Africa's response to childhood infection

Journal of the African Society for Paediatric Infectious Diseases

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EDITOR'S COMMENT

PROGRESS TOWARDS TRANSFORMING THE AfSPID BULLETIN

The recent editorial board meeting focussed on measures required to fully establish a journal for the African Society for Paediatric Infectious Diseases (AfSPID). It was noted that there are no African journals exclusively devoted to paediatric infectious diseases and AfSPID is the only pan-African paediatric infectious diseases society. The discussion of that recent editorial board meeting is summarised in this edition of the journal. One of the decisions taken was to change the name of the journal to Journal of the African Society for Paediatric Infectious Diseases, shortened to JAfSPID. Henceforth this name will be used. Furthermore, all articles are now published under the Creative Commons CC-BY licence.

Brian Eley, editor

SOCIETY NEWS

SUMMARY OF THE 3RD EDITORIAL BOARD MEETING

The third meeting of the editorial board of the AfSPID Bulletin was held on 10 October 2022.

Attendees: Brian Eley (chair), Ombeva Malande, Colleen Bamford, Olukukola Idoko, Babatunde Ogunbosi, Paula Vaz, Mulugeta Gebremicael, Harsha Lochan, Heloise Buys, Adegoke Falade, Mark Cotton, Charles Hammond, Charles Wiysonge, Tisungane Mvalo, Norbertta Washaya, Hafsah Tootla, Julie Copelyn, Ebelechuku Ugochukwu, Lisa Frigati, Ebunoluwa Adejuyigbe, Mohammad Issack, Sabrina Bakeera-Kitaka

Apologies: Regina Oladokun, Tinsae Alemayehu, Anthony Enimil, Ayebo Sadoh, Joycelyn Dame, & Elizabeth Prentice

Meeting summary

1. Response to action points arising from the 2nd editorial board meeting that was held on 4 October 2021:

a. Confirm that most board members are in favour of converting the newsletter to a journal – done!
b. Approach the AfSPID EXCO for approval to convert the newsletter to a journal – done!
c. Draft a mission statement; revise the aims and scope of the AfSPID Bulletin – done!
d. Continue expanding the editorial board, focussing (1) on African countries with limited / no representation and (2) diversifying the skill set of the editorial board – 4 additional editorial board members were added in April 2022
e. Copy editing & proofreading functions: Two board members have offered to assist with these functions, Thus, currently Patti Apolles, Regina Oladokun and Lisa Frigati are assisting.
f. Develop a peer review procedure for the newsletter: peer-review template was developed and utilised from December 2021
g. Arrange a webinar on the peer review procedure for editorial board members: a few of the senior members of the editorial board who have in depth experience of the peer review process will be approached to conduct a webinar for all board members – not done but is a consideration for the next 12 months.

h. Registration and International Standard Serial Number – delayed because it is tied up with migration to an open access platform.
i. Additional measures:
    a. Consider what publishing license to offer authors – forms part of the discussion on migration to an open access platform.
    b. Consider a plagiarism policy and practice guidelines for the journal – not done but may need to be addressed in the near-future.
    c. Review best practice guidelines on ethical publishing and implement relevant measures – not done but will need addressing and form part of the further strengthening of the publication.
j. Arrange discussion with online hosting companies / websites – outcome of discussion was presented.
k. Aim to increase frequency to 4 editions per annum in 2023 or 2024 – may no longer be necessary if we migrate to an open access platform.

2. Migration to an open access platform
    a. Several types of open access platforms exist, notably:
        i. Commercial platforms such as AOSIS Open Access Journal Publishing
        ii. Non-for-profit organizations such as African Journals Online
        iii. Academic platforms: there may be several on the African continent; the University of Cape Town has a dedicated platform: UCT Open Access Journals: https://journals.uct.ac.za

    b. Advantages of placing journal on an open access platform were discussed. They include:
        i. International registration, International Standard Serial Number
        ii. Each paper will need to be formatted in pdf format.
        iii. Each paper will have a unique digital object identifier (DOIs)
        iv. Previously published papers will also be given DOIs and archived on the open access platform.
        v. Manuscript submission and aspects of the processing will be done on the open access platform.
        vi. Copyright (publishing licence) for published articles should be clarified.
        vii. Journal and article metrics will be possible.
        viii. Accreditation with the directory of open access journals (DOAJ): https://doaj.org will become possible provided we can demonstrate consistency for another year.
        ix. Accreditation with Department of Higher Education and Training will be possible once DOAJ accreditation is achieved. This is of relevance to researchers based at SA institutions of higher learning and will make publication attractive to these researchers.
        x. Increased visibility and accessibility

Editorial board decisions

The following decisions were unanimously adopted:

(1) Given the current stage of development of the publication, placing the journal on an academic platform will be most beneficial.
(2) Discussion with UCT should continue towards placing the journal on the UCT Open Access Journals platform.
(3) Copyright decision: Creative Commons Licence was approved.

3. Do we change the name of the journal?

Noting that there are no African journals focusing exclusively on PID and AfSPID is the only pan-African PID society the options include:

a. Retain current name: AfSPID Bulletin
b. Journal of the African Society for Paediatric Infectious Diseases (can be shortened to JAfSPID)
c. African Paediatric Infectious Diseases Journal

Editorial board decision: the name should be changed to Journal of the African Society for Paediatric Infectious Diseases

4. Next steps in the development of the journal

    a. Communicate the above editorial board decisions to the AfSPID EXCO by email.
    b. Communicate the decisions to the managers of UCT Open Access Journals
    c. Arrange a virtual meeting between the editorial board and the managers of UCT Open Access Journals in the forthcoming weeks.
    d. Establish a management team to assist the editor with the migration to the UCT Open Access Journals platform, overseeing the peer-review process, copy editing and proofreading, type setting / formatting, and transmittal of proofs to authors.
    e. A responsibility for all members of the editorial board is to maintain the rate at which articles are sourced for the journal so that we can demonstrate consistency, needed for accreditation with the DOAJ.

5. Additional discussion points
    a. Editorial board commitment to solicit articles, notably research articles.

b. Volunteers for the editorial management team
c. Additional editorial board members
d. Development of a cover letter check list
e. Ethics standards

The next editorial board meeting will be held in November / December 2023. Suitable dates will be circulated for consideration during the second half of 2023.

EDITORIAL

THE CHALLENGES OF TREATING HIV-INFECTED ADOLESCENTS

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Key words: HIV infection in adolescents, adolescence, epidemiology, antiretroviral therapy, adherence, treatment and care challenges

Editorial

Adolescents and young people represent a growing share of people living with HIV worldwide. In 2020 alone, 410,000 [194,000-690,000] young people between the ages of 10 to 24 were newly infected with HIV, of whom 150,000 [44,000-310,000] were adolescents between the ages of 10 and 19. To compound this, most recent data indicate that only 25 per cent of adolescent girls and 17 per cent of adolescent boys aged 15-19 in Eastern and Southern Africa – the region most affected by HIV – have been tested for HIV in the past 12 months and received the result of the last test. The testing rates in West and Central Africa and South Asia are even lower. If current trends continue, hundreds of thousands more will become HIV-positive in the coming years, and without knowing their status, adolescents will miss out on life-saving treatment. Additionally, a large population of children infected with HIV perinatally over the last decade are growing into adolescence.

In 2020, about 1.75 million [1.16 million-2.3 million] adolescents between the ages of 10 and 19 were living with HIV worldwide. Adolescents account for about 5 per cent of all people living with HIV and about 11 per cent of new adult HIV infections. About 1.5 million [1.0 million-2.1 million] (88 percent) live in sub-Saharan Africa. Outside of sub-Saharan Africa, the highest numbers of HIV-positive adolescents are in Asia and Latin America. Even though adolescents represent a growing proportion of people living with HIV worldwide and the highest risk population group for treatment attrition and AIDS-related mortality, there are very few specific interventions targeting this population. In fact, previous systematic reviews show scarce and inconclusive evidence of effective interventions for this age group. Therefore, there is an urgent need to design, implement, and test interventions that keep young people in HIV treatment and care.

Recent years have seen an increase in focus on adolescent health and a rapidly changing programmatic environment particularly aimed at improving antiretroviral therapy adherence and retention among adolescents (10–19) and youth (15–24) living with HIV. There remains high attrition of children with regards to early testing and linking those patients who are positive to early treatment. Barriers to screening and testing in children and adolescents are multifactorial. Linkage to pre-antiretroviral therapy care and retention in care are the main steps at which attrition occurs.

There are a number of new formulations available for use in adolescents and children which offer more options for antiretroviral therapy treatment, of particular interest is the single dose combination pill containing Dolutegravir, Lamivudine and Tenofovir which has revolutionized adherence during first line treatment. Despite this, adolescents may fail to adhere to their optimized therapy and fail to become virally suppressed. A recent national survey in Uganda (UPHIA report 2022) placed the adherence rate of adolescents at 68%. In one of the large centres treating children and adolescents with HIV it was reported that an increasing number failed their 1st and second line treatment, resulting in up to 1.8% optimized to 3rd line treatment regimens. Adherence levels among adolescents living in Africa and Asia vary from moderate to high; however, achieving viral load suppression remains a challenge. 90 percent of adolescents living with HIV live in sub–Saharan Africa, a continent which has the least advanced adolescent focused care, resulting in unattended healthcare needs.

There are gender disparities in the care of HIV-infected adolescents. In some sub-Saharan countries, adolescent girls are two to three times more likely to be infected with HIV than boys of the same age group. According to WHO and UNAIDS, HIV among children and adolescents presents unique features that affect how diagnosis, treatment and care is provided across the age continuum of 0–19 years.

Optimal antiretroviral drug regimens may require changes as children age and grow. There is need to adapt and tailor service delivery for younger adolescents (10–14 years old) and older adolescents (15–19 years old) due to significant differences in health-seeking behaviour, number of adolescents acquiring HIV infection and health outcomes including AIDS-related causes. Further, models of care to retain children and adolescents on treatment and ensure that they have suppressed viral loads must leverage different opportunities and address various challenges over the life-course. It is a well-known fact that children and adolescents have lower reported treatment coverage, adherence to treatment and viral suppression rates than older age groups.

Adolescence is a unique time of transition during which a person needs access to quality health, education, and other social services. Considering that adolescence is characterized by a strong desire for autonomy and a rise in sexual expression and exploration, many adolescents living with HIV, like their peers without HIV, initiate sexual activity during this stage. Unfortunately, young people tend to have both low levels of sexual health knowledge and limited access to sexual and reproductive health (SRH) services, which are linked to higher engagement in sexual risk behaviours, unplanned pregnancies, and higher rates of sexually transmitted infections (STIs). While these outcomes are concerning for all young people, the consequences are far more concerning for adolescents living with HIV (ALHIV), as they are at risk for transmitting the virus to their sexual partners and for young women, their infants, and experiencing worse health outcomes due to STI co-infection. Disclosure to intimate partners remains a challenge especially for the adolescent girls and young women, and this may further compound their ability to

adhere to treatment while in relationships or worsen the rates of intimate partner violence.

Evidence shows that ALHIV are more likely to experience mental health challenges compared to their peers who do not have HIV. Mental health problems are prevalent in ALHIV, often remain untreated, and may negatively affect antiretroviral therapy (ART) adherence, viral suppression, and retention in care. The integration of routine mental health screening in paediatric ART programmes is a feasible approach for identifying and referring adolescents with mental health and adherence problems to counselling and psychosocial support services and if needed to psychiatric care. Adolescent-focused health services and individual-level interventions are needed to improve adherence and retention in care while focusing on all their health needs.

