MINISTRY OF HEALTH UGANDA

UNIPH

Epidemiological Bulletin

Volume 7| Issue 2| April-June, 2022

Quarterly Epidemiological Bulletin of the Uganda National Institute of Public Health, Ministry of Health

April—June, 2022

Dear Reader,

We take great pleasure in welcoming you to Issue 2, Volume 7 of the Uganda National Institute of Public Health (UNIPH) Quarterly Epidemiological Bulletin.

We aim to inform the district, national, and global stakeholders on disease outbreak investigations, public health surveillance, and interventions undertaken in detecting, preventing, and responding to public health events in Uganda.

In this issue, we present a variety of articles including; effects of seasonal malaria chemoprevention, trends and distribution of birth asphyxia, factors associated with death among hospitalized COVID-19 patients, HIV positivity rate and recent HIV Infections among Adolescent Girls and Young Women, and black water fever in eastern Uganda.

Should you have any questions or require additional information related to articles in this bulletin please contact us on: aasio@musph.ac.ug, pkawungezi@musph.ac.ug, nmackline@musph.ac.ug, rakunzirwe@musph.ac.ug, OR lbulage@musph.ac.ug

We hope you find this information valuable and we shall appreciate any feedback from you.

Thank you

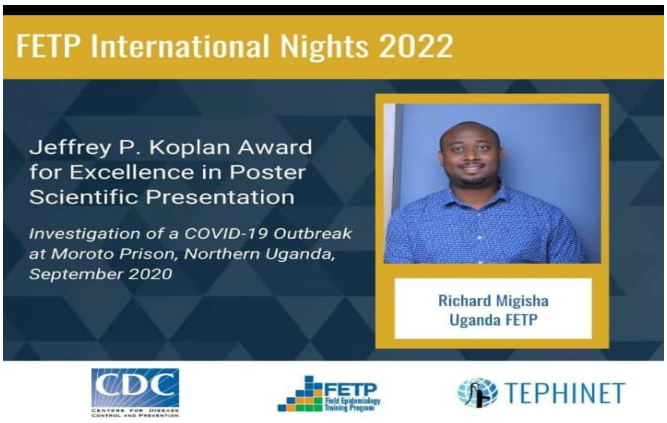
Inside this issue:

Updates

Uganda Public Health Fellowship Program Once Again Won Awards at Epidemic Intelligence Services-2022-Field Epidemiology Training Program International Nights Conference

Author: Alice Asio, Uganda Public Health Fellowship Program-Field Epidemiology Fellow, Cohort 2021, Email: aasio@musph.ac.ug, Tel: +256-788-006-553

Since inception in 2015, the Uganda Public Health Fellowship Program (PHFP) has won many major awards at the Epidemic Intelligence Service (EIS)-International Nights conference and other conferences. Once again, at the EIS-2022-International Nights Conference held during 10th-11th May, PHFP won another Jeffrey P. Koplan award for excellence in scientific poster presentation. The Jeffrey P. Koplan award (Left picture) was won by Dr. Richard Migisha, Fellow Cohort 2020. During the same conference, Job Morukileng, Fellow cohort 2020, was voted a winner in a photo contest to showcase the visual communication of field epidemiological work (Right picture). This brings to a total 7 awards won by PHFP since its inception in 2015.



World Malaria day, 25th April 2022

Author: Alice Asio, Uganda Public Health Fellowship Program-Field Epidemiology Fellow, Cohort 2021, Email: aasio@musph.ac.ug, Tel: +256-788-006-553

Uganda joined the rest of the world on 25th April 2022 to celebrate the World Malaria Day under the theme "Domesticating malaria fight." The National Malaria Control Division, Ministry of Health, conducted a malaria conference (18th - 22nd April 2022) a head of the day. The Minister of Health, Hon Jane Ruth Aceng graced the occasion. Scientists and researchers shared knowledge based on their works. In commemoration of World Malaria Day on 24th April 2022, different activities like 'bulungi bwansi' (general cleanliness) and bicycle riding to raise awareness on malaria prevention were conducted. Rt. Hon. Prime Minister Robinah Nabbanja flagged off the bicycle riding competition at Namboole Stadium.

Rt. Hon. Prime Minister Robinah Nabbanja (right) and Hon. Minister of Health, DR. Jane Ruth Aceng at Namboole Stadium during malaria bicycle ride, 2022

U.S. Ambassador Natalia E. Brown at World malaria commemoration at Namboole stadium

COVID-19 Inter-Action Review, June 2022

Author: Petranilla Nakamya, Uganda Public Health Fellowship Program-Field Epidemiology Fellow, Cohort 2021, hosted at Public Health Emergency Operations Center, Email: nakamy-petra@musph.ac.ug, Tel: +256-773-464-431

In June 2022, Uganda Ministry of Health organ-

Continued from page 2

ised an Inter-Action Review (IAR) on implementation of the resurgence plan for COVID-19. The IAR was aimed at sharing experiences on implementation of the response plan, so as to identify challenges and best practices in order to improve the country's strategic preparedness and response plan.

The review brought together key stakeholders from national and sub-national levels to share their experience during the response and built consensus on priorities to be implemented in the next phase of the response. Reviews were obtained from the different pillars of the response including: case management, logistics, risk communication, community engagement and social protection, laboratory, Incident Management Team (IMT) coordination, Information Communications Technology and advanced mobile phone services; innovations, and surveillance. The process involved: obtaining internal reviews from each pillar, a district-level IAR which was inclusive of regional referral hospitals and finally a workshop to bring all the information obtained together. Results of this will be shared widely to all stakeholders of the COIVD-19 response.

We appreciate the technical and financial support received from the US Centres for Disease Control and Prevention, World Health Organisation, UNICEF, International Organisation for Migration, Baylor Children's Foundation Uganda, Infectious Diseases Institute, UNIPH, the academia, civil society and the Uganda Ministry of Health.

Upcoming events

The Uganda Public Health Fellowship Program to Feature at 11th TEPHINET Global Scientific Conference

Author: Alice Asio, Uganda Public Health Fellowship Program-Field Epidemiology Fellow, Cohort 2021, Email: aasio@musph.ac.ug, Tel: +256-788-006-553

The 11th TEPHINET Global Scientific Conference will take place on 4th-9th September, 2022 in Panama City, Panama. Two abstracts ("Effect of Seasonal Malaria Chemoprevention on Incidence of Malaria Among Children Under Five Years in Kotido and Moroto Districts, Uganda, 2021", by Andrew Kwiringira, Fellow, Cohort 2021 and "Black Water Fever among children in Districts of Bugisu, Bukedi, and Busoga Regions in Eastern Uganda, January 2019 – May 2022", by Alice Asio, Fellow, Cohort 2021) were selected for oral presentation and one ("Preparedness and risk assessment for plague in West Nile region- Uganda, August 2021", by Immaculate Atuhaire, Fellow, Cohort 2021) for poster presentation.

The Public Health Fellowship Program for Laboratory Leaders in Uganda; a Golden Opportunity to Advance Public Health Service

Author: Samuel Gidudu, Uganda Public Health Fellowship Program-Laboratory Leadership Program, Uganda National Institute of Public Health Email: gidudusam@uniph.go.ug, Tel: +256-782-269-108

The capacity to detect, assess, notify and report potential public health events of both national and international concern relies heavily on an efficient laboratory system. However, Uganda faces are a number of challenges that compromise the quality of laboratory systems performance especially in public health laboratories. Examples of such challenges include lack of specialized training for laboratory professionals in the areas of leadership and management, lack of adequate management training in laboratory science education, uncertain career path, and limited input into the national financial planning for health funding by laboratory leaders.

In order to address the above challenges, the Uganda National Institute of Public Health (UNIPH) (https://uniph.go.ug/) at the ministry of health (MOH) through the Public Health Fellowship Program (PHFP), the human resources' capacity building arm of UNIPH, will be implementing a two-year field-based laboratory leadership fellowship program with funding from US Centers for Disease Control and Prevention (CDC). This program will build laboratory leaders in Uganda with key competencies in laboratory systems and infrastructure, leadership, laboratory-based disease surveillance and outbreak investigation, laboratory quality management systems, policy and program management, research and communication. The target beneficiaries to this program include laboratory professionals with a master's degree in a medical laboratory related field of practice.

