa, 1990-2017: results from the Global Burden of Disease Study 2017. *The Lancet Global health* 2019;7(10):e1375-e87. DOI: 10.1016/S2214-109X(19)30374-2.
7. Djalante R, Shaw R, DeWit A. Building resilience against biological hazards and pandemics: COVID-19 and its implications for the Sendai Framework. *Progress in Disaster Science* 2020;6:100080. DOI: 10.1016/j.pdisas.2020.100080,
8. Chen Q, Liang M, Li Y, et al. Mental health care for medical staff in China during the COVID-19 outbreak. *Lancet Psychiatry*. 2020 Apr;7(4):e15-e16. DOI: 10.1016/S2215-0366(20)30078-X
9. Wind TR, Rijkeboer M, Andersson G, Riper H. The COVID-19 pandemic: The 'black swan' for mental health care and a turning point for e-health. *Internet Interv.* 2020 Apr;20:100317. DOI: 10.1016/j.invent.2020.100317
10. Eshraghi AA, Li C, Alessandri M, et al. COVID-19: overcoming the challenges faced by individuals with autism and their families. *Lancet Psychiatry* 2020;7(6):481-3. DOI: 10.1016/S2215-0366(20)30197-8

11. World Health Organization. *Global tuberculosis report 2019*. https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1. (accessed 5 June 2020)
12. Pang Y, Liu Y, Du J, Gao J, Li L. Impact of COVID-19 on tuberculosis control in China. *Int J Tuberc Lung Dis* 2020;24(5):545-7. DOI: 10.5588/ijtld.20.0127.
13. World Health Organization. *Trends in maternal mortality 2000 to 2017: Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division.* https://apps.who.int/iris/handle/10665/327596 (accessed 6 June 2020)
14. World Health Organization. *World Malaria Report; 2019*. https://www.who.int/malaria/publications/world-malaria-report-2019/en/. (accessed 2 June 2020).
15. World Health Organization. *WHO DRAFT landscape of COVID-19 candidate vaccines* https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines (accessed 15th November, 2020)
16. Mahase E. Covid-19: Pfizer and BioNTech submit vaccine for US authorisation *BMJ* 2020; 371 :m4552. DOI: https://doi.org/10.1136/bmj.m4552
17. Mahase E. Covid-19: Moderna vaccine is nearly 95% effective, trial involving high risk and elderly people shows *BMJ* 2020; 371:m4471. DOI: https://doi.org/10.1136/bmj.m4471
18. Mahase E. Covid-19: Oxford researchers halt vaccine trial while adverse reaction is investigated *BMJ* 2020; 370 :m3525. DOI: https://doi.org/10.1136/bmj.m3525
19. World Health Organization. *Working for global equitable access to COVID-19 vaccines.* https://www.who.int/initiatives/act-accelerator/covax . (accessed 27 August 2020).
20. World Health Organization. *Fair allocation mechanism for COVID-19 vaccines through COVAX facility*. https://www.who.int/publications/m/item/fair-allocation-mechanism-for-covid-19-vaccines-through-the-covax-facility (accessed 24 November 2020)


## RESEARCH

# ACCESS TO COVID-19 TESTING AMONG PAEDIATRICIANS IN ETHIOPIA


Tinsae Alemayehu, American Medical Center AND St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia

Corresponding author: tigisttinsae@gmail.com


Health workers (anyone working or volunteering in a healthcare facility or long-term care facilities such as those offered for the elderly) are one of the population groups with the highest risk of acquiring COVID-19 infection. Nguyen et al estimated the risk of front-line health workers for acquisition of the infection to be 3.4 times higher than the general community in the U.K. and the U.S. [1]. Another prospective observational study found that healthcare workers in Scotland were three times more likely to be seropositive for antibodies against the receptor-binding domain (RBD) of the SARS-CoV-2 spike (S1) protein compared to the community[2].

Back in July 2020, the World Health Organization had announced that 10% of infections globally had been recorded in health workers[3]. In the same month, WHO Africa estimated that more than 10,000 health workers had been infected with COVID-19 in Africa or 1.33% of infections in the continent at that time[4]. Of course, the discrepancy in proportion of infected health workers compared to the general population in Africa and the rest of the world should be thought of in context with the paucity of the health-force in the continent: an average of less than one physician and less than two nurses or midwives per 1000 people[5].