Current adolescent health care training programs, including those that are high quality and interdisciplinary, are insufficient in number and worse still inaccessible for health care providers in low resource settings. Health care providers need to be skilled with adolescent responsiveness to address many of the health needs of adolescents in particular ALHIV, if we are to achieve the target of ending AIDS and unnecessary early mortality by 2030 in this population.

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RESEARCH

ADHERENCE TO ANTIRETROVIRAL THERAPY AMONG HIV-POSITIVE ADOLESCENTS ATTENDING THE KORLE BU TEACHING HOSPITAL

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Abstract

Background: As a result of increased access to antiretroviral therapy, children with perinatal infections are surviving into adolescence. However, challenges during adolescence may result in poor adherence to treatment. Studies documenting poor adherence in adolescents have revealed that factors such as older adolescents, lack of HIV disclosure, and forgetfulness are some leading causes of non-adherence. Adherence is a key determinant in minimising the emergence of HIV drug resistance.

Aim: To determine the adherence rate to antiretroviral therapy among adolescents attending a tertiary hospital and the factors associated with adherence.

Methods: A cross-sectional study was done amongst adolescents (10-19 years) with HIV infection at Korle Bu Teaching Hospital, Ghana. The data was collected by face-to-face structured interviews and a medical record review. The tool used to determine adherence was the 3-day self-recall tool. The percentage of medication doses taken (≥95%) was used to define adherence, which translated as not missing any dose in the 3 days prior to the study interview. The predictors of adherence were explored using univariate and multivariate logistic regression analyses.

Results: There were 210 adolescents enrolled, mostly younger adolescents (10-14years); 71.8%, and a slightly high male population of 52.4%. The adherence rate was 50.0%. Taking medication at the same time daily and having other people taking antiretroviral therapy in the same house were predictors of adherence.

Conclusion: There was a low adherence rate of 50.0% among the adolescents. Interventions toward improving adherence among adolescents in this setting are needed. Taking antiretroviral therapy at the same time daily and having others in the home who take antiretroviral therapy can help to improve their adherence.

Key words: HIV infection, antiretroviral therapy adherence, adolescents, Africa

Introduction

Increased access to Antiretroviral therapy (ART) in the past decade has ensured that children with perinatal HIV infections are now surviving into adolescence.[1] HIV has become a chronic illness among adolescents in light of the increased survival. During adolescence, specific challenges such as low self-esteem, cyber addiction, excessive alcohol intake, and use of tobacco and other illicit drugs occur.[2] In addition, adolescents deal with early sexual debut, teenage pregnancies, and sexually transmitted diseases, including HIV. Those with chronic illnesses such as HIV have an increased risk to their health from these behaviours and poor adherence to treatment. The transition of adolescents from paediatric to adult HIV care services might further disrupt adherence in the absence of transition services.[3]

In HIV, an adherence level of ≥95% has been considered the gold standard for ART[4], with a lower level of ≥90% set by the Pharmacy Quality Alliance.[5] In a Southern African cohort, the number of adolescents achieving 100% adherence was lower than adults at each time point; 20.7% at 6 months, 14.3% at 12 months, 6.6% at 24 months, compared to adults with 40.5% at 6 months, 27.9% at 12 months, and 20.6% at 24 months.[6] In a cross-sectional survey of HIV-infected children and adolescents in Port Harcourt, Nigeria, only 126 (59.2%) were completely (100%) adherent in the previous 1 month.[7]

Studies examining adherence in adolescents have revealed a range of diverse factors. Non-disclosure, prolonged duration on ART resulting in drug fatigue, especially among perinatally infected HIV adolescents, and complex regimens may poorly influence adherence.[8,9] Double orphans, especially those with a sibling as a caregiver, were at the highest risk of ART non-adherence among different orphan categories in Kigali, Rwanda.[10]School attendance with busy and varied schedules and other lifestyle barriers like forgetting and falling asleep before taking ART negatively impact ART adherence(9). To address these issues, simplified regimens, cognitive age-appropriate education that addresses adherence and HIV disclosure, and regimens with fixed-dose formulations that offer high barriers to resistance, such as dolutegravir (DTG) containing regimens, are among the solutions.

Antiretroviral therapy aims to reduce HIV-related mortality and morbidity with the initial goal of viral suppression. Viral suppression maintains the immune function and minimises the emergence of drug-resistant viruses.[11] Adherence is

one of the critical determinants in minimising the emergence of drug resistance.[9,11]

Despite the importance of adherence in the clinical management of HIV infection, there is limited adherence data among adolescents in Sub-Saharan Africa, where most of those living with HIV are. In Ghana, no separate official guidelines exist for adolescent HIV care. This study sought to contribute to the knowledge about adherence among adolescents in sub-Saharan Africa.

This study aimed to determine the adherence rate among adolescents and the factors associated with non-adherence.

Methods

Study Design, setting and inclusion criteria

The study was a questionnaire-based cross-sectional study conducted at Korle Bu Teaching Hospital (KBTH), Accra, the largest tertiary hospital in Ghana. It has a paediatric HIV clinic at the Department of Child Health (DCH), which sees patients up to 14 years on Wednesdays and an adult HIV clinic under the Department of Adult Medicine, which runs an adolescent clinic on Thursdays. The study was done at these two sites. Patients at these clinics come mainly from southern Ghana, with the majority living in the Greater Accra Region. The category of patients seen is mostly perinatally infected HIV adolescents. The number of adolescents seen during the week usually depends on the school term. It ranges from an average of 3 during school to 10 during vacations. There are protocols in the clinic used to guide management. These protocols are always based on the most recent national guidelines in the country. During the study period, the first line treatment regimen was tenofovir+ lamivudine + efavirenz for adolescents ≥ 35kg. The alternative regimens were zidovudine + lamivudine + efavirenz or zidovudine + lamivudine + nevirapine. The most common regimen available was zidovudine + lamivudine + efavirenz. Disclosure is actively encouraged at the clinic from the age of 10 years if not already done. Trained paediatric ART counsellors counsel adolescents and their caregivers prior to initiation of treatment and during treatment. Three counselling sessions, each covering different aspects of the disease process, practical issues around treatment, and a formal demonstration of administering ART, are performed prior to and during ART initiation. After initiation of treatment, adherence is assessed by the attending physician and the pharmacist at each clinic visit using a self-report tool and announced pill count, respectively. Adolescents aged 10-19 years with HIV who received care in either clinic and had been on ART for at least 6 months were enrolled in the study.

Sample size estimation

Based on an average adherence rate of 60% among adolescents with HIV from the existing literature,[7,12] and with 95% confidence level and 10% allowable error, the minimum sample size was calculated as 200. Adolescents were enrolled by convenience sampling until a final sample size of 210 was achieved.

Adherence assessment

Adherence was calculated using the 3-day self-recall tool, that assesses adolescents' responses to medication taken yesterday, 2 days ago and 3 days ago. Self-report is a commonly used adherence measure in clinical and research settings. It requires a low staff and respondent burden, is inexpensive, flexible, and takes little time to administer. However, it is subject to recall bias and social desirability. Despite its limitation of overestimating adherence, self-report was used in this study due to its clinical value in predicting viral load and screening for poor adherence.

Moreover, the absence of electronic pharmacy records made the use of a pharmacy refill tool not possible and unannounced pills counts could not be done because some adolescents were in secondary school. Due to the inability to access viral load during the study period, adherence could not be corroborated with viral load. If any ART drug was missed in the past 3-days, the participant was classified as non-adherent. In addition, a structured questionnaire with a checklist of validated barriers to adherence adapted from the Reaching for Excellence in Adolescent Care and Health (REACH) project was explored for adolescents missing doses. Barriers inquired into included forgot, too tired, busy, and too many pills.

Data Collection

Face-to-face structured interviews were conducted by a trained interviewer and lasted about 20 minutes. The questionnaire was administered mainly in English, and to minimise the risk of underreporting non-adherence, interviewers were trained to initially acknowledge the known difficulty in taking medication daily. Information was collected on demographic characteristics such as age, residence, education, supervision of HIV medication, the timing of taking ART, and others taking the same medication at home.

Medical records were transcribed onto a data extraction form. They included the following information: the reported transmission route, family type (biologic parents, adoptive/foster, extended), type of caregiver, disease severity as determined by WHO clinical staging, current ART regimen, date at treatment initiation, co-morbidities such as opportunistic infections, tuberculosis, and other illnesses. In addition, the viral load measured 6 months to the interview date was recorded from the medical records. Those without a viral load within that period were to have one taken. Unfortunately, viral loads could not be done for all the adolescents due to the absence of reagents for the viral load at certain times during the study period and other technical challenges. HIV disclosure which is always recorded in the clinical notes after each clinic visit was extracted from the medical records to avoid inadvertent disclosure of a child's status.

Definitions

Disclosure of HIV status: If the adolescent knew explicitly, they had HIV.
Adherence: Not missing any antiretroviral drug dose in the 3 days prior to the study visit.
Non-adherence: Missing at least 1 antiretroviral drug in the 3 days prior to the study visit.
Adherence rate: The proportion of adolescents classified as adherent.
Primary caregiver: A person who lives with the adolescent, participates in the child's daily care and is the most knowledgeable about the adolescent's health. They were either biological parents or guardians acting as surrogate parents to the adolescent.
Single orphan: An adolescent who has lost one parent.[13]
Double orphan: An adolescent who has lost both parents (13).
HIV viral load suppression: HIV viral load copies less than1000 copies/ml.[14]

Outcome

The primary outcome variables were adherence and non-adherence.

Data Analysis

The data was analysed using STATA Statistical software, release 11 (College Station, Texas, USA). Adherence was calculated as the proportion of adolescents classified as adherent, expressed as a percentage. Proportions were depicted as percentages. Chi-squared and Fisher's exact tests were used to compare categorical data. A two-sided significance level of $p < 0.05$ was considered statistically significant. Predictors of adherence were explored using univariable and multivariable logistic regression analyses. The logistic regression model was built by the stepwise backward selection, incorporating variables which, in the univariate analysis, had a p-value < 0.40. The logistic regression model results were expressed as adjusted odds ratio (aOR) and 95% confidence intervals (CIs).

Results

Between 1 January and 31 June 2017, 210 adolescents with HIV from the paediatric and adult HIV clinics at KBTH participated in the study. Most adolescents were from the paediatric HIV clinic, and sampling was unsuccessful in obtaining any horizontally acquired infections in adolescents. This was due primarily to very low numbers of behaviourally infected adolescents at the adult clinic and none at the paediatric clinic.

Characteristics of the study adolescents

There was a higher number of younger adolescents (10-14 years), 150 (71.8%) and a slightly higher male preponderance, 110(52.4%), enrolled in the study. Most adolescents were in primary education, 184 (87.6%). Among the primary caregivers, the majority, 86 (40%), were others. These others comprised grandparent(s) 42 (48.8%), aunt or uncles 21 (24.4%), other relatives 14 (16.3%) and caregivers from an institution where the adolescent lives, 9 (10.5%). Table 1 details the demographic characteristics of the study adolescents.