The first cohort will kick start work come January, 2023 with didactic sessions which are 25% of the 2 years' period and thereafter be deployed to the field for the remaining 75%-time frame. Graduates from the PHFP-Laboratory Leadership Program will be employed by minis-

Continues to page 4

try of health, and or non-government organizations among others to lead the public health laboratory activities using the one health approach and will work alongside the field epidemiologists. This program stems from the global laboratory leadership program that was designed and is being implemented by US CDC, Association of Public Health Laboratories, European Centre for Disease Prevention and Control, Food and Agriculture Organization of the United Nations, World Organization for Animal Health and World Health Organization. Eligible applicants are highly encouraged to look out for the advert in local newspapers and the UNIPH website to apply for the Public Health Fellowship Program for Laboratory Leaders in Uganda.

First Malaria Vaccine Roll out among the Under Five Year Old Children, Uganda, September 2022

Author: Alice Asio, Uganda Public Health Fellowship Program-Field Epidemiology Fellow, Cohort 2021, hosted at National Malaria Control Division, Email: aasio@musph.ac.ug, Tel: +256-788-006-553

Uganda will roll out the first malaria vaccine for children under five years of age in September 2022 under the leadership of the National Malaria Control Division-Ministry of Health with support from the World Health Organisation and Global Alliance for Vaccines and Immunizations. The roll out will be conducted in phases beginning with high malaria burdened districts.

Evaluation of the adoption, fidelity, and effectiveness of the national Prevention of Mother to Child Transmission of HIV retention interventions for mother-baby pairs: 2015 and 2020

Author: Peter Kawungezi, Uganda Public Health Fellowship Program-Field Epidemiology Fellow, Cohort 2022, hosted at AIDS Control Program
Email: pkawungezi@musph.ac.ug, Tel: +256783401306

The Ministry of Health, AIDS Control Program with support from United Nations Children's Fund (UNICEF) will conduct a nationwide evaluation of the adoption, fidelity, and effectiveness of the national PMTCT retention interventions for mother-baby pairs in 2022. This is based on the fact that despite the well-planned and carefully thought interventions since 2015, retention of mother-baby pairs in care in Uganda is still a challenge. This evaluation seeks to measure the extent to which the PMTCT retention interventions for mother-baby pairs were adopted and implemented to fidelity. These interventions include an appointment tracking system, pre-appointment giving/ expected date of delivery cohorts for mothers, early retention monitoring, birth cohort monitoring, and Dry Blood Spot stickers, among others. Understanding the degree of adoption and implementation of these interventions will facilitate the synthesis of the contribution the interventions had on the observed PMTCT retention rates during the intervention period. The findings will be used to support the improved implementation of initiatives for the retention of mother-baby pairs in care. Some of the PHFP Fellows will participate in conducting interviews with the targeted respondents, data cleaning, analysis, and interpretation.

Roll out of Viral Load Point of care Testing, Uganda, 2022

Author: Peter Kawungezi, Uganda Public Health Fellowship Program-Field Epidemiology Fellow, Cohort 2022, hosted at AIDS Control Program
Email: pkawungezi@musph.ac.ug, Tel: +256-783-401-306

The Ministry of Health, AIDS Control Program with support from partners including United Nations Children's Fund (UNICEF) is planning to roll out Point of Care (POC) Viral Load (VL) testing during year 2022 starting with pregnant and breastfeeding mothers using the available testing platforms (GeneXpert and m-Pima). This was informed by the Prevention of Mother Transmission of HIV (PMTCT) impact evaluation 2017- 2019 which showed close to half of pregnant and Breast-Feeding women did not access a viral load. This was worse among pregnant and Breastfeeding Adolescents and Young Women. Initially, the roll out will target 100 sites across the country. Ministry of Health will continue working with partners to scale up POC VL testing services among other sub-populations.

Continued from page 4

Effect of Seasonal Malaria Chemoprevention on Incidence of Malaria Among Children Under Five Years in Kotido and Moroto Districts, Uganda, 2021: Time Series Analysis

Authors: *Andrew Kwiringira[1,2*], Benon Kwesiga[1,2], Richard Migisha[1,2], Lilian Bulage[1,2], Daniel Kadobera[1,2], Damian Rutazaana[3], Julius Ssempiira[3], and Alex R. Ario[1,2]*

[1]Uganda Public Health Fellowship Program, Kampala, Uganda
[2]Uganda National Institute of Public Health, Kampala, Uganda
[3]National Malaria Control Division, Ministry of Health, Kampala, Uganda

[*]Correspondence: Email: akwiringira@musph.ac.ug,Tel: +256775997741

Abstract

Background: *Seasonal malaria chemoprevention (SMC) refers to monthly administration of full treatment courses of antimalarial medicine to children <5 years during high malaria transmission season. SMC has demonstrated effectiveness in Sahel and sub-Sahel countries in Africa but had never been implemented in Uganda until April 2021, when Uganda began SMC in Kotido and Moroto Districts. We assessed the effect of SMC on malaria incidence among children <5 years of age in Kotido and Moroto Districts.*

Methods: *We conducted an interrupted time-series analysis using monthly national health data from the Uganda Ministry of Health District Health Information System-2.*

We extracted monthly data of outpatient (uncomplicated) malaria among children <5 years, 52 months before SMC (Jan 2017-Apr 2021), and 8 months during SMC implementation (May-Dec 2021). We computed monthly incidence per 1,000 children <5 years.

We checked for seasonality, and stationarity in the data. We evaluated the incidence of uncomplicated malaria among children <5 years before and during SMC implementation.

Results: *In Kotido District, malaria incidence was 693/1,000 during SMC implementation period, compared to an expected 1,216/1,000 if SMC had not been implemented. The mean monthly malaria incidence was 87/1,000, compared to an expected mean of 152/1,000 if SMC had not been implemented. This represents a statistically significant mean monthly change of -65.4 [-104.6, -26.2] malaria cases/1,000 during SMC implementation.*

In Moroto District, malaria incidence was 713/1,000 during SMC implementation period, compared to an expected 905/1,000 if SMC had not been implemented. The mean monthly malaria incidence was 89/1,000, compared to an expected 113/1,000 if SMC had not been deployed. This represents a statistically significant mean monthly change of -24.0 [-41.1, -6.8] malaria cases/1,000 during SMC implementation.

Conclusion: *Implementation of SMC substantially reduced incidence of uncomplicated malaria among children <5 years in Moroto and Kotido Districts. The government should consider scaling up SMC in other districts with high malaria transmission.*

Introduction

Malaria is the leading cause of death and illness in Uganda and accounts for close to 30% of all inpatient deaths among children under five years of age (1). Interventions to reduce the transmission and burden of malaria have intensified over the past 10 years with increasing coverage of malaria control interventions such as long-lasting insecticidal nets (LLINs), indoor residual spraying (IRS), and treatment of malaria cases with artemisinin-based combination therapy (ACTs). However, malaria prevalence in some areas, such as the Karamoja region, remains well above the Uganda Malaria Reduction strategic plan (UMRSP) target of 7% (2). To reduce the burden of malaria in children <5 years, Malaria Consortium supported Ministry of Health to roll out Seasonal Malaria Chemoprevention (SMC) in Kotido and Moroto Districts in April 2021.

Seasonal Malaria Chemoprevention is defined as the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season. The World Health Organization (WHO) recommends administering four monthly courses of two antimalarial drugs to children aged between 3-59 months: sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) (3). Each monthly SMC course involves one dose of SP and three daily doses of AQ, with SP and the first dose of AQ given under the supervision of the community distributor, and the remaining two doses of AQ given by the caregiver over the following two days.

Malaria data is collected from paper registers sourced from outpatient departments (OPD),

Continues to page 6

inpatient units, laboratories, pharmacies, and village health teams. Collected data are aggregated at health facilities and submitted, as paper reports, to the district level where information is entered into the web-based District Health Information Software version 2 (DHIS2) (4).
In 2018, SMC was implemented in 12 countries of the Sahel and demonstrated effectiveness in this region (5). Evidence that shows that SMC is a promising intervention largely comes from randomized control trials and modelling studies(6, 7), but evidence from routine implementation is limited. This study evaluated the effect of SMC on incidence of uncomplicated malaria among children <5years, when SMC is delivered through routine programmes by community health workers in Kotido and Moroto districts, Uganda.