Ethiopia has at present the fourth largest number of recorded cases of COVID-19 in Africa with 84 cases diagnosed per 100,000 population (25th October 2020) and also the fourth highest rate of testing in the continent (1.44 million tests, 25th October 2020)[6]. In September 2020, the Ethiopian Ministry of Health reported that close to 2% of infections nationwide had been diagnosed among health workers (1311 of 67,000, 17th September 2020)[7].

As the number of testing facilities in Ethiopia keeps rising, a survey was conducted among paediatric residents and paediatricians in Addis Ababa to assess access for COVID-19 testing following occupational exposures. An invitation to fill out a questionnaire was sent out for paediatric residents and paediatricians.

A total of 46 respondents filled in responses on personal and professional backgrounds, experience with exposure for COVID19 and details of testing measures which followed. Half of the respondents were aged 20 – 29 years with 77% of respondents having a professional experience of 10 years or less. Employment in the private sector was reported by 28% with the rest serving in public hospitals with or without designated COVID-19 treatment centres. The level of training of respondents varied from residents (21) to paediatricians (17), fellows in sub-specialty training (2) and sub-specialists (6).

Most respondents (89%) reported having had close contact with a confirmed or probable COVID-19 infection. Symptomatic illness developed in 41% of exposed respondents with the majority having only mild symptoms. Following exposure, 80% were tested. All received RT-PCR tests on nasopharyngeal or pharyngeal specimens. Two-thirds were not charged for their tests while the remaining third had to pay a fee for their tests or pre-test evaluations.

After deciding to seek testing, only 23% accessed testing facilities within 24 hours; while a further 27% spent more than 72 hours identifying a laboratory to take their test sample. Most (86%) were tested at the hospital they worked in which begs the question why testing was delayed even for health workers working in the same facility. After being tested, only 2 of the 46 respondents received their results within 24 hours of sampling. For 43% of health workers, test results were delayed by 72 hours or more. The majority (78%) continued working with appropriate precautions while waiting for their test results.

Early diagnosis in health workers helps them to get timely treatment, protects their patients and families and allows hospital administrators to have timely information to manage resources. This survey suggests that there are gaps in achieving universal access for free of charge testing for health workers in Ethiopia. Findings also pointed to a gap in communication between lab test service providers and health workers as a large proportion failed to identify centres early, even when those laboratories were located within the same hospitals. Test results were delayed while most of the health force (often understaffed) continued working till confirmation of test results.

As the safety of health workers equates to the well-being of themselves and their patients, clear protocols on evaluation of exposed health workers including fast-track testing are of paramount importance[8]. Even among health workers themselves, risk stratification and expediting testing for groups with the highest risks should be planned for. In studies in the U.K., porters and cleaners of hospitals were seen to have a higher infection risk[9]. Mortality relating to COVID-19 among healthcare personnel was highest for older males with or without underlying medical comorbidities in the U.S[10]. Routine screening of health workers has also been recommended during this outbreak as attack rates in hospitals due to asymptomatic health force exposed for COVID-19 can be arrested early on[11].

In conclusion, post-exposure COVID-19 testing services deserve due attention towards achieving timely and accessible tests for health workers. A study on a larger group of more diverse health workers is underway by our research team to inform policy makers.

**References**


1. Nguyen LH, Drew DA, Graham MS, Joshi AD, Guo CG, Ma W et al. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. *Lancet Public Health* 2020; 5: e475–83. https://doi.org/10.1016/S2468-2667(20)30164-X
2. Abo-Leyah H, Gallant S, Cassidy D, Giam YH, Killick J, Marshall B et al. Seroprevalence of SARS-COV-2 Antibodies in Scottish Healthcare Workers. medRxiv 2020.10.02.20205641; doi: https://doi.org/10.1101/2020.10.02.20205641
3. https://www.dw.com/en/coronavirus-latest-who-says-health-workers-account-for-10-of-global-infections/a-54208221
4. https://www.afro.who.int/news/over-10-000-health-workers-africa-infected-covid-19
5. https://data.worldbank.org/indicator/SH.MED.PHYS.ZS
6. https://africacdc.org/covid-19/
7. https://ethiopianmonitor.com/2020/09/17/covid-19-over-1-300-health-workers-tested-positive/
8. Chersich, M.F., Gray, G., Fairlie, L, Eichbaum Q, Mayhew S, Allwood B *et al.* COVID-19 in Africa: care and protection for frontline healthcare workers. *Global Health* 16, 46 (2020). https://doi.org/10.1186/s12992-020-00574-3
9. Eyre DW, Lumley SF, O'Donnell D, Campbell M, Sims E, Lawson E et al. Differential occupational risks to healthcare workers from SARS-CoV-2 observed during a prospective observational study. eLife 2020;9:e60675 DOI: 10.7554/eLife.60675
10. Hughes MM, Groenewold MR, Leesem SE, Xu K, Ussery EN, Wiegand REet al. Update: Characteristics of Health Care Personnel with COVID-19 – United States, February 12 – July 16, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1364 – 1368. doi: http://dx.doi.org/10.15585/mmwr.mm6938a3
11. Saksirisampan B, Rodsuk T, Nittayasoot N, Samphao R, Pingkan R, Plernprom P et al. An outbreak of coronavirus disease (COVID-19) among healthcare personnel in a private hospital related to delayed detection of SARS-CoV-2 infection Foci. OSIR. 2020 Sep;13(3):110 - 9