Table 1: Characteristics of study adolescents, N=210

Variable	Number (%)
Study site	
Paediatric HIV clinic	170 (80.9)
Adult HIV clinic	40 (19.1)
Age in years	
10-14 years	150 (71.8)
15-19 years	60 (28.2)
Gender	
Female	100 (47.6)
Male	110 (52.4)
Level of education	
None	8 (3.8)
Primary	184 (87.6)
Secondary	18 (8.6)
Primary Caregivers	
Self	5 (3.3)
Parents	63 (30.0)
Mother only	56 (26.7)
Others	86 (40.0)
Orphan status	
No	180 (85.7)
Single orphan	24 (11.4)
Double orphan	6 (2.9)
Body Mass Index	
Severe underweight	26 (12.5)
Underweight	48 (22.8)
Normal	124 (59.1)
Overweight	12 (5.6)

HIV clinical characteristics of study adolescents

The overall rate of adherence among the adolescents was 50.0%. The most common ART regimen was efavirenz with zidovudine and lamivudine, 160 (76.2%) and the majority, 157 (74.8%), had been on treatment for more than 2 years. Only 52 (24.8%) of the study adolescents took their ART at the same time daily in the three days before the study visit. There were 112 (53.3%) other persons taking ART in the home in addition to the study participant. This comprised mother only 70 (62.5%), father only 15 (13.3%), both parents 13 (11.6%), siblings 4 (3.6%), and other relatives or housemates 10 (8.9%). The 12 co-morbidities were tuberculosis 6/12 (50.0%), asthma 2/12 (16.7%) and sickle cell disease 4/12 (33.3%). Viral load results were available for 123 (58.6%) study adolescents due to the unavailability of test reagents.

Table 2: HIV clinical characteristics of study adolescents N=210

Variable	Number (%)
Adherence	
Yes	105 (50.0)
No	105 (50.0)
Duration on ART	
6 months - 2 years	53 (25.2)
>2 years	157 (74.8)
ART regimen	
Efavirenz based	160 (76.2)
Nevirapine based	35 (16.7)
Lopinavir-Ritonavir based	15 (7.1)
Medication supervision	
Self	83 (39.6)
Mother	53 (25.2)
Others	74 (35.2)
ART taken at the same time daily	
No	158 (75.2)
Yes	52 (24.8)
Disclosure of HIV status	
No	128 (61.0)
Yes	82 (39.0)
Others taking ART at home	
No	112 (53.3)
Yes	98 (46.7)
Use of Cotrimoxazole	
No	35 (16.7)
Yes	175 (83.3)
Other co-morbidities	
No	198 (94.3)
Yes	12 (5.7)
Recent hospitalisation[1]	
No	185 (88.1)
Yes	25 (11.9)
Viral load in past 6 months[2]	
<1000 copies/ml	59 (48.0)
≥1000 copies/ml	64 (52.0)
Viral suppression	
<50 copies/ml	36 (29.3)
≥ 50 copies/ml	87 (70.7)

[1]Hospitalisations within the past year; all had stage 3 and 4 disease
[2]Missing data 87, viral load results = 123

Factors associated with adherence

The study found statistically significant associations in univariate analysis between adherence and medication taken at the same time daily, $p<0.0001$ and when others in the home took ART, $p < 0.03$. Virologic treatment failure was described almost equally among adherent and non-adherent adolescents, 31 (48.0%) and 33 (51.6%), respectively. This was not significantly associated with adherence, $p=0.94$. The factors associated with adherence are illustrated in Table 3

Table 3: Factors associated with adherence

Factor	Adherence 105 (50%)	Non-adherence 105 (50%)	Total 210 (100%)	P value[1]
Age				
10-14 years	72 (69.5)	78 (74.3)	150 (71.4)	0.417
15-19 years	33 (30.5)	27 (25.7)	60 (28.6)	
Gender				
Female	51 (50.5)	49 (49.1)	100 (47.6)	0.90
Male	54 (49.5)	56 (50.9)	110 (52.4)	
Level of education				
None	4 (3.8)	4 (3.8)	8 (3.8)	0.38
Primary	87 (82.9)	97 (92.4)	184 (87.6)	
Secondary	14 (13.3)	4 (3.8)	18 (8.6)	
Orphan Status				
No	89 (87.8)	91 (86.7)	180 (85.7)	0.73
Orphan	11 (10.4)	13 (12.4)	24 (11.4)	
Double Orphan	5 (4.8)	1 (0.9)	6 (2.9)	
Disclosure				
No	65 (61.9)	63 (60.0)	128 (61.0)	0.70
Yes	40 (38.1)	42 (40.0)	82 (39.0)	
Medication supervision				
Self	41 (39.1)	42 (40.0)	83 (39.6)	0.70
Mother	29 (27.6)	24 (22.9)	53 (25.2)	
Other	35 (33.3)	39 (37.1)	74 (35.2)	
ART taken at the same time daily				
No	64 (61.0)	94 (89.5)	158 (75.2)	**<0.0001**
Yes	41 (39.0)	11 (10.5)	52 (24.8)	
Others take ART at home				
No	49 (46.7)	63 (60.0)	112 (53.3)	**0.03**
Yes	56 (53.3)	42 (40.0)	98 (46.7)	
Other co-morbidities				
No	101 (96.2)	97 (92.4)	198 (94.3)	0.54
Yes	4 (3.8)	8 (7.6)	12 (5.7)	
Recent hospitalisations				
No	93 (88.6)	92 (87.6)	185 (88.1)	0.89
Yes	12 (11.4)	13 (12.4)	25 (11.9)	
ART regimen				
Efavirenz based	77 (74.3)	83 (79.0)	160 (76.2)	0.77
Nevirapine based	19 (18.1)	16 (15.3)	35 (16.7)	
Lopinavir based	9 (8.8)	6 (5.7)	15 (7.1)	
Duration on ART				
6 months to ≤ 2 years	25 (24.0)	28 (26.4)	53 (25.2)	0.40
>2 years	79 (76.0)	78 (73.6)	157 (74.8)	
Viral load past 6 months				
< 1000 copies/ml	29 (48.3)	30 (47.6)	59 (48.0)	0.94

[1]Significant P value: < 0.05

Predictors of ART adherence

Multivariate analyses using logistic regression models were used to determine the demographic and clinical characteristics that could predict ART treatment adherence. All the factors associated with HIV treatment adherence at the 0.40 level in the univariate analysis were included in the multivariate analysis. Age, gender, duration of ART, taking ART at the same time daily, and others taking ART at home were used. In the unadjusted models' adolescents who took their medication at the same time daily were 5 times more likely to adhere to ART, aOR 5.62 (CI 95% 2.57-12.33); and almost 2 times in an adjusted model, aOR 1.85 (CI 95% 2.88-14.29); p<0.0001. In univariate analysis, those who had others in the home taking ART were about 2 times more likely to adhere to their medication, aOR 1.83 (CI 95% 1.04-3.20); p =0.038 and in an adjusted model, 2.5 times more likely to adhere to their medication. aOR 2.47 (CI 95% 1.30-4.69); p= 0.045. The logistic regression model is summarised in Table 4.

Table 4: Predictors of antiretroviral treatment adherence

4a. Unadjusted analysis

	Unadjusted Odds ratio	95% confidence interval	p-value
Age ≥ 15yrs	0.78	0.42-1.43	0.42
Male gender	0.86	0.50-1.48	0.29
> 2 years on ART	0.82	1.01-3.89	0.34
ART taken at the same time daily	5.62	2.57-12.33	**<0.0001**
Others taking ART at home	1.83	1.04-3.20	**0.038**

4b. Adjusted analysis

	Adjusted Odds ratio	95% confidence interval	p-value
Age ≥ 15yrs	0.84	0.43-1.63	0.61
Male gender	0.76	0.53-1.69	0.86
> 2 years on ART	0.99	0.89-3.72	0.101
ART taken at the same time daily	1.82	2.88-14.29	**<0.0001**
Others taking ART at home	2.47	1.30-4.69	**0.04**

Reasons for missing ART

The most common reason for the adolescents' missing their drug doses was forgetfulness, 102 (97.1%). This was followed by "other" responses, 46 (43.8%). These were: watching TV, playing, and helping with housework. Only 3 of them complained of too many pills as a barrier. This was a multiple response answer, and all the reasons are expressed graphically in Figure 1.

Discussion

This study evaluated adherence to antiretroviral medication and its associated factors among HIV-positive adolescents attending KBTH. The overall rate of complete adherence (100%) to ART among adolescents (10-19) years, using the 3-day self-report, was 50.0%. In Ethiopia, Firdu et al. found an adherence rate of 71.8% among 273 HIV-infected

adolescents receiving ART from three hospitals in Addis Ababa[15]. Among 519 HIV-positive adolescents attending two large HIV clinics in central and south-eastern Malawi, 153 (30%) reported having missed ART doses within the past week and 234 (45%) in the past month.[16] These low rates reflect the challenges adolescents living with HIV face, such as poor transitioning from children to adolescent services, behavioural problems, multiple schedules, treatment fatigue and medication burden, all previously reported.[8,9,17] In Ghana, there are no separate comprehensive adolescent health care services and a lack of formal transitioning from paediatric to adult care. As a result, healthcare providers (HCP) may be unaware of adolescents' poor adherence, and the clinic appointments may not address their specific needs. In contrast, Williams *et al.*[12] found a high adherence rate of 84% among adolescents enrolled in the PACTG 219C study, which was attributed to the increased attention given to them at the clinic.

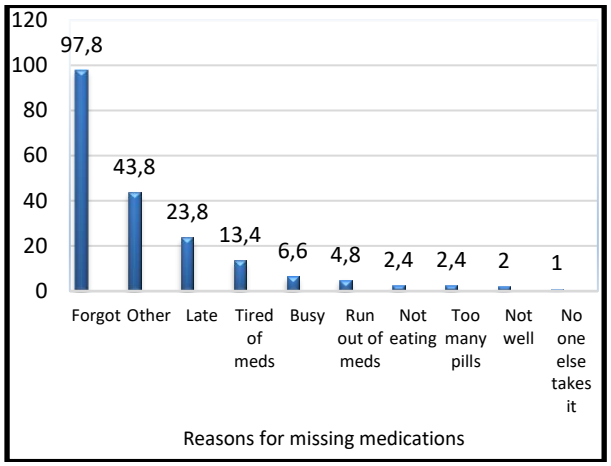

Figure 1: Reasons for missing ART presented as a proportion (%) of all adolescents

Newer ARTs such as dolutegravir, recommended by WHO in 2019 as the 1st line antiretroviral therapy, may allow a lower level of adherence while maintaining complete suppression of viral replication due to higher potency and longer half-life.[18] However, in a prospective cohort study to determine adherence among children and adolescents in Tanzania who were on a dolutegravir- based regimen, adherence, which was found to be a key predictor in viral load suppression, was 71%. Thus, even though Ghana has since 2020 made the switch to dolutegravir 50mg for adolescents and all those eligible, it is essential to assess adherence in adolescents continually.

In this study, taking the ART at the same time daily, which was seen in less than a third of the study adolescents, 52 (24.8%) was a strong predictor of adherence; aOR 1.82(CI 95% 2.88-14.29); p<0.0001. It has been suggested that patients may believe that taking ART off schedule is less likely to jeopardise the effectiveness of ART than missing actual doses.[19] This perception reflects the failure of the HCP to provide sufficient patient education and counselling. Dose timing is an essential aspect of ART, and inconsistent intervals may negatively affect the response to therapy due to viral replication, mutation, and treatment resistance(19). In a study conducted among HIV-positive adolescents in Tennessee, USA, Garvie et al. found that off-schedule dosing was a sensitive predictor of non-adherence. In that study, each per cent increase in interval dose increased the viral load by 2%.[20] Therefore, the HCP must include scheduled dosing as an essential component of the education on medication adherence throughout treatment.