Methods

Implementation of seasonal malaria chemoprevention in Uganda

Malaria Consortium, in partnership with the National Malaria Control and Elimination programme implemented the SMC in Uganda. District led planning meetings were held before implementation and the meetings involved enumeration of households and the number of children under five years. Training of Village health teams (VHTs) and their supervisors were held a few days prior to the start of SMC implementation — so that knowledge is retained — and three levels of supervision took place; at the district, parish, and village level. After the training, VHTs administered monthly therapeutic courses of antimalarial drugs sulfadoxine-pyrimethamine and amodiaquine (SP+AQ) to about 65,000 children in Moroto and Kotido districts in the Karamoja region. Village health teams are volunteers, but they received special duty allowanceper diem for every day they worked during the campaign. Children who were sick during the time of implementation of SMC were advised to seek clinical care from existing healthcare facilities within their catchment area and records were captured in the health management information system. Whereas SMC is implemented in the Sahel region and western Africa under a 4-month cycle (5), in Karamoja it was implemented under a 5-month cycle—in one rainy season from May to October 2021, when the region records the highest malaria cases (8). Seasonal Malaria Chemoprevention was also implemented during the COVID-19 pandemic in Uganda.

Data source

We obtained monthly data of outpatient (uncomplicated) malaria among children <5 years from the Uganda Ministry of Health District Health Information System 2 (DHIS2), 52 months before SMC (January 2017-March 2021), and 8 months during SMC implementation
(April-December 2021). The DHIS-2 is an open-source platform where each licensed health facility reports monthly data on priority indicators. The platform allows for aggregation of these facility-level data across different administrative levels of the health system, i.e., from sub-location through national level. It does not cover care received in unlicensed facilities or in private pharmacies. We used district-level data because aggregated data smooths out random variations in health service use that occur at health facility-level.

Statistical analysis

We employed an interrupted time series analysis (ITSA) model to compare trends in incidence of uncomplicated malaria among children < 5 years before and during SMC implementation. We computed monthly incidence per 1,000 children <5 years.
Interrupted Time Series Analysis and other time series models assume that preintervention trends, seasonal variations, and levels would remain unchanged in the post-intervention period under a non-intervention counterfactual state(9). The estimated intervention impact is the difference between the forecasted counterfactual-state and observed data during the post-period. The validity of these approaches depends on accounting for any competing processes that could affect these pre-intervention trends and levels – concomitant policies, changes in data recording/measurement, or population composition – thereby biasing the post-intervention counterfactual trend estimates.
We assume that there were no other competing events (structural breaks) other than SMC implementation, that could drive the results. We checked this assumption using Supremum Wald tests for unknown structural breaks, and Wald tests for known structural breaks in the data.
We first conducted descriptive analyses; assessed distributions and outliers of the outcome; decomposed the data to check for seasonality, trends, and random noise; and checked for autocorrelation and partial autocorrelation. We then conducted unit root tests to estimate the number of lags required to make the data stationary.

Continued from page 6

The ITSA model was specified as follows(10):

$$\_\square\square = \square 0 + \square 1\square + \square 2D\square + \square 3[t-T1]\, D\square + \square\square$$

where $\square\square$ represents the outcome. *TI* represents the interruption (SMC implementation) time. *Dt* is a dummy variable where 1 represents the post-intervention period. *t* is time from the start of the series. Note that under this formulation $[t-TI]$ will be zero for the pre-intervention period, and 1, 2, ..., *n* for the post-intervention in equal time intervals. The error term, $\square\square$, uses Newey-West standard errors to account for serial $\square\square$ correlation(11)
The interpretation of the estimates is as follows:

$\square 0$ is the intercept
$\square 1$ is the pre-intervention trajectory
$\square 2$ is the immediate intervention effect
$\square 3$ is the effect of the intervention over time i.e., the difference in the pre-shock and post-shock trajectories
The number of lags in this formulation is calculated for using the following formula (12):

$$m=0.75T1/3$$

We compared the forecasts against the actual observed values in the dataset.

Ethical approval and consent of participants
We obtained permission from the Ministry of Health (MOH) to conduct this evaluation. The Office of Science, U.S. Centers for Disease Control and Prevention, determined that the primary intent of this evaluation was public health practice. The study was conducted by using open access aggregate data in Uganda Ministry of Health DHIS2 and therefore consent to participate in this study is not applicable.

Results

Effect of seasonal malaria chemoprevention on malaria incidence among children under five years, Kotido District

In Kotido District, malaria incidence was 693 per 1,000 population of children under 5 years during SMC implementation period, compare to an expected 1,216 per 1,000 population if SMC had not been implemented. The mean monthly malaria incidence was 87 per 1,000 population compared to an expected mean of 152 per 1,000 population if SMC had not been implemented (Figure 1). This represents a statistically significant mean monthly change of -65.4 [-104.6, -26.2] malaria cases per 1,000 population during SMC implementation.

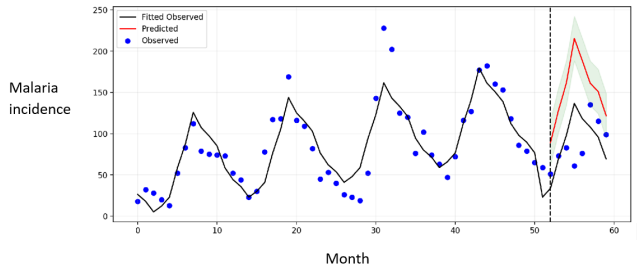


Figure 1: Effect of seasonal malaria chemoprevention on malaria incidence among children under five years, Kotido District

Effect of seasonal malaria chemoprevention on malaria incidence among children under five years, Moroto District

In Moroto District, incidence of uncomplicated malaria was 713 per 1,000 population of children <5 years during SMC implementation period, compared to an expected 905 per 1,000 if SMC had not been implemented. The mean monthly malaria incidence was 89/1,000, compared to an expected 113 per 1,000 if SMC had not been deployed (Figure 2). This represents a statistically significant mean monthly change of -24.0 [-41.1, -6.8] malaria cases per 1,000 during SMC implementation.

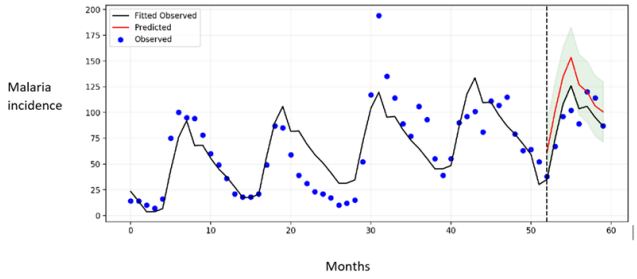


Figure 2: Effect of seasonal malaria chemoprevention on malaria incidence among children under five years, Moroto District

Discussion

In our evaluation of effect of SMC on incidence of uncomplicated malaria in Moroto and Kotido districts in Uganda, we found that SMC implementation substantially reduced incidence of uncomplicated malaria among children <5 years in both districts. Our findings are consistent with results from Mali and Burkina Faso where SMC was delivered by community health teams like the case of Uganda (13, 14).
Although SMC reduced malaria incidence by 43% and 21% in Kotido and Moroto district respectively. This is lower than what was ob-

Continues to page 8

served when SMC was delivered by a similar approach using community health workers; in Burkina Faso, SMC reduced malaria incidence by 69% (14). The observed difference may be partly since SMC was implemented during COVID-19 pandemic in Uganda. A report of lessons learnt from supporting SMC during COVID-19 showed that support supervision was minimised and was less physical (15). More so, there are reports of disruptions of other routine malaria interventions like supply of long-lasting insecticide treated nets (LLINs) at health facilities that could have negatively impacted malaria control (16).

The reduction in malaria incidence in Moroto District was half the reduction observed in Kotido District following SMC implementation. Since SMC was implemented at the same time (during high transmission season) and given that the two neighbouring districts have similar local epidemiological conditions (8), possible explanation for the observed lower reduction in malaria incidence in Moroto may be internal factors like political will. Indeed, lack of political will has been shown to be an obstacle to implementation of public health programs (17). We did not explore reasons for the observed difference in malaria incidence reduction in the two districts following SMC implementation.

This study has limitations. First, DHIS2 data are often incomplete and subject to recording error. Second, aggregated data can mask significant data quality variations in policy impact. These results should not be extrapolated beyond the analysis timeframe as it is unclear if the effects will persist, dissipate, or evolve with time. Future studies can also assess differences in outcomes between facilities known to have higher quality data and compare the results against national aggregates.

Conclusion

Implementation of SMC substantially reduced incidence of uncomplicated malaria among children <5 years in Moroto and Kotido district. The government should consider scaling up SMC in other districts with high malaria transmission.

Acknowledgments

We acknowledge Malaria consortium and NMCD for implementing SMC, and Uganda Ministry of Health for the giving us permission to access the data. The authors are grateful to the districts and VHTs that participated in implementation of SMC and for the technical and administrative support provided by the Uganda Public Health Fellowship Program, National Institute of Public Health, and the US Centers for Disease Control and Prevention.