## PERTUSSIS IN AFRICA: RECENT PATTERNS OF PCR CONFIRMED DISEASE ON THE CONTINENT


Rudzani Muloiwa, Department of Paediatrics & Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town South Africa

Corresponding author: rudzani.muloiwa@uct.ac.za


**BACKGROUND**

A model done by the World Health Organisation (WHO) estimated that over 24 million cases of pertussis may have occurred worldwide in 2014, leading to 160 700 deaths. What is disturbing is that nearly 60% of these deaths are thought to have occurred in African children.[1] Unfortunately, while there are good surveillance programs to track the burden of pertussis in High Income Countries (HICs), very little data exists to give a clear picture on the state of the disease in Africa.

The uncertainty created by lack of surveillance data is further compounded by recent signals suggesting that the high burden of HIV in Sub-Saharan Africa may in fact increase the risk of pertussis, especially in the context of low vaccine coverage.[2,3]

Most of the countries in Africa have had a pertussis containing vaccine in their vaccination schedules since the early 1980s. For a large proportion of the continent this now comes as a whole cell vaccine (wP) contained in a GAVI-sponsored pentavalent preparation. A few countries such as South Africa, Libya and Mauritius have changed to an acellular vaccine over the past decade in anticipation of the polio endgame.

This minireview was conducted in order to understand the recent burden of pertussis, including case fatality rate, of confirmed pertussis in Africa. It also sought to assess the impact of HIV status on the risk of laboratory confirmed clinical pertussis. The minireview makes use of some of the data that was collected during the conducting of a systematic review to determine the burden of pertussis in LMICs between 1974 and 2018.[4]

**METHODS**

**Search strategy and reporting on selected studies**

A number of electronic databases including MEDLINE, Scopus, Africa-Wide, PDQ-Evidence, WHOLIS, CINAHL, CENTRAL and Web of Science were systematically searched. Search terms used included "pertussis," "*Bordetella pertussis*", "*Bordetella parapertussis*," and "whooping cough" combined with "burden", "epidemiology", "incidence", "prevalence", and "case(s)". The results were filtered to look only at African studies published after the year 2000.

Only studies with polymerase chain reaction (PCR) confirmed disease were included to avoid missing 'atypical' pertussis due to the effect of factors such age, previous immunisation or infection, and antibiotic use that may modify clinical presentation. Included studies had to have clear numerators (number of participants testing positive) and denominators (number of participants tested for pertussis).

Where available, data was also extracted to assess the impact of HIV status on risk of pertussis. This was classified as HIV infected (HIV+), HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU).

Data on mortality resulting from pertussis was also captured.

Proportions or percentage point-estimates were calculated to represent prevalence of laboratory-confirmed pertussis. The Mantel-Haenszel method was used to pool together prevalence data from individual studies using random-

effects meta-analysis after Freeman-Tukey transformation while relative risks (RR) were used to assess the impact of HIV status on pertussis. Both types of findings are shown on forest plots with 95% confidence intervals (CI).

## RESULTS

### Studies over the last two decades

In total, we found 14 studies involving symptomatic individuals from 11 countries. These represented all African regions. There was however an over representation of South African data (7 studies) which is likely a reflection of available infrastructure for confirming cases. The report by Barger-Kamate *et al* presents data from several countries that were collected during a multicentre PERCH study.[5] With the exception of South Africa, the vaccine in use in all other included countries was wP.