For 112 (53.3%) adolescents, other people took ART in the house, and 85 (75.9%) were mothers. The study found that when other persons in the home took ART, they were 2.5 times more likely to adhere to it than when no one else took it, aOR 2.47 (CI 95% 1.30-4.69); p =0.04. Firstly, when others take their medication, they may remind the adolescents to take theirs, as the study found "forgetting" as the most common reason for missing medication. Secondly, this could help them take the medications at the same time daily, which will improve their adherence, according to existing literature and this study's findings. Finally, the other person on ART, especially a treatment-experienced caregiver, may act as the unofficial treatment partner. Treatment partnering is an intervention developed in sub-Saharan Africa among HIV-positive adults to improve adherence to medication and keep hospital appointments. They may be family members or friends who assume a measure of responsibility for the adherence success of the patient they support.[21] Thus, peer motivators or adherence clubs may benefit this cohort.

Adolescents miss medications for several reasons. In this study, "forgetfulness" was the most common reason for missing medication. Research has commonly found 'forgetfulness' among the top reasons for poor adherence in youth living with HIV.[7,17,22] In a qualitative study to describe barriers and facilitators to ART among HIV-positive adolescents in Ghana, all the 19 adolescents interviewed mentioned forgetfulness as the primary reason for missing medications.[23] In Peru, it was the most common reason for missing ART among adolescents aged 13-15.[24] They may sometimes report that they ''forgot'' to take medications when they decided not to take them or have other reasons for not taking them. ''I forgot'' might sometimes be a dismissive or evasive answer for not taking medications rather than actual forgetting.[17] This may be particularly pertinent to adolescents with HIV, given their developmental challenges of asserting independence and desiring autonomy from caregivers and authority figures during their transition to adulthood.[22] Forgetting may also result from cognitive or behavioural issues, such as poor planning and lack of executive functioning.[25]

Other reasons for missing medications in this study were: late to school, 25 (23.8%), watching television, doing housework and being busy. These responses, which are part of the normal day-to-day activities, suggest that they have been unable to integrate their ART medication into their lifestyle. To optimise adherence amid life's daily demands, dose-time schedules linked to realistic daily activities and times of the day must be considered.[25] In addition, medication reminders must be incorporated into any intervention to address adherence.

Limitations

The single adherence self-report may have overestimated adherence prevalence because of both recall bias and the inability to capture intermittent non-adherence over extended periods. In addition, the cross-sectional design only evaluated the association between adherence and other factors at a point in time rather than the variability and consistency of adherence over time. Finally, we had challenges obtaining viral load results for all the study adolescents.

Conclusion

There was a low adherence rate (50.0%) to ART among the study adolescents, consistent with other HIV adherence studies in adolescents. Interventions aimed toward improving adherence among adolescents in this setting are needed. Taking ART on schedule and having others in the home who take ART can help to improve adherence. In

addition, assessing and addressing the underlying causes of forgetting may facilitate adherence.

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Ethics approval and consent: The study was completed in accordance with the Declaration of Helsinki and approved by the Korle Bu Teaching Hospital's Institutional Review Board, reference number: KBTH/IRB/00038/2016. Furthermore, the hospital research committee approved the study. Informed consent was obtained from caregivers of the adolescents under 18 years, and informed assent was obtained from them after the study was explained to them and they agreed to participate. In addition, informed consent was obtained from adolescents 18-19 years. Patient details were anonymised before data analysis.

Competing interests: The authors declare no competing interests.

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COMMENTERIES & REVIEWS

ADOLESCENT VACCINATION IN NIGERIA: THE WHAT, WHY AND WHO

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Abstract

Adolescents are individuals aged 10 – 19 years. Having survived vaccine-preventable childhood diseases some of them remain susceptible because they either did not receive or did not complete their childhood immunization

schedule. They also become exposed to other vaccine-preventable organisms such as human papillomavirus. Adolescent immunization is thus an important strategy to consolidate on the gains of childhood survival programmes while ensuring that the adolescent reaches adulthood healthy and protected from vaccine preventable diseases. This article discusses the status of adolescent immunization in Nigeria, explores reasons for the status-quo, provides reasons for the consideration of an adolescent immunization programme and suggests possible vaccines for inclusion as well as possible strategies for implementing the programme.

Keywords: Adolescent health services, Immunization programme, Nigeria

Introduction

Immunization is one of the major pillars of preventive health care.[1] Despite its huge successes which include the eradication of the dreaded smallpox disease, immunization programmes still face a lot of challenges[1] Vaccination programmes have traditionally and universally targeted children.[2,3] Expanding immunization services to adolescents (persons aged 10 to 19 years) on the other hand has lagged behind especially in the African region.[3] Many countries utilize the Expanded Programme on Immunization (EPI) schedule which started out targeting six killer childhood diseases namely- tuberculosis, diphtheria, pertussis, tetanus, measles and poliomyelitis.[4] Although the schedule has been expanded to include vaccines against more diseases, countries determine which new vaccines to introduce and at what pace. The World Health Organization's most recent immunization table recommends a booster dose of tetanus diphtheria for adolescents as well as 3 doses of hepatitis B for those who missed their childhood doses.[5] Countries are also being encouraged to introduce the human Papilloma Virus (HPV) vaccine but these are not the only vaccines that adolescents could benefit from.

Nigeria uses the EPI schedule and in recent times has included a second dose of inactivated polio virus (IPV) vaccine, meningococcal vaccine, rotavirus vaccine and second dose of measles vaccine into the immunization schedule.[6] Despite the presence of HPV vaccine in the schedule, it is either not available in the public health service (which provides vaccines for free to the general population) or is available at a cost beyond the reach of the general population. The vaccine is however, available at variable prices (often unaffordable to majority of Nigerians) in private health facilities. Additionally, the recommended boosters and the hepatitis B vaccination programme for adolescents have not been implemented.

In this write up we review the current status of adolescent immunization in Nigeria, some of the reasons why Nigeria should focus on adolescent immunization and discuss some vaccine preventable diseases with impact on adolescent health that should be considered in an adolescent immunization programme for Nigeria and possibly other low- and middle-income countries.

Adolescent immunization in Nigeria

As in other countries, Nigeria developed a formal immunization programme for children following the inception of EPI.[7] The initial target was for infants with immunization commencing at birth and the last vaccine given at 9 months. More recently with the introduction of the second dose of measles at 15 months of age, the last vaccine in the series, it is expected that every child should be completely vaccinated by 2 years of age.[6]

As part of the EPI schedule, Nigeria provides HPV vaccine for girls aged 9 to 13 years. This is the only vaccine that specifically targets adolescents but is not yet available in the public sector and a strategy for its deployment is yet to be enunciated. Tetanus toxoid now given as tetanus diphtheria combination is offered to women of childbearing age (15-49 years). Though covering some part of the spectrum of the age of adolescence the vaccine is offered through antenatal care clinics to pregnant women and as such is not targeted specifically in the adolescent age group. In fact, its main objective is for the prevention of neonatal tetanus.

With the advent of the Covid-19 pandemic, some countries have included Covid-19 vaccines in their vaccination schedules following the approval of the vaccines for different age groups including the adolescent age range.[8] Nigeria is yet to approve the vaccines for persons below the age of 18 years except for those who wish to receive the vaccines for educational and international travel purposes.[8] Thus, to all intents and purposes, Nigeria does not have a functional adolescent immunization programme.

Rationale for adolescent vaccination

The period of adolescence straddles childhood and adulthood. Even though this period is considered as a healthy stage of life significant death, illness and injury occur during this period.[9] In 2017, 56 million people died globally.[10] The lowest contribution to this death toll was from the age groups 10-14 years (319,600) and 15-19 years (516,500) reflecting their relative good health.[10] Most of the deaths, injury and illness in adolescence is preventable but it has been recognized that the existing health services serve adolescents the least well.[11] This is especially so in resource limited countries. Not many African countries have adopted the WHO recommendation on adolescent vaccination.[3]

In Nigeria, adolescents make up 23% of the national population of 200 million people.[12] The adolescent mortality rate though much lower than the under-five mortality rate at 8/1000 for those aged 10-14 years and 9/1000 for those aged 15-19 years, is significant.[12] It is pertinent to note that that the top three causes of mortality in the adolescent age group in Nigeria are lower respiratory tract infections, diarrhoea and meningitis.[13] Some of the causes of these conditions are vaccine preventable . Thus, the lives and health of adolescents could be better safe guarded through vaccination. The current approach to vaccination looks at the life course noting that events in the first decade of life could impact adolescence while those in adolescence could impact adulthood.[11] This is a compelling reason to address adolescent immunization. The life-course approach to immunization requires that immunization schedules and access respond to an individual's stage in life, their lifestyle and specific vulnerabilities/risks to infectious disease that they may face.[14] It recognizes the role of immunization as a strategy to prevent diseases and maximize health over one's entire life regardless of an individual's age.[14]

Immunization coverage in Nigeria has been perennially low since the 1980s when vaccination coverage reached 81.6%.[15] The low immunization coverage means that many children are either unimmunized or incompletely immunized. Meanwhile, there is no provision in the Nigerian schedule for catch-up immunization for those who missed or did not complete their immunization in the first 2 years of life. This would result in large numbers of children growing into adolescence incompletely immunized or not immunized at all. This has serious implications for disease outbreaks which may involve older groups including adolescents.

Nigeria is one of ten countries contributing to the 23 million children who are unvaccinated or under-vaccinated

globally.[16,17] In 2018, only 31% of Nigerian children received all requisite vaccines while 19% did not receive any vaccines.[18] This means almost 70% of children are either unvaccinated or under-vaccinated. With no catch-up immunization schedule these children remain susceptible through adolescence into adulthood. It is also well documented that the immunity garnered by immunization (some vaccines) in infancy may wane and immunization can result in an epidemiological shift with the average of age at occurrence of diseases increasing thus increasing the risk to the unvaccinated adolescent.[19] The period of adolescence is a good point to boost waned immunity and provide initial vaccination (some vaccines) for those who missed immunization in infancy and childhood. WHO recommends catch-up schedules as part of a well-functioning immunization system.[20]

Adolescence is an age group in which risk-taking is common and this may result in injuries which the adolescent may attempt to hide from caregivers or avoid optimal treatment.[21] Many instances of tetanus have been recorded in this age group speaking to a need for boosters for those with waned immunity or primary vaccination against tetanus in those who missed infant immunizations.[22-24] Adolescents may also be involved in risky behaviour that may predispose them to infections like Hepatitis B.[25] Unwanted pregnancies are also common in this age group and such teenage mothers may not access orthodox care and their babies may be born unprotected against neonatal tetanus.[26]

Some diseases do not pose a risk until adolescence. For example, HPV exposure begins to occur at sexual debut in adolescence and as such the vaccine should be administered in early adolescence prior to sexual debut.[27] Also, some diseases such as chickenpox cause greater morbidity and potential for complications in adolescence.[28]

Adolescents have been implicated in the spread of infections within their households. They have been known to spread pertussis to young infants who are yet to be vaccinated.[29]The potential benefits of adolescent vaccination in terms of disease control in general and in contribution to the health of the adolescent makes it imperative that this strategy should be considered by Nigeria and indeed low- and middle-income countries that do not have such a programme in place.