References

1. Ministry of Health. Uganda Malaria Reduction Strategic Plan (UMRSP) 2014-2020. Ministry of Health; 2020.
2. Nambuusi BB, Ssempiira J, Makumbi FE, Kasasa S, Vounatsou P. Associations and contribution of childhood diseases to fever risk among children less than five years in Uganda. Journal of Global Health Reports. 2020;4:e2020052.
3. World Health Organization. Policy recommendation: seasonal malaria chemoprevention (SMC) for plasmodium falciparum malaria control in highly seasonal transmission areas of the Sahel sub-region in Africa. World Health Organisation; 2012.
4. Kiberu VM, Matovu JK, Makumbi F, Kyozira C, Mukooyo E, Wanyenze RK. Strengthening district-based health reporting through the district health management information software system: the Ugandan experience. BMC medical informatics and decision making. 2014;14(1):1-9.
5. Baba E, Hamade P, Kivumbi H, Marasciulo M, Maxwell K, Moroso D, et al. Effectiveness of seasonal malaria chemoprevention at scale in west and central Africa: an observational study. The Lancet. 2020;396 (10265):1829-40.
6. Griffin JT, Bhatt S, Sinka ME, Gething PW, Lynch M, Patouillard E, et al. Potential for reduction of burden and local elimination of malaria by reducing Plasmodium falciparum malaria transmission: a mathematical modelling study. The Lancet Infectious Diseases. 2016;16 (4):465-72.
7. Noor AM, Kibuchi E, Mitto B, Coulibaly D, Doumbo OK, Snow RW. Sub-national targeting of seasonal malaria chemoprevention in the Sahelian countries of the Nouakchott Initiative. Plos one. 2015;10(8):e0136919.
8. Kigozi SP, Kigozi RN, Sebuguzi CM, Cano J, Rutazaana D, Opigo J, et al. Spatial-temporal patterns of malaria incidence in Uganda using HMIS data from 2015 to 2019. BMC public health. 2020;20(1):1-14.
9. Linden A. Conducting interrupted time-series analysis for single-and multiple-group comparisons. The Stata Journal. 2015;15 (2):480-500.
10. Huitema BE, McKean JW. Identifying autocorrelation generated by various error processes in interrupted time-series regression designs: A comparison of AR1 and portmanteau

Continued from page 8

tests. Educational and psychological measurement. 2007;67(3):447-59.
11. Linden A. Persistent threats to validity in single-group interrupted time series analysis with a cross over design. Journal of evaluation in clinical practice. 2017;23(2):419-25.
12. Stock JH, Watson M. Forecasting in dynamic factor models subject to structural instability. The Methodology and Practice of Econometrics A Festschrift in Honour of David F Hendry. 2009;173:205.
13. Diawara F, Steinhardt LC, Mahamar A, Traore T, Kone DT, Diawara H, et al. Measuring the impact of seasonal malaria chemoprevention as part of routine malaria control in Kita, Mali. Malaria journal. 2017;16(1):1-12.
14. Kirakoya-Samadoulougou F, De Brouwere V, Fokam AF, Ouédraogo M, Yé Y. Assessing the effect of seasonal malaria chemoprevention on malaria burden among children under 5 years in Burkina Faso. Malaria Journal. 2022;21(1):143.
15. MC. Implementing seasonal malaria chemoprevention during pandemic. Malaria consortium; 2021.
16. IGC. The COVID-19 impact on Ugandan supply chains 2020.
17. Zalmanovitch Y, Cohen N. The pursuit of political will: politicians' motivation and health promotion. The International Journal of Health Planning and Management. 2015;30(1):31-44.

Trends and distribution of birth asphyxia, Uganda, 2017-2020: a retrospective Analysis of Public Health Surveillance Data

Authors: Allan Komakech[1,2,3,4], Stella M. Migamba[1,2,3], Petranilla Nakamya[1,3], Edirisa Nsubuga Juniour[1,3], Job Morukileng[1,2,3], Freda Aceng[5], Robert Mutumba[2], Lilian Bulage[1,3] Benon Kwesiga[1,3], Alex R. Ario[1,3]*

Institutional affiliations

[1]Uganda Public Health Fellowship Program, Kampala, Uganda, [2]Reproductive Health Department, Ministry of Health, Kampala, Uganda, [3]Uganda National Institute of Public Health, Kampala, Uganda, [4]Clarke International University, Kampala, Uganda, [5]Department of Integrated Epidemiology, Surveillance and Public Health Emergencies, Ministry of Health, Kampala, Uganda

**Correspondence: Email: akomackech@musph.ac.ug, Tel: +256789185617*

Summary

Background: *In 2015, Uganda adopted the interventions as advised by the Every Newborn Action Plan; these included a renewed focus on surveillance of birth asphyxia cases and adoption of a national strategic plan on managing birth asphyxia and other childhood related illnesses. In 2016, Ministry of Health integrated the Helping Babies Breathe (HBB) initiative, an evidence-based educational program to teach birth attendants about neonatal resuscitation techniques into the health system to improve management of birth asphyxia. We described the trends and distribution of birth asphyxia in Uganda during 2017–2020 in the era following the renewed efforts.*

Methods: *We analysed birth asphyxia surveillance data during January 2017–December 2020 obtained from the District Health Information System (DHIS2). We calculated incidence rates of birth asphyxia per 1,000 deliveries at district, regional, and national levels. We used line graphs to demonstrate the trend of annual incidence of birth asphyxia incidence with the corresponding reporting rates at nation-*

Continues to page 10

al and regional levels. We used logistic regression to determine significance of trends.
Results: *The average national annual incidence of birth asphyxia increased by 4.5% from 2017 to 2020 (OR=1.05; 95%CI=1.04-1.05, p=0.001), concurrent with a decline in reporting rates from 73% to 46% during the same period. The Northern and Eastern Region had a significant increase of 6% (OR=1.06; 95%CI=1.05-1.07, p=0.001) and 5% (OR=1.05; 95% CI=1.03-1.05, p=0.001) over the study period, respectively. The districts with highest incidence were Bundibugyo, Iganga, and Mubende with persistent rates of >60 cases of birth asphyxia/1,000 deliveries. The least affected district was Kazo District, with 3 cases of birth asphyxia/1,000 deliveries.*
Conclusion: *The incidence of birth asphyxia increased nationally from 2017-2020, even with declines in surveillance data reporting. There is a need to emphasize consistent reporting of birth asphyxia to ensure useful surveillance data. We also recommend continuous capacity building in managing birth asphyxia, with emphasis on the most affected districts.*

Background

The World Health Organization (WHO) defines birth asphyxia as the failure to initiate and sustain breathing at birth (1). Birth asphyxia is a leading cause of brain damage among new born children with up to 80% of survivors suffering from lifelong health problems such as disabilities, developmental delays, palsy, intellectual disabilities, and behavioural problems (2,3). Worldwide, birth asphyxia is responsible for an estimated 600,000 (24%) of all neonatal deaths per annum (4). In developed countries, birth asphyxia incidence is 2 per 1,000 births, which increases 10 fold in low-income countries with limited access to basic quality obstetrics care during pregnancy, intrapartum, and postpartum period (5). In studies done in Nigeria and Bangladesh, birth asphyxia was responsible for 30% and 39% of all neonatal deaths in the two countries respectively (6,7).

Birth asphyxia is associated with risk factors, which are grouped according to whether they are before birth (antepartum risk factors), during birth (intrapartum risk factors) or after birth (postpartum risk factors). Antepartum risk factors include severe maternal hypotension or hypertensive diseases during pregnancy, history of stillbirth, young maternal age, and advanced maternal age. Intrapartum risk factors include malpresentation, prolonged second stage of labour, and home delivery. Postpartum risk factors include low birth weight, high birth weight, preterm delivery, and poor resuscitation efforts. The majority of these causes are preventable, as evidenced by the regional variations across the world (8–11).

During 2018-2020, almost half of all neonatal deaths reviewed in Uganda were due to birth asphyxia (12). Studies done in Uganda implicated antepartum and intrapartum risk factors as the major culprits (13–16). Significant modifiable challenges in prevention of birth asphyxia include; complexities of referral systems, non-attendance of antenatal care by mothers, knowledge gaps among health workers, lack of equipment and high health worker: patient ratio (16).

In 2015, Uganda adopted the interventions as advised by the Every Newborn Action Plan; these included a renewed focus on surveillance of birth asphyxia cases and adoption of a national strategic plan on managing birth asphyxia and other childhood related illnesses. Furthermore, the Ministry of Health rolled out the Helping Babies Breathe (HBB) initiative in 2016; an initiative meant to improve prevention and management of birth asphyxia among health workers. However, the impact of these interventions on birth asphyxia incidence was unknown. We described the trends and distribution of birth asphyxia in Uganda during 2017-2020, the era following these renewed efforts.