### Prevalence of confirmed pertussis

The overall prevalence of PCR- confirmed disease due to *Bordetella pertussis* was 8% (95% CI, 5-12%. Figure 1. The point-estimated positive detection rate ranged from 1% to over 50%. The observed variability most likely reflects differences in study design and selection criteria for testing of cases in each study. For example, some of the studies were community based, while others were hospital based; some tested all individuals with respiratory symptoms, while in other children were tested only if they were clinically suspected to have pertussis.

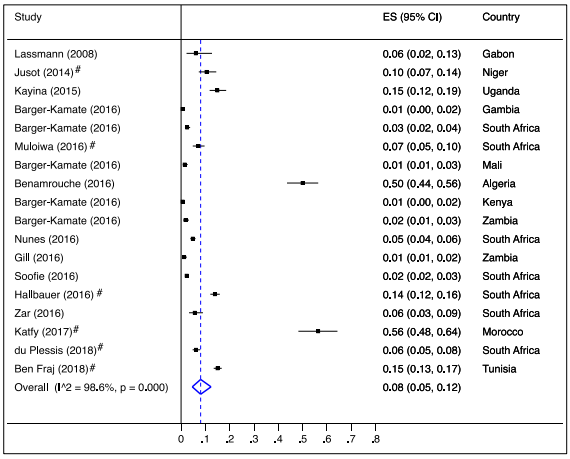



***Figure 1: Prevalence of Bordetella pertussis using polymerase chain reaction. # = study also tested for Bordetella parapertussis***

In addition to *Bordetella pertussis* six studies also reported on PCR confirmed *Bordetella parapertussis* infection as a cause of illness. Figure 1. As expected, the organism occurred less frequently with a pooled estimate of 1% (95% CI, 1-2%). Three studies each reported point estimates of 1% and 2%.

### Risk of pertussis in HIV exposed and infected

Ten studies investigated the impact of HIV status on the risk of pertussis. Data from six of these could be pooled together in a comparative meta-analysis. Individuals who were HIV+ had RR 2.4 (95% CI, 1.1-5.1) when compared to HUU. Although slightly low, the risk of pertussis in HEU was RR 1.4 (95% CI, 1.0-2.0) when a similar comparison was made with HUU. Figure 3. In a study by Hallbauer *et al.,* (data from this study could not be pooled with the others due to lack of stratification in the report), HIV+ cases made only 14% of the tested sample but accounted for 19% of pertussis cases.[9]

There was an increase in the risk of community pertussis in the study by Nunes *et al* who reported an incidence rate of 7.4/1000 infant-months in HEU infants and 5.5/1000 in HUU infants. Similarly, the rates in HIV+ and HIV uninfected mothers of these infants were 6.8 and 3.9/1000, respectively.[14]

There was also some indication that HIV status may be associated with severe disease as seen in a hospitalisation rate of 2.9 (95% CI, 1.8-4.5) per 1000 compared to 1.9 (95% CI, 1.3-2.6) per 1000 rrespectively in HIV-exposed infants and HIV-unexposed infants with pertussis. This study by Soofie *et al* reported case fatality rate of 4.8% which was only due to deaths in HIV-exposed infants (there were no HIV infected infants in the study).[15]

The highest risk of pertussis was reported by Anukam *et al.,* in a cohort of wP vaccinated HIV infected adolescents who were not on antiretroviral therapy with RR 22.8 (95% CI, 6.9-75.1).[19]

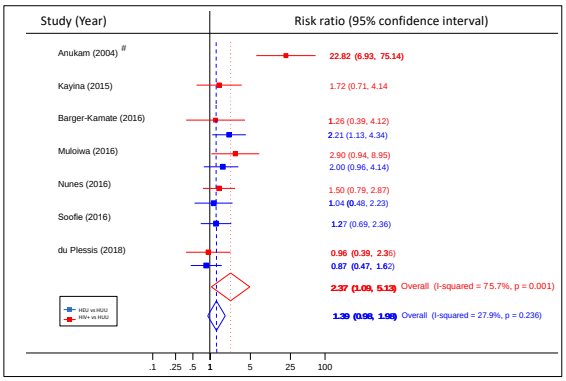



***Figure 2: Meta-analysis of relative risk of polymerase chain reaction confirmed Bordetella pertussis by HIV status. Risk of pertussis increases with HIV exposure (blue) or infection (red). HEU = HIV exposed uninfected, HUU = HIV unexposed uninfected, HIV+ = HIV infected, # = study did not use PCR but was added to give an idea of the high risk in HIV infected individuals not on treatment***

### Deaths and case fatality rate

As with HIV data, most of the data came from South Africa. All deaths were associated with *Bordetella pertussis* with none attributed to *Bordetella parapertussis.* The case fatality rate was 7% (95% CI, 3-12%), and all deaths occurred in infancy with the majority younger than six months of age. Figure 3.