Benefits of vaccination

In the past many children died from vaccine preventable diseases. Those who survive to adolescence and adulthood may become immune and sometimes with the scars of vaccine preventable diseases such as limb paralysis from poliomyelitis. With the development of immunization, children survived with immunity but without the scars of the diseases. Vaccines are noted to have contributed significantly to the reduction of under-five mortality from 12.6 million deaths in the 1990 to 5.2 million in 2019.[30] Vaccines are documented to save 2-3 million lives yearly.[4] There are statistics that indicate the role of vaccines in the reduction of the incidence of vaccine preventable diseases such as diphtheria, pertussis and poliomyelitis which is at the verge of global eradication.[31] Vaccines prevent morbidity and disability from vaccine preventable diseases.[6]

Vaccines are noted to be one of the most cost-effective interventions of public health. For every dollar spent on vaccines there is a return of 26 dollars.[32] Vaccines contribute to economic development of countries and are also important in preventing antibiotic resistance, a condition that is reputed to cause up to 10 million deaths annually.[33] The benefits of vaccines are thus well documented and would accrue to adolescents specifically and the population in general if deployed to target adolescents specifically. Also vaccinating adolescents will help in consolidating the gains of child survival activities which have succeeded in increasing the survival of children into adolescence.

Introducing new vaccines

To achieve maximal protection from vaccine preventable diseases for adolescents, new vaccines may need to be introduced into existing vaccination programmes while strengthening those programmes and the health system. The WHO has a document that details the guidelines and principles of the introduction of new vaccines into vaccination programmes.[34] The key issues to be considered are categorized into factors that pertain to the disease, those related to the vaccine and factors related to the capacity of the programme and health system to successfully introduce and continue to deliver the vaccine sustainably over the long term.[34] It is important to determine if the target disease is a public health priority based on the magnitude of the disease burden, the perception of the health community and lay public, recommendation of WHO and the availability of other prevention/control measures for the target disease.[34] The vaccine efficacy, the safety, cost effectiveness and availability of a reliable supply are important factors to consider. Other factors such as funding and competing priorities are very important in deciding on which vaccines to include in a vaccination programme.[34]

The addition of a new vaccine into a vaccination programme has effects which may or may not be beneficial. A vaccination programme that is weak and unable to reach large sections of the target population may record worse performance if a new vaccine is added on.[34] Thus, considerations of the ability of the health system to accommodate the new vaccine in terms of storage, handling additional doses of vaccine, the schedule and the number/training requirements of the health workforce must be evaluated.[34] The prevailing attitude of the public towards the vaccination programme and vaccines in general should be assessed to determine if they are conducive to introducing a new vaccine as vaccine hesitancy may result in very low acceptance of an introduced vaccine.

Potential vaccine candidates for adolescent vaccination programmes

The following vaccines target diseases that are prevalent in Nigeria and many low- and middle-income countries. These vaccines may be considered for introduction into vaccine programmes.

Human papilloma virus vaccine: Cervical cancer, the fourth most common cancer in women globally and the commonest gynaecologic cancer in Nigerian women is caused by the human papilloma virus.[35,36] It was responsible 342,000 deaths globally in 2020 and about 90% of the deaths and new cases are in low- and middle-income countries.[35] The age-standardized incidence rate of cervical cancer in Nigeria is in the range 14.9-18.6 per 100,000 population with mortality in the range of 11.4-19.0 per 100,000 population.[37] HPV is sexually transmitted; the risk for acquiring the virus increases following sexual debut of girls. In males the virus is implicated in the cause of penile cancer in addition to venereal warts which affect both genders. Early screening for cervical cancer involves a vaginal examination for visual assessment of the cervix and testing using acetic acid on the cervix or obtaining a Papanicolaou (Pap) smear which requires the expertise of a histopathologist to read the slides or testing for HPV DNA.[35] These basic investigations are not available/accessible to many women in sub-Saharan Africa including Nigeria.[38] Many women with cervical cancer

present at very late stages when the outcome of care is poor.[39] Awareness about the disease is equally poor not only among adults but also among adolescents.[40-42] .

Vaccination is a major strategy in the control of cervical cancer. The available vaccination strategies include vaccinating all adolescents (male and female) or prioritizing females where funding is not adequate. According to the WHO achieving high vaccination coverage in girls (>80%) reduces the risk of HPV infection in boys too.[43]

The HPV vaccine, a recombinant vaccine is known to be efficacious and has been reported to decrease the incidence of cervical cancer by 90% [44] and has a good safety profile. There are bivalent vaccines targeting serotypes 11 and 18 of the HPV which are commonly implicated in cervical cancer and the quadrivalent which targets 4 serotypes- 6, 11, 16 and 18 and the more recent nonavalent vaccine which targets 9 serotypes. The vaccine has been available since 2014 but its uptake has been challenged with a lot of vaccine hesitancy. In Nigeria, lack of awareness and accessibility as it is currently not available for free from the routine immunization service providers are documented challenges.[42]

Varicella vaccine: Varicella also known as chickenpox is a highly contagious infection with potential for serious complications such as bacterial infection of the skin lesions, pneumonia, central nervous system involvement, glomerulonephritis and hepatitis. Varicella is responsible for many school days lost. Adolescents are recognized as one of the subgroups with more severe disease.[28] Death has been reported in immunocompromised persons and children on immunosuppressant therapy.[45]

In Nigeria, varicella is a common infection although there is no national data; a study reported 68% prevalence rate of chicken pox antibodies among children aged 6- 15 years indicating a high rate of exposure.[46]

Varicella vaccine is a live attenuated vaccine with an efficacy of 92%. It may be given alone or in combination with MMR. The introduction of universal varicella immunization programme led to 98% reduction of varicella cases in all age groups in the United States.[28] A single dose of the vaccine is protective in >95% of recipients for adolescents less than 13 years. Above 13 years, two doses separated by 4-8 weeks interval is recommended. The vaccine should not be given to pregnant adolescents or those intending to get pregnant within one month.

Hepatitis B vaccine: The hepatitis B virus (HBV) is a DNA virus which is spread through vertical transmission to newborns from infected mothers as well as through percutaneous and per mucosal contact with infectious body fluids (blood, semen, vaginal secretions, serum), sharing/use of contaminated sharps. Hepatitis B virus is also sexually transmitted.

Nigeria is classified as being highly endemic with a pooled prevalence rate of 9.5%.[47] Infection with HBV presents a range of clinical features from asymptomatic to symptomatic. Thus, a patient could have acute HBV infection or chronic HBV infection. Complications of the acute infection include acute fulminant disease. Chronic infection which is the persistence of HBsAg for six months or more is more likely to develop in children (90%) who acquire the infection perinatally or during the first year of life.[28] Only about 5-10% of those who acquire the infection as adolescents and adults develop chronic infection. However, chronic HBV infection acquired during later childhood or adolescence is usually accompanied by more active liver disease and increased serum aminotransferase concentrations.[28] Chronic HBV infection may be complicated by chronic liver disease (hepatic failure, chronic active hepatitis, chronic persistent hepatitis, liver cirrhosis) and hepatocellular cancer.

The hepatitis B vaccine is a recombinant vaccine. It is 70-85% effective in preventing vertical transmission if given within 48 hours of birth and up to 95% effective if given simultaneously with hepatitis B immunoglobulin.[48] It also prevents horizontal infection. In Nigeria, coverage of the birth dose is about 53% while coverage for the third dose is 50%.[18,49] This suggests that many adolescents are susceptible because they did not get their infant immunization. Sexual exposure, illegal injection drug use, contact with infected persons and living in an endemic area also increase the susceptibility of the Nigerian adolescent to HBV. Unvaccinated adolescents should receive 3 doses of the vaccine at 0-, 1-2- and 4-6-month time points at 11-12 years of age before onset of risk factors for HBV infection.

Rubella vaccine: Rubella is a viral infection which manifests as postnatal and congenital forms. The postnatal form is generally a mild disease with up to 25-50% of adults being asymptomatic. Congenital rubella on the other hand results in catastrophic events ranging from spontaneous abortions and foetal death to a constellation of congenital abnormalities (the congenital rubella syndrome).

The public health significance of rubella is due to the congenital rubella syndrome. In Nigeria there is no national prevalence value for congenital rubella syndrome but different authors have reported cases of congenital rubella while sero-epidemiological studies have shown rubella to be endemic with rubella seropositivity increasing with age but with significant sero-negativity amongst female adolescents and women of child bearing age (indicating susceptibility).[47-49] The immunization schedule does not include a rubella containing vaccine.

Different strategies for rubella control have included adolescent vaccination, universal infant vaccination, and health worker vaccination. For rapid and significant control to occur a combination of strategies is needed. Indeed, for immediate impact adolescent immunization must be included as adolescents are the very next cohort of mothers.

The rubella vaccine is a live attenuated vaccine. It is available in combination with measles, or measles and mumps or measles, mumps and varicella vaccines. A single dose of the vaccine confers long term immunity in more than 90% of recipients.[28] Rubella should not be given to adolescents who are known to be pregnant or those considering becoming pregnant within 3 months of vaccination.

Meningoccocal vaccine: *Neisseria meningitidis* is a gram-negative intracellular diplococcus which causes meningitis, a disease with high potential for mortality. *N. meningitidis* causes various infections such as meningococcaemia, pneumonia, septic arthritis and pericarditis. Adolescents are at considerable risk for infection with this organism especially those living in crowded environments like hostels.

N. meningitidis has 12 serogroups. Serogroup A has been known to cause epidemics in the meningitis belt of sub-Saharan Africa.[53] Northern Nigeria is part of the meningitis belt and has witnessed several epidemics in the past.[53] However, following the phased introduction of meningococcal vaccine against serogroup A in 20 countries of the meningitis belt from 2010 there has been dramatic reduction in serogroup A cases while other seroroups have become more prevalent.[54] In Nigeria a large epidemic due to serogroup C occurred in 2016/17 which speaks to the

need of multivalent vaccine, as replacement by non-vaccine serotypes can cause outbreaks.[53]

Meningococcal vaccines include monovalent type (MenAfric A), bivalent type against serogroups A and C, trivalent type against serogroups A, C and W as well as quadrivalent vaccines which cover the serogroups A, C, W and Y.[54] There are polysaccharide and polysaccharide conjugate vaccine types

Tetanus toxoid: Tetanus is a fatal infection caused by *Clostridium tetani*. Tetanus occurs in two forms. Neonatal tetanus results from contamination of the umbilical cord, ear piercing or a male circumcision wound in infants of mothers who are unvaccinated against tetanus. Post neonatal tetanus occurs in older children who did not receive / complete their primary vaccinations and often follows wound contamination and occasionally chronic otitis media.

Neonatal tetanus is preventable by mothers being vaccinated as they may transmit anti-tetanus antibodies to their babies. In Nigeria the schedule recommends 5 doses for women of reproductive age (15-49 years) and this is able to prevent neonatal tetanus in newborns throughout the reproductive period of the mother. This regimen also serves to prevent puerperal tetanus in the mother.

The maternally acquired antibodies often wane in the first few months of life thus, infants are recommended to commence their primary series of vaccination at the age of 6 weeks in Nigeria by receiving pentavalent vaccine which contains tetanus toxoid in addition to other antigens.

Nigeria continues to report cases of neonatal tetanus as coverage of two doses of tetanus toxoid containing vaccine is suboptimal. In addition, the majority of deliveries take place outside of orthodox health care with a high risk of exposure to unclean environment and the attendant risk of tetanus.[18,55] One of the challenges is that the schedule for mothers only operates for pregnant women who access antenatal care and starts at age 15. Thus, non-gravid adolescent females and adolescent males are excluded. Several reports on post-neonatal tetanus indicate that up to 50% of the cases are aged above 10 years.[22-24] This may be an under representation as most of the studies did not cover the entire age range of adolescence.[22-24] In these studies, the cases often had no/incomplete vaccinations and no booster doses. Another important fact is that these studies reported male predominance amongst the cases.