Methods

Study setting

This study considered data that was collected nation-wide. Uganda is located in East Africa with an estimated projected population size of 41.6 million people (17). There are four broad regions in Uganda, each region is partitioned into districts making a total of 135 districts (17,18). In Uganda, the health system is comprised of public and private health sectors (19). Health is provided through a decentralized

Continued from page 10

health care system whereby health services are delivered within seven tiers, including national referral hospitals, regional referral hospitals, district hospitals, health centre IV, health centre III, health centre II, and community health workers (CHWs), locally referred to as the Village Health Teams (VHTs) (20). In Uganda, birth asphyxia is a condition that can be managed at the level of HCII facilities and above.

Study design and data source

We conducted a nationwide retrospective surveillance data analysis of birth asphyxia cases from 2017 to 2020 using data abstracted from the Uganda District Health Information System (DHIS-2). Data on birth asphyxia was first entered in the DHIS-2 in 2017. DHIS-2 is a web-based reporting tool introduced to Uganda in 2012. It is a tool for collection, validation, analysis, and presentation of aggregate and patient based statistical data, tailored (but not limited) to integrated health information management activities. Data on birth asphyxia data are routinely generated at health facilities using the integrated maternity register. The data from these registers are aggregated into a health facility monthly report (paper form) which is initially submitted to health sub-district, then to the district health offices. At district health office, the data from the paper-based reports are entered into DHIS-2. Data in DHIS-2 is then grouped accordingly at national, regional, district, subcounty and facility levels. At the national level, the Reproductive and Infant Health Department of the Ministry of Health and other stakeholders use data from DHIS -2 to make informed decisions and plan interventions on reproductive and infant health.

Study variables, data abstraction and analysis

We abstracted data for birth asphyxia cases and total deliveries during 2017–2020 from the DHIS-2. We disaggregated the data into national, regional, and district levels. We calculated the annual incidence rates for birth asphyxia cases for each level (national, regional, and district level), by dividing the total birth asphyxia cases during the year by the total deliveries during that year and multiplying by 1,000. We obtained the mean annual incidence rates for the national and regional levels by adding annual incidence rates for the four years of study and dividing by four.

We drew line graphs by plotting the quarterly mean incidence of birth asphyxia against the period in years to present the trend of incidence rates for national and regional levels from 2017 –2020. We used logistic regression to establish the significance of trends of birth asphyxia incidence over the four years at national and regional level. We also used choropleth maps generated using Quantum Geographic Information System (QGIS) to present the district distribution of the birth asphyxia incidence across the country.

Ethical considerations

Our study utilized routinely generated aggregated surveillance data with no personal identifiers in reproductive and infant health department, Ministry of Health (MoH) through the DHIS-2. The MoH of Uganda through the office of the Director General Health Services gave approval to access data for birth asphyxia cases from the DHIS-2. We stored the abstracted data set in a password-protected computer and only shared it with the investigation team. In addition, The Office of the Associate Director for Science, U.S. Centers for Disease Control and Prevention, determined that this study was not a human subjects research with the primary intent of improving use of surveillance data to guide public health planning and practice.

Results

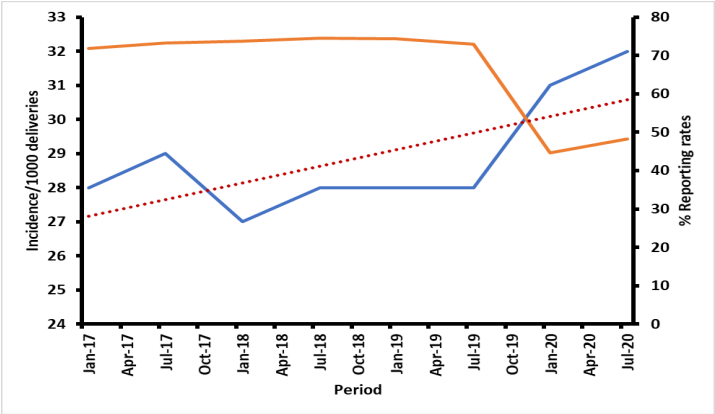
Trend of annual incidence rate of birth asphyxia, national level, Uganda, 2017–2020

In Uganda, there were a total of 134,801 birth asphyxia cases and 4,625,336 total deliveries during 2017-2020. The average national incidence of birth asphyxia over the four years in Uganda was 29 per 1,000 total deliveries. The highest annual incidence (32 birth asphyxia cases per 1,000 total deliveries) over the four years was recorded in 2020.

The incidence of birth asphyxia steadily increased by 5% from 2017–2020 and the increasing trend was shown to be statistically significant (OR 1.045; 95% CI 1.04, 1.05) **(Figure 1)**. A concurrent decline in reporting rates from

Continues to page 12

73% to 46% is noted during the same period, 2017–2020.



Note

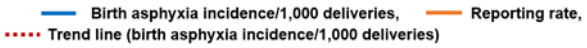


Figure 1: Four-year quarterly trends of birth asphyxia incidence/1,000 total deliveries, Uganda, 2017–2020

Trend of annual incidence rate of birth asphyxia cases, regional level, Uganda, 2017-2020

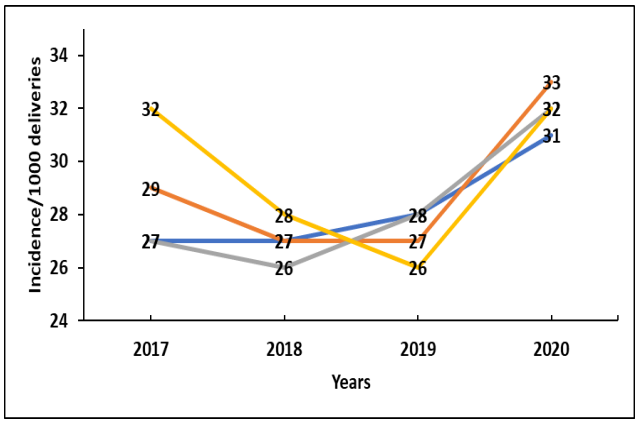
We also observed a statistically significant increase in the incidence rates of birth asphyxia/1,000 total deliveries in the Northern and Eastern regions of Uganda. Northern region had a 7% increment in birth asphyxia incidence while Eastern Region had a 5% increment in birth asphyxia incidence during 2017–2020 **(Table 1)**.

Central region registered the highest mean annual incidence rate of 30 birth asphyxia cases/1,000 total deliveries over the four years and the Northern Region registered the lowest mean incidence rate of 28 per 1,000 deliveries over the four years. Although no major decreases or increases in the trends were noted in the Central region, incidence above the national average are consistently noted over the four years (**Figure 2).**

Table 1: Significance of trends of birth asphyxia incidence at regional level, Uganda, 2017–2020

Region 2017/2020	Odds Ratio	95% CI	P-Value
Northern	1.07	1.05-1.08	<0.001*
Eastern	1.05	1.04-1.06	<0.001*
Central	1.00	0.99-1.01	0.54
Western	0.99	0.99-1.01	0.75

*indicates p value<0.05



Note: Central Eastern Northern Western

Figure 2: Trend of annual birth asphyxia cases/1,000 total deliveries, regional level, Uganda, 2017–2020

Spatial distribution of birth asphyxia incidence rates, district level, Uganda, 2017-2020

The spatial distribution of birth asphyxia cases over the four years shows a minimal clustering of high burden districts with similar patterns noted during all the four years of the study. The districts shaded in deep red had the highest incidence rates greater than 60 cases per 1,000 deliveries**.** The districts that had persistently high birth asphyxia incidence rates over the study period included Bundibugyo, Mubende, and Iganga. Moroto, Kabarole, and Kamwenge were also highly affected over the years. The districts with the white were the least affected (<20 birth asphyxia cases per 1,000 deliveries) **(Figure 3**).