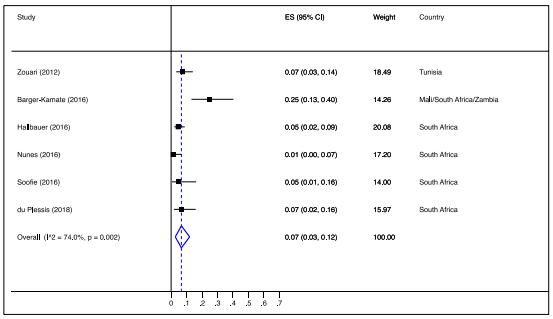



***Figure 3: Pertussis case-fatality rate***

## DISCUSSION

What this minireview shows is that many countries in Africa still lack laboratory resources to confirm pertussis. When PCR is available it confirms high prevalence of pertussis, with most of the disease due to *Bordetella pertussis* and only a few cases due to *Bordetela parapertussis*. The case fatality rate of 7%, with all deaths due to *Bordetella pertussis,* is almost double the international average of 4%.[21]

The difficulty involved in culturing Bordetella species makes culture - otherwise regarded as the reference standard - a less favourable tool than PCR for both confirming clinical diagnosis and surveillance. Although culture is useful for antibiotic sensitivity testing, it has a long turnaround time and missed up to 85% of PCR-confirmed cases in the systematic review that uses some of the data shown here.[4]

Clinical risk these data demonstrate indicate that reduced or impaired immune responses against vaccine antigens observed in HIV+ and HEU individuals, is not be limited to laboratory findings. Even as the success of prevention of mother to child transmission of HIV reduces new cases of paediatric HIV infection, the continent will still need to take into consideration the high proportion of HIV exposed children in designing pertussis control strategies.[3]

In an attempt to better understand the burden of disease on the content, the Global Pertussis Initiative (GPI) brought together a number of African scholars with an interest in pertussis for a two day meeting four years ago in 2016.[22] Following on this engagement, the GPI made a series of recommendations for the African continent. These included:

- **Improvement of public health and laboratory-confirmed pertussis surveillance at regional and national levels to better understand the pertussis burden and to make better policy informed decisions.**
- **More contextual research on pertussis aetiology, disease pattern and vaccine development**
- **Improvement of vaccination coverage through education and better outreach programs in rural areas.**
- **Prioritisation of infant and toddler vaccination followed by pregnant women and other risk groups based on available local resources, and**
- **Better disease and treatment awareness should be advocated to help prevent pertussis.**

It is hoped that the limited data shown has demonstrated the need to consider some of the recommendation by the GPI. The response should perhaps start with prioritisation of generating epidemiological data to aid surveillance programs in the continent, while simultaneously optimising vaccine coverage using currently available vaccines.