The tetanus vaccine is a toxoid and it may be given alone or in combination with diphtheria toxoid (Td) or with diphtheria toxoid and acellular pertussis vaccine (Tdap). Booster doses of Td vaccine are recommended from 11-12 years as immunity to tetanus toxin is documented to wane from 9-13 years.[56]

Diphtheria toxoid: Diphtheria, a disease with high fatality rate is caused by *Corynebacterium diphtheriae*. Although no longer as common as it used to be, outbreaks have been reported and adolescents have been represented in such outbreaks.[57] In a study on infant mother pairs, it was documented that up to 30% of infants are born unprotected against diphtheria because their mothers were either not vaccinated and not naturally exposed to the causative organism.[58] Nigeria now offers tetanus diphtheria (Td) vaccine to pregnant women instead of tetanus toxoid. This is commendable but requires that the intervention be expanded to involve all adolescents both male and female which will cater for those who missed the primary immunization series in infancy while serving as a booster for those whose immunity has waned.

Diphtheria vaccine is a toxoid and is often given in combination with tetanus toxoid (Td) or with tetanus toxoid and acellular pertussis vaccine (Tdap). Booster doses of Td vaccine are recommended from 11-12 years.[56]

Pertussis vaccine: Pertussis also known as whooping cough is caused by *Bordetella pertussis*. In well resourced countries the resurgence of pertussis despite high coverage with the vaccine was attributable to waned immunity.[59] Involvement of newborns led to renewed efforts at vaccination with such vaccination strategies as cocooning. This involves vaccinating all adults, adolescents and children who would be in contact with a given infant.[60] Adolescents have been particularly indicted as potential contacts infecting young infants.[29,61] In Nigeria, data are not reliable mainly because of the difficulty of making bacteriological diagnosis. The disease may thus be underreported. Considering that the vaccine is often in combination with other vaccines (diphtheria, tetanus) it may be more beneficial to use these combination vaccines as booster dosing for adolescents who received their primary vaccination while also providing an opportunity to vaccinate those who didn't receive infant vaccinations.

Yellow fever vaccine: Yellow fever is a viral haemorrhagic fever caused by the yellow fever virus. It is spread by the bite of an *Aedes aegypti* mosquito. Epidemics of yellow fever have been recurrent in Nigeria and in the African continent. In a review of the outbreaks that occurred between 2017 and 2019 in Nigeria, 7894 persons were affected of which 1794 (23%) were aged between 11 and 20 years. The case fatality rate was 2.7%.[62]

Yellow fever vaccine is a live attenuated vaccine produced in chicken egg. It is given at the age of 9 months in Nigeria and a single dose of yellow fever vaccine is protective for life. However, the coverage for the vaccine is only about 54% meaning that many children grow into adolescence and adulthood unprotected.[18] Yellow fever vaccine is only given to other age groups than infants during outbreaks or as a requirement for international travel. Routinely vaccinating adolescents may result in smaller outbreaks and less intense response to contain an outbreak.

Pneumococcal vaccine: There is a high prevalence of pneumococcal disease and its complications among children and adults with chronic diseases.[63] These include adolescents with anatomic or functional asplenia (including sickle cell disease), nephrotic syndrome, cerebrospinal-fluid leaks, or immunosuppression (including human immunodeficiency virus [HIV], organ transplantation etc. Also, vaccination is indicated in malignancies like Hodgkin's disease and other lymphomas, chronic kidney disease. The high prevalence of sickle cell anaemia in sub-Saharan Africa requires the incorporation of pneumococcal vaccine into the sickle cell care programs which exist in secondary and tertiary health institutions in the region.

Pneumoccocal vaccines are either protein conjugate or polyssacharide. The protein conjugate vaccines are recommended for children under five years of age. For adolescents at risk as already identified the conjugate vaccine is given followed by the polysaccharide vaccine at least 8 weeks later.

Covid-19 vaccines: These are vaccines developed against the the corona virus disease caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). At least 6 of the various vaccines targeting the virus have been approved for use in children.[8] Although, the disease seemed to be milder in sub-Saharan Africa compared to other WHO regions some countries in Africa like South Africa did record significant morbidity and mortality.[64] Children and adolescents have been affected resulting in a minority of deaths. This may be an underestimation based on the testing algorithms of many countries which generally exclude children and adolescents. However, Sam-Agudu et

al[8] have called for children and adolescents to be included in the Covid immunization programme in Africa. Vaccination of children and adolescents they opined, would obviate the need for school closures thus avoiding academic and psychologic impacts of disruption in education and intergenerational (adolescents to parents/grandparents) transmission of SARS-CoV-2. They recommend that at the least children at high risk for severe disease and mortality and older adolescents living with adults at high risk should be prioritized for vaccination. It is noted that for coverage of 70% to be achieved in all African countries, children (at least 10 years and older) will need to be vaccinated.[8] While some African countries have included children in their covid-19 vaccination programmes, Nigeria is yet to do so.[8]

Future Vaccines

Much research is currently ongoing in the area of vaccines against HIV and tuberculosis. These are likely to target adolescents. It is thus important to be proactive to commence a programme for adolescents in countries that do not have adolescent programmes while existing programmes should be strengthened.

Challenges to implementing adolescent vaccination

A potential challenge to implementing adolescent vaccination programme in Nigeria is choosing a delivery strategy. Multiple strategies may be required to achieve the objective of reaching all adolescents with vaccines. While school-based vaccination programme would reach a lot of adolescents, this would not be adequate as secondary school enrolment rate is only 54.4%.[65] Mass immunization may rapidly increase coverage in the target age group but this will not be sustainable as mass immunization programmes require a lot of resources which are often unavailable in low- and middle-income countries. Using all health care visits will only reach few adolescents as most adolescents do not visit the hospital. Of importance for any delivery strategy will be demand creation. This would require creating adequate awareness among all stakeholders – parents, adolescents, health care providers and society in general.

Vaccine hesitancy is another likely challenge. In many countries where the HPV vaccine was introduced coverage has been variable with a global coverage of 12.2% in 2018.[66] Vaccine hesitancy has been a significant factor mitigating against the uptake of vaccines in many countries including Nigeria.[67,68] Vaccine hesitancy has also been a major determinant of low uptake of the more recent Covid-19 vaccines. Vaccine hesitancy may accrue from parents and from the adolescents themselves. Community engagement and adequate information dissemination will be required to elicit vaccine confidence in order to generate adequate demand and uptake of vaccines.

It is important that political commitment is garnered and that important stakeholders are aware and interested. In the strategic plan for adolescent development for the period 2007-2011 adolescent immunization was not mentioned.[9] A more recent assessment of needs also did not allude to adolescent immunization despite recognizing the potential of HPV infections.[69] This writeup aims to create the needed awareness amongst health care workers who are major stakeholders.

As it has been for other vaccines that have been introduced funding will be a major challenge to implementing a comprehensive adolescent vaccination programme. It is also pertinent to note that the infant vaccination programme and the more recent covid-19 vaccination programme have not achieved optimal coverage. This a major factor that is already recognized in efforts to strengthen the immunization programme in Nigeria.[70] In recognition of the fact that coverage is variable in the different sections of the country with some of the least performing states in terms of coverage having a higher burden of disease, and to allow for equity the strategy of phased introduction of vaccines has been employed.[70] This involves introducing new vaccines in states that meet the set criteria of performance. While contemplating adolescent immunization, efforts must be put in place to ensure the success of the current childhood immunization programme as well as the covid-19 vaccination programme. As the success of these two programmes will be the springboard on which to introduce adolescent immunization.

Promoting Adolescent vaccination in Nigeria- next steps

Multi-sectoral collaborations involving the health, education and communication sectors, communities and their leaders and donor agencies would be required to ensure that adolescent immunization becomes a reality in Nigeria. There is need for political will and commitment culminating in appropriate budgetary provisions for adolescent immunization programme. Nationally representative research to generate evidence for the burden and epidemiology of vaccine preventable diseases in adolescence and implementation strategies for adolescent immunization programmes in Nigeria will be needed. The evidence generated will be germane to decisions on prioritization. Much advocacy for the establishment of adolescent immunization programmes will be required. Demand creation through public enlightenment and training/retraining of health care workers on the importance and benefits of adolescent immunization are necessary inputs for a successful adolescent immunization programme. In addition, the expansion of well child visits to include visits in adolescence/inclusion of immunization assessments at school entry would ensure that children at all ages including adolescents are age-appropriately immunized. Vaccine production and supplies within Nigeria would also need to be considered.

Conclusion

Adolescents make up a significant proportion of the Nigerian population and many low- and middle-income countries. Introducing and maintaining an adolescent immunization programme will not only consolidate the gains of childhood survival interventions but ensure that the next generation of adults reach adulthood in good health.

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CASE REPORTS

A CASE OF NON-TOXIGENIC *CORYNEBACTERIUM DIPHTHERIAE* INFECTIVE ENDOCARDITIS IN A NINE-YEAR OLD CHILD

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Abstract

Invasive non-toxigenic *Corynebacterium diphtheriae* infections are uncommon but increasingly being recognised as causing significant morbidity and mortality. They are non-vaccine preventable and may occur sporadically or within the context of outbreaks. Clinicians need to be aware of their potentially devastating consequences. There are limited reports from sub-Saharan Africa. We, therefore, describe a paediatric case of non-toxigenic *C. diphtheriae* infective endocarditis highlighting aspects relevant to infectious disease management.

Key words: *Corynebacterium diphtheriae,* endocarditis, non-toxigenic, children, adolescents

Introduction

Corynebacterium diphtheriae is historically known for causing toxigenic diphtheria, a major public health threat in the pre-vaccine era.[1] The successful uptake of the diphtheria toxoid vaccine in routine primary immunisation precipitously reduced the global incidence, though intermittent outbreaks have occurred especially during

disruptions of healthcare systems or vaccination programmes.[1] With this decline, the pathogenicity of non-toxigenic *C. diphtheriae* (NTCD) isolates is increasingly being recognised, and invasive disease has been associated with significant morbidity and mortality.[1-2]
Invasive NTCD disease presents as bacteraemia with metastatic sequelae including infective endocarditis, septic arthritis, osteomyelitis, and mycotic aneurysms, with a clinical course that may be fulminant or fatal.[2-3] NTCD infective endocarditis (NTCD IE) is uncommon. We describe a patient with NTCD IE who presented to a tertiary Children's Hospital in Cape Town, South Africa.

Case report

A 9-year-old girl presented in July 2021 with a 5-day history of fever. She had underlying unrepaired congenital cyanotic heart disease, characterised by complete atrio-ventricular septal defect, pulmonary valve stenosis and a double-chambered right ventricle. On examination, she was acutely ill, febrile (temperature, 39°C), tachycardic, clubbed and cyanotic but not in shock or cardiac failure. Her total white cell count was 23.6 x 10^9/L with neutrophilia and the C-reactive protein (CRP) was 59 mg/L. She tested negative for Human Immunodeficiency Virus 1/2 and Severe Acute Respiratory Syndrome Coronavirus 2. She was unwell but haemodynamically stable and commenced empirically on intravenous ceftriaxone while awaiting blood culture results and cardiac imaging.