Continued from page 12

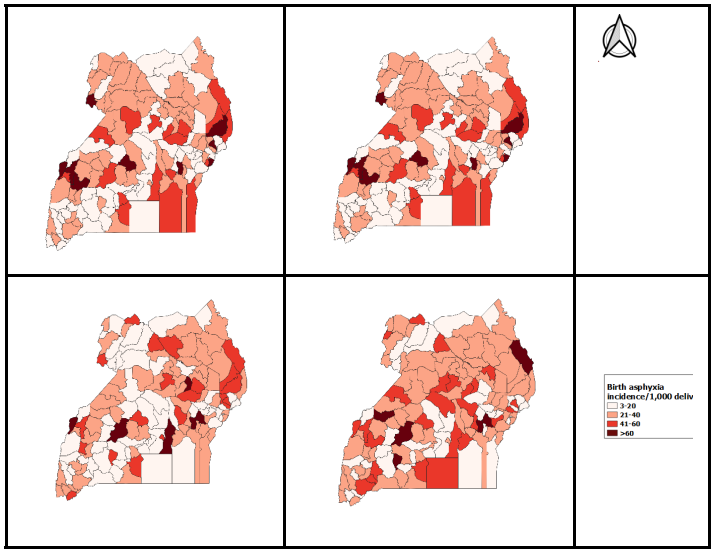


Figure 3: Spatial distribution of birth asphyxia cases/1,000 total deliveries, Uganda, 2017–2020

Discussion

Birth asphyxia incidence rates increased significantly by 5% in Uganda during 2017-2020. We also noted a statistically significant increase of 6% in the Northern region and 5% in the Eastern Region. The highest annual incidence of birth asphyxia cases was recorded in 2020 (32 birth asphyxia cases/1,000 total deliveries), compared to 28/1000 total deliveries in 2017, 2018, and 2019. Spatial trends showed minimal clustering of birth asphyxia incidence in the country with districts such as Bundibugyo, Iganga, and Mubende having persistently high birth asphyxia incidence rates over the four years (>60 cases per 1,000 deliveries).

In our study, the incidence of birth asphyxia increased steadily by 5% over the study period despite a decrease in reporting rates over the same period. The increase in birth asphyxia incidence over the study period is not clearly understood. However, the burden of birth asphyxia is particularly high in East and Central Africa compared to other regions of Sub-Saharan Africa (21). This is due to poor obstetrics coverage, inequity and inequality because of gaps in local health financing models, inaccessible health facilities, socio-cultural norms, low literacy levels, shortage in health workers and supplies and poor health care spending (21). Our study could not gather sufficient literature on birth asphyxia incidence in similar settings as Uganda. On the contrary, we noted a decrease in birth asphyxia incidence in a study done in Netherlands from 0.13% to 0.10% in a 9-year period preceding 2019 (0R 0.97; 95% CI 0.95, 0.99) (22). The decrease might have been attributed to a difference in setting. Uganda is a low-income country with low per capita GDP whereas Netherlands is a developed country with free health care and adequate resources for health for all citizens. Funding health services can lead to provision of services vital to reduce and prevent birth asphyxia. A key lesson to learn therefore is that increasing financing can improve newborn outcomes.

The highest incidence of birth asphyxia during the study period occurred in 2020 at 32 birth asphyxia cases per 1,000 deliveries compared to 28/1000 total deliveries in the three previous years. The spike is likely due to the delayed access of mothers to health facilities following the imposition of the COVID-19 lockdown travel restrictions (23). A study in Uganda showed an increase of 7% in birth asphyxia incidence in the period before versus during the early phase of the COVID-19 lockdown (24). The COVID-19 pandemic caused massive disruptions throughout many Africa countries affecting many lives and livelihoods (25). These findings were supported by findings in Malawi, Ghana, Sierra Leone, and Nigeria during the COVID-19 lockdown (26,27). Furthermore, crisis situations do not necessarily lead to reduction in reproduction and yet access to health services is greatly affected during such periods (28). Special considerations should therefore be ensured to facilitate the movement of mothers during lockdown situations to improve access to health care.

In our spatial analysis, districts such as Bundibugyo, Iganga, and Mubende had persistently high incidence of >60 cases of birth asphyxia/1,000 deliveries. Kazo District was the least affected district with 3 cases of birth asphyx-

Continues to page 14

ia/1,000 deliveries. Although no particular reason can be identified to explain the non-clustered patterns of birth asphyxia in Uganda, all regions of Uganda have their fair share of poverty (29), issues with access to- and availability of health facilities (30), and differing cultural and social norms (31), known factors that can lead to birth asphyxia. Studies done to establish socio-demographic and health facility factors associated with birth asphyxia, particularly in the highly affected regions would be beneficial.

Study limitations

Secondary data in DHIS2 is limited in terms of variables to provide a sufficient assessment of birth asphyxia incidence in Uganda. Studies using primary data to determine associated factors may be more beneficial in understanding increasing birth asphyxia trends in Uganda. This will help to improve already-existing evidence-based interventions. Secondly, given the low average reporting rates over the study period (<80%), a true representation of birth asphyxia incidence might be limited. It should also be noted that some deliveries occur outside the hospital; it is therefore possible that the incidence rates we are reporting here are an underestimate.

Conclusion

Birth asphyxia incidence increased over the four years of our study period despite a decrease in reporting rates. The highest incidence over the four years was recorded in 2020. Bundibugyo, Iganga, and Mubende districts had a persistently high birth asphyxia incidence (>60/1,000 deliveries). Kazo district was the least affected district (3/1000 deliveries).

We recommend the Ministry of Health to emphasize consistent reporting of birth asphyxia to ensure useful surveillance data. We also recommend continuous capacity building in managing birth asphyxia, with emphasis on the most affected districts.

Acknowledgements

We would like to thank the Ministry of Health for providing access to DHIS2 data that was used for this analysis. We appreciate the technical support provided by the Reproductive Health Department of the Ministry of Health. Finally, we thank the US-CDC for supporting the activities of the Uganda Public Health Fellowship Program (UPHFP).

References

1. Abdo RA, Halil HM, Kebede BA, Anshebo AA, Gejo NG. Prevalence and contributing factors of birth asphyxia among the neonates delivered at Nigist Eleni Mohammed memorial teaching hospital, Southern Ethiopia: A cross-sectional study. BMC Pregnancy Childbirth [Internet]. 2019 Dec 30 [cited 2021 Jun 7];19(1):1–7. Available from: https://doi.org/10.1186/s12884-019-2696-6
2. Zhang S, Li B, Zhang X, Zhu C, Wang X. Birth Asphyxia Is Associated With Increased Risk of Cerebral Palsy: A Meta-Analysis. Front Neurol [Internet]. 2020 Jul 16 [cited 2021 Jun 7];11:704. Available from: www.frontiersin.org
3. Pospelov AS, Puskarjov M, Kaila K, Voipio J. Endogenous brain-sparing responses in brain pH and PO2 in a rodent model of birth asphyxia. Acta Physiol [Internet]. 2020 Jul 1 [cited 2021 Jun 7];229(3):e13467. Available from: https://doi.org/10.1111/apha.13467
4. Ahmed R, Mosa H, Sultan M, Helill SE, Assefa B, Abdu M, et al. Prevalence and risk factors associated with birth asphyxia among neonates delivered in Ethiopia: A systematic review and meta-analysis. PLoS One [Internet]. 2021 Aug 1 [cited 2022 May 16];16(8):e0255488. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0255488
5. Kune G, Oljira H, Wakgari N, Zerihun E, Aboma M. Determinants of birth asphyxia among newborns delivered in public hospitals of West Shoa Zone, Central Ethiopia: A case-control study. PLoS One [Internet]. 2021 Mar 1 [cited 2022 May 18];16(3):e0248504. Available from:

Continued from page 14

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0248504

6. Adebami OJ. Maternal and fetal determinants of mortality in babies with birth asphyxia at Osogbo, Southwestern Nigeria Autosomal recessive polycystic kidney (ARPKD) in a Nigerian newborn: a case report View project Management of Neonatal Jaundice View project. 2016 [cited 2022 May 18]; Available from: http://garj.org/garjmms

7. Sampa RP, Hossain QZ, Sultana S. Observation of Birth Asphyxia and Its Impact on Neonatal Mortality in Khulna Urban Slum Bangladesh. Int J Adv Nutr Heal Sci. 2013 Dec 13;1(1):1–8.