### References


1. Yeung KHT, Duclos P, Nelson EAS, Hutubessy RCW. An update of the global burden of pertussis in children younger than 5 years: a modelling study. *Lancet Infect Dis* 2017; **17**(9): 974-80.
2. Machingaidze S, Wiysonge CS, Hussey GD. Strengthening the expanded programme on immunization in Africa: looking beyond 2015. *PLoS medicine* 2013; **10**(3): e1001405.
3. Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2017. http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf
4. Muloiwa R, Kagina BM, Engel ME, Hussey GD. The burden of laboratory-confirmed pertussis in low- and middle-income countries since the inception of the Expanded Programme on Immunisation (EPI) in 1974: a systematic review and meta-analysis. *BMC Med* 2020; **18**(1): 233.
5. Barger-Kamate B, Deloria Knoll M, Kagucia EW, et al. Pertussis-Associated Pneumonia in Infants and Children From Low- and Middle-Income Countries Participating in the PERCH Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016; **63**(suppl 4): S187-s96.
6. Ben Fraj I, Kechrid A, Guillot S, et al. Pertussis epidemiology in Tunisian infants and children and characterization of Bordetella pertussis isolates: results of a 9-year surveillance study, 2007 to 2016. *J Med Microbiol* 2019; **68**(2): 241-7.
7. du Plessis L, O'Connell N, Hesseling AC, du Preez K, Stellenbosch University SA. Burden, spectrum and outcomes of children with tuberculosis diagnosed at a district-level hospital in South Africa. *The International Journal of Tuberculosis and Lung Disease* 2018; **22**(9): 1037-43.
8. Gill CJ, Mwananyanda L, MacLeod W, et al. Incidence of Severe and Nonsevere Pertussis Among HIV-Exposed and -Unexposed Zambian Infants Through 14 Weeks of Age: Results From the Southern Africa Mother Infant Pertussis Study (SAMIPS), a Longitudinal Birth Cohort Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016; **63**(suppl 4): S154-s64.
9. Hallbauer UM, Joubert G, Goosen Y. Pertussis in children in Bloemfontein, South Africa: A 7-year retrospective review. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde* 2016; **106**(10): 1042-6.
10. Jusot V, Aberrane S, Ale F, et al. Prevalence of Bordetella infection in a hospital setting in niamey, niger. *J Trop Pediatr* 2014; **60**(3): 223-30.
11. Kayina V, Kyobe S, Katabazi FA, et al. Pertussis prevalence and its determinants among children with persistent cough in urban Uganda. *PLoS One* 2015; **10**(4): e0123240.
12. Lassmann B, Poetschke M, Ninteretse B, et al. Community-acquired pneumonia in children in Lambarene, Gabon. *Am J Trop Med Hyg* 2008; **79**(1): 109-14.
13. Muloiwa R, Dube FS, Nicol MP, Zar HJ, Hussey GD. Incidence and Diagnosis of Pertussis in South African Children Hospitalized With Lower Respiratory Tract Infection. *Pediatr Infect Dis J* 2016; **35**(6): 611-6.
14. Nunes MC, Downs S, Jones S, van Niekerk N, Cutland CL, Madhi SA. Bordetella pertussis Infection in South African HIV-Infected and HIV-Uninfected Mother-Infant Dyads: A Longitudinal Cohort Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016; **63**(suppl 4): S174-s80.
15. Soofie N, Nunes MC, Kgagudi P, et al. The Burden of Pertussis Hospitalization in HIV-Exposed and HIV-Unexposed South African Infants. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2016; **63**(suppl 4): S165-s73.
16. Zar HJ, Barnett W, Stadler A, Gardner-Lubbe S, Myer L, Nicol MP. Aetiology of childhood pneumonia in a well vaccinated South African birth cohort: a nested

case-control study of the Drakenstein Child Health Study. *Lancet Respir Med* 2016.

17. Benamrouche N, Tali Maamar H, Lazri M, et al. Pertussis in north-central and northwestern regions of Algeria. *J Infect Dev Ctries* 2016; **10**(11): 1191-9.

18. Katfy K, Diawara I, Maaloum F, et al. Pertussis in infants, in their mothers and other contacts in Casablanca, Morocco. *BMC infectious diseases* 2020; **20**(1): 43.

19. Anukam KC, Osazuwa EE, Mbata TI, Ahonkhai IN. Increased incidence of pertussis and parapertussis in HIV-1-positive adolescents vaccinated previously with whole-cell pertussis vaccine. *World J Microbiol Biotechnol* 2004; **20**(3): 231-4.

20. Zouari A, Smaoui H, Brun D, et al. Prevalence of Bordetella pertussis and Bordetella parapertussis infections in Tunisian hospitalized infants: results of a 4-year prospective study. *Diagnostic microbiology and infectious disease* 2012; **72**(4): 303-17.

21. World Health Organization. Managing pertussis outbreaks during humanitarian emergencies : WHO technical note, February 2008. Geneva: World Health Organization; 2008.

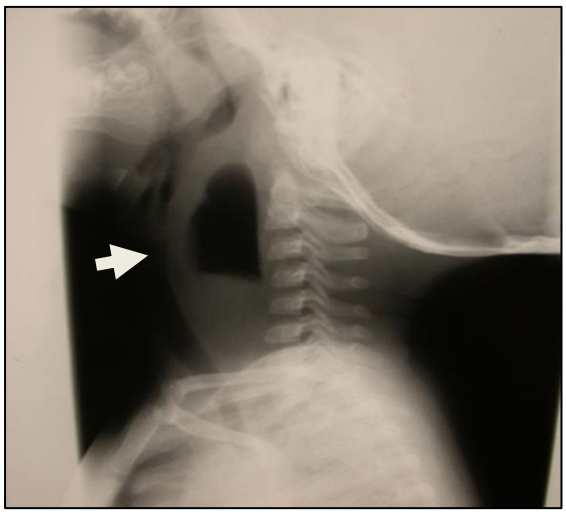
22. Muloiwa R, Wolter N, Mupere E, et al. Pertussis in Africa: Findings and recommendations of the Global Pertussis Initiative (GPI). *Vaccine* 2018; **36**(18): 2385-93.