Two positive blood cultures collected early during admission, revealed small Gram-positive bacilli on light microscopy similar to that shown in Figure 1. Grey, catalase-positive colonies were cultured on blood agar media, and black colonies were cultured on tellurite-containing agar media (both incubated aerobically at ~37°C). These microbiological features were suggestive of potential *Corynebacterium diphtheriae* infection, and organism identification was confirmed using the VITEK 2 automated system (bioMérieux, Marcy-l'Étoile, France). Minimum inhibitory concentration (MIC) to determine antibiotic susceptibility was performed using the E-TEST (bioMérieux, France) gradient diffusion method. The isolate was intermediately resistant to penicillin (MIC=0.25 ug/mL), but susceptible to ceftriaxone (MIC=1 ug/ml), and vancomycin (MIC=0.5 ug/mL) using the Clinical Laboratory and Standards Institute M45 Guideline. The absence of the *tox* gene was confirmed using a real-time polymerase chain reaction assay (RT-PCR) at the National Institute for Communicable Diseases (NICD), Johannesburg, South Africa.

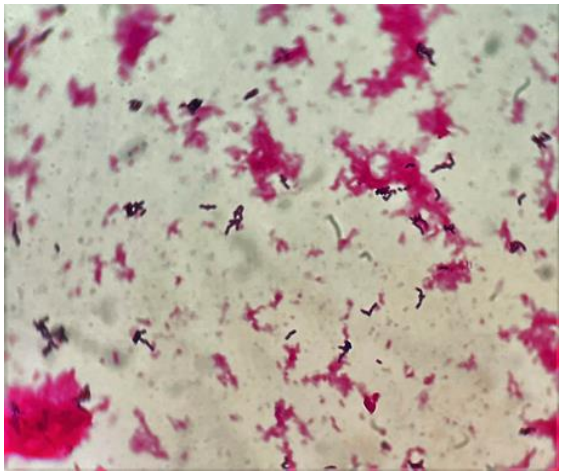

Figure 1: Small Gram-positive bacilli (purple) visualised using Gram stain and light microscopy (Courtesy of Dr Gert Marais)

A transthoracic echocardiogram (TTE) on day 2 of hospitalisation initially showed the absence of cardiac vegetations. However, on repeat TTE on day 12 of hospitalisation, a vegetation measuring 8 mm x 6.5 mm was visualised on the pulmonary valve (Figure 2). Intravenous gentamicin (for synergism) was added to the ceftriaxone in response to the confirmed vegetation. Repeat TTE on day 19 demonstrated persistence of the vegetation which had increased in size to 10 mm x 8 mm, but still without any pulmonary valve regurgitation. She continued to experience elevated temperature measurements.

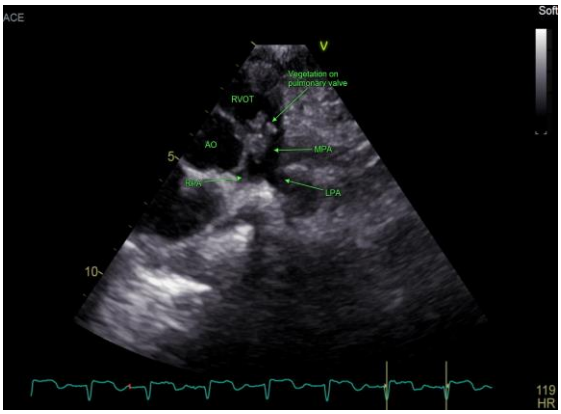

Figure 2: An Echocardiogram showing the vegetation 8 x 6.5 mm (arrow) in the parasternal short axis view (AO aorta, MPA main pulmonary artery, LPA left pulmonary artery, RVOT Right ventricular outflow tract)

Consequently, the vegetation was excised on day 26 of hospitalisation via an open-heart surgical procedure. The pulmonary valve was not significantly damaged by the vegetation. During the same surgical procedure, the underlying cardiac defects were repaired. Histopathological analysis of the excised vegetation confirmed bacterial endocarditis by demonstrating Gram-positive bacilli. Defervescence and a downward CRP trend were observed post-operatively. She completed a total antibiotic duration of 6 weeks. Screening did not reveal any evidence of nasal or oropharyngeal carriage of *C. diphtheriae* from our patient or her close contacts.

This case was one of a cluster of seven cases of suspected or culture confirmed NTCD infective endocarditis, diagnosed in the Western Cape Province of South Africa between 18 May 2021 and 2 July 2021. Their ages ranged from 9 years to 38 years. These seven patients resided in two districts in the province. Five out of these seven cases died. No clear epidemiological links between these cases were established.[4]

Discussion

There is a growing recognition of NTCD as a cause of invasive disease such as IE. The published literature, however, is limited to case reports and series primarily from well-resourced settings. In one developed setting, 11.8% of 85 episodes of paediatric IE over a period of 18 years were due to NTCD.[5] In New Zealand, a case series identified 10 *C. diphtheriae* IE cases with 80% being non-toxigenic over a 14-year period among adults and children.[6] Similarly, another case series among young adults described 4 patients with NTCD IE over a 10-year period in Australia[2]. Among African countries, a meta-analysis of IE determined culture-positivity to be 48.6% with only 18 out of 42 countries providing microbiological data and none reporting *C. diphtheriae.*[7] In our hospital, out of 49 cases of

paediatric IE identified over a 5-year period, 89% were culture-positive.[8] *Corynebacterium* species was identified in one of these culture-positive cases[8]. Under-reporting from sub-Saharan Africa may reflect the lack of laboratory capacity to identify and/or ascertain toxigenicity of *C. diphtheriae* in cultured isolates. Additionally, limited resources to perform investigations, frequent use of antibiotics before blood collection, and inadequate blood sampling procedures may contribute to low blood culture yields.[7]

NTCD are strains which do not produce exotoxin because they lack the *tox* gene acquired from lysogenic corynebacteriophages, therefore, diseases caused by these strains are not prevented by the diphtheria toxoid vaccine as disease is not toxin mediated.[1,3] Likewise, there are non-toxigenic strains which possess an inactive *tox* gene. These *tox*-bearing non-toxigenic strains (NTTB) may attain toxigenicity through lysogenic acquisition of new functional genes underscoring its public health significance.[1] Humans are natural hosts for *C. diphtheriae* and healthy individuals have demonstrated throat carriage of NTCD.[3] Although cutaneous lesions are more frequently culpable as potential sources, throat carriage of NTCD may be the source of infection.[3] In NTCD IE, detection of *C. diphtheriae* is normally via isolation from blood, excised heart valve or vegetation tissue cultures, or alternatively, *C. diphtheriae* DNA detection using molecular methods like PCR from excised valve tissue.

Risk factors for NTCD IE include congenital or acquired heart diseases, prosthetic valves, alcoholism, diabetes mellitus and intravenous drug use.[2,6] In our patient, the only identifiable risk factor was the underlying congenital heart anomaly, and no embolic phenomena or destroyed valves were noted. A recent case report from Brazil highlighted the aggressive embolic propensity of NTCD in a 21-year-old cocaine user with IE who had damaged heart valves and valvular dysfunction, complicated by an extensive splenic abscess and limb gangrene.[9] Destroyed heart valves have previously been described in NTCD IE.[2]

Although the mechanisms of pathogenicity of non-toxigenic strains are not fully understood, *C. diphtheriae* organisms rely on pili and adhesins for adherence to host cells. They also form biofilms potentially compromising antibiotic therapy.[1,3] This may have occurred in our patient where the organisms demonstrated in the excised tissue were probably protected by biofilms and could explain the sustained fever and progressive enlargement of the vegetation despite prolonged appropriate antibiotic therapy. This underscores the fact that IE is often a surgical disease requiring surgical excision of vegetations in addition to targeted antibiotics to achieve source control as well as concomitant repair of any underlying congenital or valvular heart defect. In our hospital, more than half of the children diagnosed with infective endocarditis required surgery with a trend towards lower mortality in the surgical group compared with medical therapy alone.[8]

Antimicrobial treatment of NTCD IE is not well defined and lacks the level of evidence available for IE caused by staphylococci and streptococci. A review of *C. diphtheriae* IE treatment showed no significant difference in outcome when penicillin-susceptible strains were treated with either a beta-lactam alone or in combination with an aminoglycoside (for synergism), and treatment duration mostly ranged from 4 to 8 weeks.[6] Surgical intervention for valvular dysfunction was required in 30% to 50% of NTCD IE in the above-mentioned case series with 100% survival in all patients irrespective of surgery.[2,6] In contrast, higher mortality rates ranging from 38% to 43% were noted in two reviews of reported toxigenic and non-toxigenic *C. diphtheriae* IE cohorts dating from the pre-vaccine era to the mid-2000s.[2,6] The differences in outcomes between now and then likely reflect increased expertise in cardiac imaging and management in well-resourced settings in the modern era.[6] Case fatality rates may, however, still be high in low- and middle-income countries (LMIC) as reflected in the provincial cluster, where five out of seven patients died. This may be partly due to lower levels of access to cardiac surgery in LMICs as mortality is known to be lower with early surgical management compared to medical therapy alone.[10]

In South Africa, invasive *C. diphtheriae* is a statutory notifiable disease and macrolides are offered to contacts who demonstrate carriage.[11] This may eliminate the potential for phage conversion and dissemination.[1] There is no role for anti-toxin in patients with invasive NTCD infection, but toxoid vaccination is offered to partially vaccinated or unvaccinated cases and contacts to prevent future toxigenic disease.

Conclusion

This report described invasive NTCD infective endocarditis in a child from sub-Saharan Africa. In our patient, a surgical intervention was needed for a favourable outcome despite almost four weeks of prior antibiotic therapy. NTCD IE can potentially be destructive, therefore clinicians need to be aware of its sequelae in bacteraemic patients. Clinical suspicion and early recognition of NTCD IE remains crucial and children should ideally be managed in centers where cardiac surgery is readily available.

Consent to publish: The authors confirm that written informed consent was obtained from the patient's biological mother to publish the clinical information and images in this case report.

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RALSTONIA MANNITOLILYTICA: AN INCREASINGLY RECOGNISED HEALTHCARE-ASSOCIATED PATHOGEN

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Abstract

Ralstonia species are more frequently being recognised as causative agents of serious healthcare-associated infection especially among immunocompromised individuals. *Ralstonia* species are environmental, non-fermenting, aerobic, Gram-negative bacilli typically found in water and soil. *Ralstonia mannitolilytica, Ralstonia pickettii* and *Ralstonia insidiosa* have been responsible for human infections such as bacteraemia and bone infection. Central nervous system infection and infection in immune competent individuals are uncommon. We report a case of ventriculoperitoneal shunt infection and meningitis caused by *R. mannitolilytica* in an immune competent 11-month-old female.

Key words: *Ralstonia mannitolilytica,* CNS infection, children, adolescents

Introduction

Ralstonia species have been identified as an emerging, healthcare-associated opportunistic pathogen especially among immunocompromised patients.[1] They are a group of Gram-negative aerobic, non-fermenting organisms which are ubiquitous in water and soil.[2] Clinically relevant species include *R. mannitolilytica*, *R. pickettii* and *R. insidiosa*. The epidemiology of infections caused by *Ralstonia* spp. has not been fully elucidated and much of the literature is in the form of case reports and case series.[1,2] We describe a case of ventriculoperitoneal (VP) shunt infection and meningitis caused by *R. mannitolilytica* in an immune competent child.

Case report

An 11-month-old, HIV-unexposed female infant with two VP shunts *in situ* was admitted with generalised seizures, a decreased level of consciousness and VP shunt infection and meningitis.

The patient was born at 33 weeks gestation and her birth weight was 1920 grams. The neonatal period was complicated by jejunal atresia requiring resection and end-to-end anastomosis on the second day of life, and *Escherichia coli* urinary tract infection with bacteraemia on day 11 of life. During this episode, cerebrospinal fluid (CSF) analysis was normal. She was treated with meropenem for 14 days, had a good clinical response, and was discharged.