8. Aslam HM, Saleem S, Afzal R, Iqbal U, Saleem SM, Shaikh MWA, et al. "Risk factors of birth asphyxia." Ital J Pediatr 2014 401 [Internet]. 2014 Dec 20 [cited 2021 Jul 22];40(1):1–9. Available from: https://ijponline.biomedcentral.com/articles/10.1186/s13052-014-0094-2

9. Igboanugo S, Chen A, Mielke JG. Maternal risk factors for birth asphyxia in low-resource communities. A systematic review of the literature. https://doi.org/101080/0144361520191679737 [Internet]. 2019 Nov 16 [cited 2021 Jul 22];40(8):1039–55. Available from: https://www.tandfonline.com/doi/abs/10.1080/01443615.2019.1679737

10. Bayih WA, Yitbarek GY, Aynalem YA, Abate BB, Tesfaw A, Ayalew MY, et al. Prevalence and associated factors of birth asphyxia among live births at Debre Tabor General Hospital, North Central Ethiopia. BMC Pregnancy Childbirth 2020 201 [Internet]. 2020 Oct 28 [cited 2021 Jul 22];20(1):1–12. Available from: https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-020-03348-2

11. Panna S. Risk Factors for Birth Asphyxia in Newborns Delivered at Nongkhai Hospital. Srinagarind Med Journal-ศรีนครินทร์เวชสาร [Internet]. 2020 Jun 20 [cited 2021 Jul 22];35(3):278–86. Available from: SMNJ/article/view/9123

12. MPDSR Report Uganda FY 2019_2020 Final report for Printing_2020.

13. Arach AAO, Tumwine JK, Nakasujja N, Ndeezi G, Kiguli J, Mukunya D, et al. Perinatal death in Northern Uganda: incidence and risk factors in a community-based prospective cohort study. https://doi.org/101080/1654971620201859823 [Internet]. 2021 [cited 2021 Jul 20];14(1). Available from: https://www.tandfonline.com/doi/abs/10.1080/16549716.2020.1859823

14. Ayebare E, Jonas W, Ndeezi G, Nankunda J, Hanson C, Tumwine JK, et al. Fetal heart rate monitoring practices at a public hospital in Northern Uganda – what health workers document, do and say. https://doi.org/101080/1654971620201711618 [Internet]. 2020 Dec 31 [cited 2021 Jul 20];13(1). Available from: https://www.tandfonline.com/doi/abs/10.1080/16549716.2020.1711618

15. Hedstrom A, Mubiri P, Nyonyintono J, Nakakande J, Magnusson B, Vaughan M, et al. Outcomes in a Rural Ugandan Neonatal Unit Before and During the Early COVID-19 Pandemic: A Retrospective Cohort Study. SSRN Electron J [Internet]. 2021 [cited 2021 Jul 20]; Available from: https://papers.ssrn.com/abstract=3872622

16. Ayebare E, Ndeezi G, Hjelmstedt A, Nankunda J, Tumwine JK, Hanson C, et al. Health care workers' experiences of managing foetal distress and birth asphyxia at health facilities in Northern

Continues to page 16

Uganda. Reprod Heal 2021 181 [Internet]. 2021 Feb 5 [cited 2021 Jul 20];18(1):1–11. Available from: https://reproductive-health-journal.biomedcentral.com/articles/10.1186/s12978-021-01083-1

17. Uganda profile – Uganda Bureau of Statistics [Internet]. [cited 2022 Mar 23]. Available from: https://www.ubos.org/uganda-profile/

18. Maps & Regions | Uganda National Web Portal [Internet]. [cited 2022 Mar 23]. Available from: https://www.gou.go.ug/about-uganda/sector/maps-regions

19. Kamya C, Abewe C, Waiswa P, Asiimwe G, Namugaya F, Opio C, et al. Uganda's increasing dependence on development partner's support for immunization – a five year resource tracking study (2012 – 2016). BMC Public Health [Internet]. 2021 Dec 1 [cited 2022 May 24];21(1):1–11. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-021-10178-0

20. Mansour W, Aryaija-Karemani A, Martineau T, Namakula J, Mubiri P, Ssengooba F, et al. Management of human resources for health in health districts in Uganda: A decision space analysis. Int J Health Plann Manage. 2022 Mar 1;37(2):770–89.

21. Usman F, Imam A, Farouk ZL, Dayyabu AL. Newborn Mortality in Sub-Saharan Africa: Why is Perinatal Asphyxia Still a Major Cause? Ann Glob Heal [Internet]. 2019 [cited 2021 Aug 12];85(1). Available from: /pmc/articles/PMC6688545/

22. Ensing S, Abu-Hanna A, Schaaf J, Mol BW, Ravelli A. 453: Trends in birth asphyxia among live born term singletons. Am J Obstet Gynecol [Internet]. 2013 Jan 1 [cited 2021 Aug 9];208(1):S197. Available from: http://www.ajog.org/article/S0002937812017024/fulltext

23. National Population Council. the State of Uganda Population Report 2020 Impact of Covid-19 on Population and Development: Challenges, Opportunities and Preparedness the Republic of Uganda. 2020;1–93.

24. Hedstrom A, Mubiri P, Nyonyintono J, Nakakande J, Magnusson B, Vaughan M, et al. Impact of the early COVID-19 pandemic on outcomes in a rural Ugandan neonatal unit: A retrospective cohort study. PLoS One [Internet]. 2021 Dec 1 [cited 2022 Apr 7];16(12):e0260006. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0260006

25. Lone SA, Ahmad A. COVID-19 pandemic-an African perspective. https://doi.org/101080/2222175120201775132 [Internet]. 2020 [cited 2021 Jun 4]; Available from: https://doi.org/10.1080/22221751.2020.1775132

26. Chimhuya S, Neal SR, Chimhini G, Gannon H, Cortina-Borja M, Crehan C, et al. Indirect impacts of the COVID-19 pandemic at two tertiary neonatal units in Zimbabwe and Malawi: an interrupted time series analysis. medRxiv [Internet]. 2021 Jan 6 [cited 2022 Apr 7];2021.01.06.21249322. Available from: https://www.medrxiv.org/content/10.1101/2021.01.06.21249322v1

27. Thaddeus S, Maine D. Too far to walk: Maternal mortality in context. Soc Sci Med. 1994 Apr 1;38(8):1091–110.

28. Foundation ER. Sexual and Reproductive Health in Uganda under the Coronavirus Pandemic. 2020.

Continued from page 16

29. Reinikka R, Mackinnon J. Lessons from Uganda on Strategies to Fight Poverty. 1999 Nov 30 [cited 2022 Apr 6]; Available from: http://elibrary.worldbank.org/doi/book/10.1596/1813-9450-2440

30. Dowhaniuk N. Exploring country-wide equitable government health care facility access in Uganda. Int J Equity Health [Internet]. 2021 Dec 1 [cited 2022 Apr 6];20(1):1–19. Available from: https://equityhealthj.biomedcentral.com/articles/10.1186/s12939-020-01371-5

31. Ogunfowora OB, Ogunlesi TA. Socio-clinical correlates of the perinatal outcome of severe perinatal asphyxia among referred newborn babies in Sagamu. Niger J Paediatr. 2020;47(2):110–8.

Factors associated with death among hospitalized COVID-19 patients in Mulago Hospital, during Uganda's third wave

Authors: Rose Nampeera[1], Petranilla Nakamya[1], Lilian Bulage[1], Benon Kwesiga[1], Daniel Kadobera[1], Alex R. Ario[1]*

Institutional affiliations

[1]Uganda Public Health Fellowship Program, Kampala, Uganda

Correspondence: rnampeera@musph.ac.ug, Tel:+256-704-367-815*

Summary

Background: *On 7 December 2021, the first case of Omicron variant was confirmed in Uganda. By 14 December 2021, COVID-19 cases rose sharply to form Uganda's third COVID-19 wave. This was followed by an increase in COVID-19 deaths by 24 December 2021. The wave was driven mainly by Omicron variant. We identified the factors associated with mortality among COVID19 hospitalized patients in Mulago Hospital during the third wave.*

Methods: *We retrieved treatment files for all COVID19 hospitalized patients at Mulago hospital, 14 December 2021-14 January 2022. We extracted data on age, sex, vaccination status, underlying conditions, and severity of COVID-19. We used modified Poisson regression to identify factors associated with mortality.*

Results: *We identified 206 patients, out of which 112(54%) were females, 127(62%) had comorbidities, 59 (29%) of the patients had received any vaccination with 38 (64%) being fully vaccinated and 40 (20%) died. Of the deaths, 19 (47%) were females, 27(67%) had comorbidities, 10(25%) of the patients had received any vaccination with 7 (17%) being fully vaccinated. The median age of the deaths was 63 years ([IQR] 49 – 78 years). The log risk of death among patients aged 45-61 years was 7.4 times (CI 1.03 – 53) that of patients aged 0-25 years and the log risk of death among patients aged 66+ years was 7.9 times (CI 1.1 – 56) that of patients aged 0-25 years. There was no association between sex, having a comorbidity, hypertension, chronic heart disease, diabetes, and vaccination status with death among the patients.*

Conclusion: *There was increased log risk of death among older patients. There was no association of vaccination status, sex, and comorbidities with death. There is need to strengthen COVID-19 monitoring, and care among older persons.*

Background

COVID-19 continues to devastate health service and health care globally [1]. The first wave of COVID-19 occurred in November December although the numbers decreased quickly in early January 2021 with approximately 90 deaths [2]. The second wave of COVID-19 in Uganda which was mainly due to the Delta variant Delta variant [3-5] occurred from April-July 2021and spread faster overwhelming the health system [6]. It had about 2,379 deaths countrywide [2].