# CASE REPORTS & MEDICAL IMAGES

## RETROPHARYNGEAL ABSCESS

Heloise Buys, Department of Paediatrics & Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town South Africa

Corresponding author: heloise.buys@uct.ac.za



**Explanatory note**

Featured is a lateral neck radiograph of an 8-month old infant who was unwell and febrile for two days. He had choked on a small pebble two days before presentation. His mother had succeeded in retrieving the pebble from the back of the infant's mouth. Since then he had been drooling and refused feeds. Two abnormalities are present on the radiograph, a large air-fluid level and marked increase of the size of the retropharyngeal space, features consistent with retropharyngeal abscess formation.

The abscess probably developed after a choking episode, or the removal of the pebble caused a traumatic break in the mucosal surface of the pharynx allowing microorganisms to infiltrate sub-mucosal tissues and establish an infection in the retropharyngeal space. Common microorganisms implicated include *Streptococcus viridans*, *Staphylococcus aureus* and beta-haemolytic streptococci.

The patient was treated with intravenous antibiotics and surgical drainage under general anaesthesia. He made a full recovery.

# JOURNAL WATCH

## INBORN ERRORS OF IMMUNITY AND SEVERE COVID-19

Brian Eley, Paediatric Infectious Diseases Unit, Red Cross War Memorial Children's Hospital and the Department of Paediatrics and Child Health, University of Cape Town.

Corresponding author: brian.eley@uct.ac.za

Two recent studies that documented altered type I interferon immunity (antiviral immunity) in a subset of patients with severe or life-threatening COVID-19 provide an explanation for the severity that they experienced.

Loss-of-function mutations in genes governing Toll-like receptor 3- and interferon regulatory factor 7-dependent type I interferon immunity were identified in 23 of 659 patients (3.5%) with life-threatening COVID-19 pneumonia. The age of these patients ranged from 17 to 77 years. The gene mutations were either autosomal recessive or dominant inborn errors of immunity (IEI). The study results suggest that the administration of type I interferon in some these patients may be beneficial, particularly if administered early in the course of COVID-19.[1] These IEI would be classified as defects in intrinsic and innate immunity in the existing International Union of Immunological Societies (IUIS) classification of IEI.[2]

The second complementary study from the same research group documented neutralizing IgG auto-antibodies against type I interferons in at least 101 of 987 patients with life-threatening COVID-19 pneumonia. The age of these patients ranged between 25 and 87 years and 95 were male. Thus, circulating neutralizing auto-antibodies were present in at least 2.6% of females and 12.5% of males with severe COVID-19 pneumonia. This high prevalence suggests that in settings where laboratory capacity exists, that patients with severe COVID-19 be screened for auto-antibodies against the 17 type I interferons. Those with auto-antibodies may benefit from interferons not neutralized by auto-antibodies or plasmapheresis.[3] According to the IUIS classification of IEI, these auto-antibody mediated type I interferon deficiencies would be classified as phenocopies of inborn errors of immunity.[2]

It Is possible that other yet to be discovered IEI, may influence the susceptibility to and course of COVID-19.

**References**


1. Zhang Q, Bastard P, Liu Zhiyong, et al. Inborn errors of type I IFN immunity in patients with life-theratening COVID-19. Science 2020 Oct 23;370(6515):eabd4570. doi: 10.1126/science.abd4570.
2. Tangye SG, Al-Herz W, Bousfiha A, et al. Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. J Clin Immunology Jan;40(1):24-64. doi: 10.1007/s10875-019-00737-x.
3. Bastard P, Rosen LB, Zhang Q, et al. Auto-antibodies against type I IFNs in patients with life-threatening COVID-19. Science 2020 Oct 23;370(6515):eabd4585. doi: 10.1126/science.abd4585.


## 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 be held from 1 to 4 December 2021 in Cancun, Mexico. 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.