At 6 weeks of life she presented with an enlarged head and a tense, bulging anterior fontanelle. A brain computerised tomography (CT) scan demonstrated ventriculomegaly with multiloculated hydrocephalus. Cerebrospinal fluid cell count was unsuccessful due to excessive debris, but biochemistry analysis revealed a low glucose (0.6mmol/L), and a very high protein (17.17g/L), with *E. coli* isolated on culture. An external ventricular drain (EVD) was inserted initially, with a left and a right VP shunt inserted thereafter to adequately drain the multiloculated hydrocephalus. Intravenous ceftriaxone (susceptible) was administered for 28 days, and once clinically well (although she did have marked neurodevelopment impairment) the patient was discharged with regular follow-up.

At 11 months of age, during a routine neurosurgical clinic visit, the child was noted to have a fluctuating swollen mass on the anterior abdominal wall near the right VP shunt. Incision and drainage (I&D) of a localised abscess along the distal shunt track was performed and intravenous ceftriaxone was administered for 5 days with good clinical response. During this episode CSF analysis was normal and the child was discharged. One week later, the child was readmitted with seizures, a decreased level of consciousness, dehiscence of the I&D wound and extrusion of the affected right VP shunt. The child was commenced on meropenem and vancomycin empirically and a brain CT scan showed a multiloculated hydrocephalus. Both the right and left VP shunts were removed as part of the source control measures for a shunt infection with meningitis, and a right and left EVD was inserted. During surgery, and prior to removal of the shunts, CSF was collected from both shunts and sent for CSF analysis and culture (Table 1). *Ralstonia mannitolilytica* was isolated from the right VP shunt only and the antibiotic susceptibility results is summarised in Table 2. Repeat CSF cultures collected during this episode were negative (Table 1). The child clinically improved to her baseline during the admission and was treated with meropenem for 22 days. After the right and left EVDs were removed, two new VP shunts were inserted and the child was discharged with outpatient clinic follow-up.

Table 1: Cerebrospinal fluid (CSF) results during the Ralstonia mannitolilytica infection episode

Day of admission	DAY 1	DAY 1	DAY 6	DAY 7	DAY 22
Site of CSF collection	CSF from right VP shunt	CSF from left VP shunt	CSF from right EVD	CSF from left EVD	CSF from new right VP shunt
CSF Glucose (mmol/L)	2.0	3.3	0.6	0.6	1.5
CSF Protein (g/L)	4.33	0.21	2.44	0.75	0.21
CSF Polymorphs (cells/µL)	2	0	0	11	0
CSF Lymphocytes (cells/µL)	91	1	10	48	0
CSF Erythrocytes (cells/µL)	15	140	8	29	14
CSF Gram stain	-ve	-ve	-ve	-ve	-ve
CSF Culture	*R. mannitol-ilytica*	No growth	No growth	No growth	No growth

-ve, negative

Table 2: Antibiotic susceptibility results of the Ralstonia mannitolilytica

Antibiotic	**Susceptibility**

Trimethoprim-sulfamethoxazole	Sensitive
Ceftazidime	Intermediate
Cefepime	Sensitive
Piperacillin-tazobactam	Intermediate
Imipenem	Sensitive
Meropenem	Sensitive
Ciprofloxacin	Sensitive
Gentamicin	Resistant
Amikacin	Resistant

Discussion

Though rare, *R. mannitolilytica* is an important cause of opportunistic infection in hospitalised patients globally.[3,4]. It has been associated with a wide variety of infections in diverse settings including hospital outbreaks. The only other report of *R. mannitolilytica* in South Africa described an outbreak of *R. mannitolilytica* bacteraemia among 16 adult dialysis patients at a tertiary hospital in Pretoria. The source of infection was a contaminated water system supplying the dialysis unit.[2] Although, to our knowledge this is the first report describing invasive *R. mannitolilytica* infection in an immune competent child in South Africa, this is the second report of infection in a young child in Africa. Owusu *et al* in Ghana first reported concomitant *R. mannitolilytica* bacteraemia in a 2-year-old child with severe *Plasmodium falciparum* malaria.[6] Infections in children outside the neonatal period remain rare. Besides the Ghanaian case, a report from Peru described a 5-year-old child with leukaemia and *R. mannitolilytica* bloodstream infection and is the only other reported childhood case outside the neonatal period.[7]

R. mannitolilytica has been associated with hospital outbreaks in neonates, immunocompromised patients, patients with chronic conditions and prolonged hospital stay.[6,7] Water contamination is a major source of infection in outbreaks, including outbreaks in dialysis units.[2] Shankar *et al* reported another outbreak among dialysed adult patients in India.[4] Outbreaks of *R. mannitolilytica* bacteraemia among adult cancer patients were reported from India and China .[1,8] Risk factors for *R. mannitolilytica* infection include indwelling catheters, central venous lines, and chemo-ports.[5,6] Besides bacteraemia, *R. mannitolilytica* has been responsible for a variety of organ specific infections including endocarditis, osteomyelitis, respiratory infection in patients with cystic fibrosis and chronic obstructive pulmonary disease, meningitis, abdominal infection and urinary tract infection.[1-10] *R. mannitolilytica* infections may affect all age groups but mainly occurs in neonates and the elderly. Those with underlying immunosuppressive conditions are at particular risk, and infection with *R. mannitolilytica* has been reported globally.[1-11]

Drug susceptibility of *R. mannitolilytica* clinical isolates is variable, with most isolates being inherently multidrug resistant.[1-11] The isolate from our patient was not susceptible to the aminoglycosides, ceftazadime and piperacillin-tazobactam, but was susceptible to cefepime, meropenem, imipenem, trimethoprim-sulfamethoxazole and ciprofloxacin. Aminoglycoside resistance is a consistent finding in many published reports, while susceptibility to beta-lactam antibiotics such as cephalosporins and carbapenems is variable.[3-8] In the outbreak in the haemodialysis unit in Pretoria all isolates had identical susceptibility results, being resistant to amoxicillin/clavulanic acid, ceftazidime, ertapenem, meropenem, tobramycin, aztreonam and colistin, while remaining susceptible to piperacillin tazobactam, ciprofloxacin, levofloxacin, co-trimoxazole, ceftriaxone, cefuroxime, cefepime and imipenem.[2]

Reported mechanisms of resistance of *Ralstonia* species to beta-lactam antibiotics have been ascribed to the presence of extended spectrum and inducible beta-lactamases such as *bla*-$_{OXA-60}$, *bla*-$_{OXA-22}$, *bla*-$_{OXA-443}$ and *bla*-$_{OXA-444}$.[5,11] Widespread resistance to aminoglycosides is due to the presence of an aminoglycoside acetyl-transferase.[12] Virulence factors permitting biofilm production have also been demonstrated in some isolates.[1]

Antimicrobial treatment for *R. mannitolilytica* is usually individualised, based on the specific susceptibility results of the cultured isolate and the site of infection.[1-11] Many isolates are multidrug resistant even when first reported in a particular geographical location.[3-6] This suggest that *R. mannitolilytica* is an inherently multidrug resistant organism (MDR) which is a concern as the organism continues to circulate in hospital settings.[8] Preventing transmission and infection through appropriate infection prevention practices is an important intervention in healthcare settings, particularly through the avoidance of contamination of hospital water systems and therapeutic products such as intravenous fluids. Timely removal of medical devices is also critical as the organism has potential to form biofilms .[2-8]

Conclusion

R. mannitolilytica is an emerging global healthcare-associated opportunistic infection. Our case is the first published report of clinical infection caused by *R. mannitolilytica* in an immune competent child in South Africa. As many clinical isolates are multi-drug resistant, optimising antibiotic therapy is dependent on susceptibility results. Optimal infection prevention practices, particularly in immunosuppressed individuals should be augmented to lower the risk of infection.

Consent to publish: The authors confirm that written informed consent was obtained from the patient's biological mother to publish the clinical information and images in this case report.

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JOURNAL OF THE AFRICAN SOCIETY FOR PAEDIATRIC INFECTIOUS DISEASES (JAfSPID)

ABOUT THE PUBLICATION

JAfSPID is the official publication of the African Society for Paediatric Infectious Diseases. It was launched as an online newsletter called the *AfSPID Bulletin* in April 2013. In April 2022 it became a peer-review journal. In March 2023 the name was changed from The AfSPID Bulletin to *Journal of the African Society for Paediatric Infectious Diseases* (*JAfSPID*). It publishes educational and research articles on all aspects of infectious diseases in neonates, children, and adolescents. The journal publishes a wide variety of manuscripts including commentaries, reviews, research manuscripts, case reports, medical images, conference reports and editorials. All articles are published under the Creative Commons CC-BY licence.

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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 manuscript should be written in UK English. 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 https://guides.lib.monash.edu/ld.php?content_id=48260115 If a reference contains less than 6 authors, then list all authors. If a reference contains 6 or more authors, list the first 6 authors followed by et al. Where available digital object identifiers (DOIs) and uniform resource locators (URLs) should be included. 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. Images, photographs or unmodified figures from published manuscripts or websites should not be copied, unless the corresponding author provides written permission from the source publisher. Submit the manuscript in Microsoft Word.

Ethics approval: Ethics approval statement with the appropriate ethics committee details and reference number should be included in manuscripts describing case series of 5 or more participants and all research studies.

Parental or patient consent is required for the publication of all case reports.

Letters to the editor: Maximum word count (excluding the references): 500 words with no more than 6 references and one figure or table.

Review or commentary: Maximum word count (excluding the abstract and references): 4000 words, with no more than 60 references, and no more than 6 tables, figures, images, or photographs. The objectives of the review or commentary should be clearly stated in the introduction. The submission should include an unstructured abstract of up to 300 words.

Brief research reports Should briefly describe original research findings or a secondary data analysis. The description should include the study aims or objectives, methods, results, and discussion, and one/two tables or figures. Word limit (excluding the abstract and references) is 1500 words. A maximum of 15 references is permitted and an unstructured abstract of up to 100 words should accompany the manuscript.

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page (components: article title, list of authors, corresponding author and his/her email address), (3) the introduction that includes the study aims or objectives, methods, results, discussion, conclusion (combined word count of these components should not exceed 4000 words), (4) acknowledgments, funding sources, author contributions and ethics approval statement, (5) references (maximum of 60 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 100 words), background that includes the aim or purpose of the case report, the case report and the discussion. Maximum word count (excluding abstract and references): 1500 words with no more than 15 references, and one/two tables, figures, images, or anonymised photographs. When submitting the completed manuscript please provide (1) parental consent to publish the report if information of minors is included in the manuscript or (2) patient consent to publish the report if information of adolescents legally old enough to give consent is included in the manuscript.

Medical image: One or two high-quality, interesting and / or instructive images or anonymised photographs with an explanatory note of less than 250 words and up to 5 references.

Publication watch submission: Commentary on a single published landmark or important research paper or clinical / technical report should not exceed 500 words and 5 references including the reviewed paper or report. Commentary on two or more landmark publications or clinical / technical reports that address a similar / related subject should not exceed 1500 words and 10 references, including the reviewed papers or reports.

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): 4000 words with no more than 30 references, and 6 tables, figures, images, or photographs. The submission should include an unstructured abstract of up to 300 words.

PEER REVIEW

As of October 2021, all submitted commentaries, reviews, research manuscripts, case reports, medical images and conference reports have been subjected to double-blind peer-review using a standardised peer-review template.

COPY EDITING AND PROOFREADING

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TRANSLATION

Portuguese version: Dr Paula Vaz

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