## HOW TO JOIN AfSPID

There is currently no subscription fee. To join AfSPID, and to receive the newsletter and information about the society, including forthcoming events please send Natasha Samuels, samuels@sun.ac.za a brief email message indicating your interest in joining AfSPID together with the following information:

- Name, surname, title
- Country of residence
- Job description (registered ID specialist, clinician / researcher / academic / registrar / nurse / masters or doctoral fellow / other / any combination of the above)
- Your institution / affiliations
- Contact details

# THE AfSPID BULLETIN

**EDITOR**

Professor Brian Eley (South Africa)

**DEPUTY-EDITOR**

Professor Regina Oladokun (Nigeria)

**EDITORIAL BOARD**

Professor Adegoke Falade (Nigeria), Dr Olubukola Idoko (The Gambia), Dr Sabrina Bakeera-Kitaka (Uganda), Professor Mark Cotton (South Africa), Dr Tinsae Alemayehu (Ethiopia), Dr Ombeva Malande (Uganda & Kenya)

Dr Harsha Lochan (South Africa), Dr Joycelyn Dame (Ghana), Dr Babatunde Ogunbosi (Nigeria)

Dr Victor Musiime (Uganda), Professor Rudzani Muloiwa (South Africa), Associate Professor Heloise Buys (South Africa)


## EDITORIAL POLICY AND DISCLAIMER

The objective of this newsletter is to impart clinical and scientific news. It is circulated free of charge. The editorial process is independent of any individual or organisation that provides financial support to AfSPID. Description of or reference to a product or publication does not imply endorsement by AfSPID.

## AUTHOR GUIDELINES

**All contributions:** The name, surname, job title, affiliation and email address of each author should be positioned immediately below the title of the article. The text should be single-spaced in 12-point Arial or Times New Roman font. The use of sub-headings is encouraged. References should be listed at the end of the manuscript in numerical order as first cited in the manuscript. References should be formatted in the Vancouver style, refer: http://www.southampton.ac.uk/library/resources/documents/vancouverreferencing.pdf (Citing & Referencing Guide: BMJ Vancouver style). If a reference contains less than 6 authors, then list all authors. If a reference contains 6 or more authors, list the first 3 authors followed by et al. Tables, figures, images or photographs should be accompanied by an explanatory legend. Tables, figures, images and photographs should be the author's own work. Figures, images and photographs should be of high-resolution quality. Ideally, images, photographs or unmodified figures from published manuscripts or websites should not be copied, unless the corresponding author obtains written permission from the source publisher. Submit the manuscript in Microsoft Word.

**Letters to the editor:** Maximum word count (excluding references): 400 words with no more than 5 references and one figure or table.

**Review or commentary:** Maximum word count (excluding references): 3500 words, with no more than 40 references, and 6 tables, figures, images or photographs.

**Research article:** All types of original articles addressing clinical and laboratory-based aspects of paediatric infectious diseases can be submitted. The submission should include (1) a structured abstract (components: background, methods, results, conclusion; word count should not exceed 250 words), (2) a title page (components: article title, list of authors, corresponding author and his/her email address), (3) the introduction, methods, results, discussion, conclusion (combined word count of these components should not exceed 3500 words), (4) acknowledgments, funding sources, author contributions and ethics approval, (5) references (maximum of 40 references), and (6) up to 6 figures or tables with legends and if necessary footnotes may be included.

**Case report:** The main elements should be an unstructured abstract (maximum of 75 words), background, the case report and the discussion. Maximum word count (excluding abstract and references): 1200 words with no more than 10 references, and one table, figure, image or anonymised photograph.

**Medical image**: One high-quality, interesting and / or instructive image or anonymised photograph with an explanatory note of less than 200 words and up to 3 references.

**Journal watch submission:** Commentary on a published landmark or important research paper should not exceed 400 words and 5 references including the reviewed paper.

**Conference report:** An introductory paragraph is recommended describing the conference details. The conference report should focus on new developments and their meaning for African settings. Maximum word count (excluding references): 3000 words with no more than 30 references, and 6 tables, figures, images or photographs.

**ARCHIVING INFORMATION**

The newsletter is archived on the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA) website at http://www.fidssa.co.za/SASPID and the World Society for Pediatric Infectious Diseases website at https://wspid.org/member-societies/

**PUBLICATION CHARGES**

There are no publication charges. Publication is free to both members and non-members.

**CONTCT DETAILS**

Should you wish to submit letters, reviews, commentaries, research articles, case reports, medical images, journal watch submissions or conference reports for publication in the AfSPID Bulletin, please email your contributions to brian.eley@uct.ac.za