On 7 December 2021, the first case of Omicron variant was confirmed in Uganda [7] and by 14 December 2021, COVID-19 cases were noted to be rising sharply again, and by 24 December 2021, more than 1,000 cases a day were being recorded. By 10 January 2022 when the study was conducted, there were 168 deaths reported since the beginning of the wave [2]. This third wave was thought to be driven mainly by Omicron variant [8]. Studies done all over the world have showed that older age [9, 10], comorbidities (cardiovascular disease, diabetes) [10, 11], (chronic lung disease and chronic neurological disease), and men [9] were all associated with mortality among COVID -19 patients. A study done in Mulago National Referral Hospital COVID -19 Treatment Unit during the second wave

Continues to page 18

showed that being female, aged 50+ years, and having oxygen saturation at admission of ≥92%, and admission pulse rate of ≥100bpm were associated with mortality [12].

In order to prevent the devastating effects of COVID-19, the Government of Uganda provided COVID-19 vaccines since March 2021 and by 9 December 2021 6,525,371 people had received at least one dose of vaccine and 1,287,799 were fully vaccinated [13]. There was mistrust and speculation about COVID-19 vaccines in the country[14, 15]. At the beginning of the third wave, there were anecdotal reports from public about deaths occurring among vaccinated cases. However, there was no data to support this. We investigated the factors associated with mortality among COVID19 hospitalized patients in Mulago Hospital during the third wave.

Methods

Study setting, design, population, and sample size consideration

We conducted a cross-sectional study at the Mulago National Referral Hospital (MNRH) COVID-19 Treatment Units (CTU) during 10th-17th January 2022. The MNRH CTU was the largest public facility in Uganda in terms of COVID-19 care and treatment with a total bed capacity of 315 beds comprising of 15 intensive care unit (ICU) beds and 300 HDU beds. We considered records of all COVID-19 patients admitted in the treatment Units, 14 December 2021-14 January 2022.

Study variables and data collection

We retrieved routine patient care files and collected data on demographic characteristics (age and sex), underlying comorbidities (hypertension, diabetes mellitus, previous or current chronic heart disease, HIV, kidney disease, liver disease, cancer, sickle cell disease, chronic lung disease, and obesity), and vaccination status. Our outcome of interest was the status of the patient as they left the hospital i.e., dead or alive. We additionally obtained data regarding the vaccination status of the patients through phone calls with either the patients or the next of kin.

We categorized patient's vaccination status as not vaccinated, partially vaccinated, and fully vaccinated. We defined not vaccinated as patients who tested positive but never received any vaccine, partially vaccinated as patients who tested positive but received one dose for two dose vaccines or tested positive in less than 2 weeks after second dose of two dose vaccines, and full vaccinated as patients who tested positive but received a full dose of the vaccine OR tested positive more than 2 weeks after the full vaccination that is 2 doses for 2 dose vaccines and 1 dose for single dose vaccines.

Data Analysis

Using Stata 14.0. for data analysis, we calculated proportions by sex, age, comorbidity, and vaccination status to describe the study population. We also calculated the p values for the tables of different categories of each predictor variable with the outcome to find out if they were significantly different. We assessed the risk factors for death among the patients with modified Poisson regression analysis because the prevalence of death was more than 10%. This was done by running the association between death and each of the study variables. Any variable with a p-value < 0.2 was carried forward for multivariate analysis. We checked for confounding and interaction. We also checked to find the best model.

Ethical considerations

COVID-19 in Uganda had been declared a public health emergency. The Uganda Ministry of Health (MoH) gave the directive to conduct epidemiological investigations and response to COVID-19 disease in the country. Additionally, the Office of the Associate Director for Science, U.S. Centers for Disease Control and Prevention, determined that this activity was in response to a public health emergency with the primary intent to guide public health practice (epidemic disease control activity) and was not human subjects research.

We received permission from the Director of Mulago National Referral Hospital and the Head of COVID-19 Treatment Unit (CTU) to conduct the study. For confidentiality reasons, data from the files was extracted from the CTU. Verbal consent was sought from each the next of kin of the patients before asking about the patient's vaccination status. We stored data in password-protected computers and data was not shared with anyone outside the investigation team.

Continued from page 18

Results

Demographic and clinical characteristics of COVID-19 patients admitted in Mulago Hospital, Uganda, during Uganda's third COVID-19 wave

We identified 206 patients whose median age was 53 years (interquartile range [IQR] 20 – 74 years). Of these, 112(54%) were females, 59 (29%) of the patients had received any vaccination with 38 (64%) being fully vaccinated, and 127(62%) had comorbidities with 43% had 2 or more commodities. Hypertension was the commonest comorbidity affecting 44% of the patients and 40 (20%) of the patients died.

Of the deaths, 19(47%) were females, 10 (25%) of the patients had received any vaccination with 7 (17%) being fully vaccinated, and 27(67%) had comorbidities with 21(52%) having hypertension. Among other commodities were liver disease, cancers, thyroid disease, obesity, and Parkinson disease. The median age of the deaths was 63 years ([IQR] 49 – 78 years).

The outcome was significantly different across the different age categories while sex, vaccination status, having a comorbidity were not significantly different across the different categories.

Table 1: Demographic and clinical characteristics of COVID-19 patients admitted in Mulago Hospital, Uganda, during Uganda's third wave

Variable	Total n (%)	Dead n (%)	Alive n (%)	P value
Total	206 (100)	40 (19)	166 (81)	
Sex				
Male	94(46)	21(53)	73(44)	
Female	112(54)	19(47)	93(56)	0.33
Age group				
0-25	30(15)	1(2)	29(18)	
26-40	35(17)	3(7)	32(19)	
41-65	69(33)	17(43)	52(31)	
66+	472(35)	19(48)	53(32)	0.012
Vaccinated				
No	145 (71)	30(75)	117(70)	
Partially	21(10)	3(8)	18(11)	
Fully	38 (19)	7(17)	31(19)	0.79
Comorbidity				
No	79(38)	13(33)	66 (40)	
Yes	127(62)	27(67)	100 (60)	0.40
Multiple comorbidities				
0	79(38)	13(32)	66(40)	
1	72(35)	15(38)	57(34)	
2+	55(27)	12(30)	43(26)	0.69
Hypertension				
No	116(56)	19(48)	97(58)	
Yes	90(44)	21(52)	69(42)	0.21
Diabetes				
No	169(82)	32(80)	137(83)	
Yes	37(18)	8(20)	29(17)	0.71
HIV				
No	187(91)	36(90)	151(91)	
Yes	19(9)	4(10)	15(9)	0.85
Lung disease				
No	194(94)	38(95)	156(94)	
Yes	12(6)	2(5)	10(6)	0.80
Kidney disease				
No	198(96)	39(98)	159(96)	
Yes	8(4)	1(2)	7(4)	0.61
Heart disease				
No	194(94)	37(93)	157(95)	
Yes	12(6)	3(7)	9(5)	0.61
Sickle Cell Disease				
No	200(97)	39(98)	161(97)	
Yes	6(3)	1(2)	5(3)	0.86
Others				
No	188(91)	37(93)	151(91)	
Yes	18(9)	3(7)	15(9)	0.76

Continues to page 20

Factors associated with death among COVID-19 patients admitted in Mulago Hospital, Uganda, during the third wave

At bivariate level, only age was significantly associated with death. Other factors including sex, comorbidities, and vaccination status had no significant association with death At multivariate level, only age was associated with death and hypertension confounded age. The log risk of death among patients aged 45-65 years were 7.6 times that of patients aged 0-25 years while the risk of death among patients aged 66+ years were 8.1 times that of those aged 0-25 years (Table 2).

Table 2: Factors associated with death among COVID-19 patients admitted in Mulago Hospital, Uganda, during Uganda's the third wave

		Unadjusted		Adjusted	
Variable	**Death n (%)**	**lnRR**	**(95%CI)**	**lnRR**	**(95%CI)**
Sex					
Male	21(53)	1			
Female	19(47)	0.76	(0.44-1.3)		
Age					
0-25	1(2)	1		1	
26-40	3(7)	2.6	(0.28 – 23)	2.6	(0.28 – 23)
41-65	17(43)	7.4	(1.03 – 53)	7.6	(1.04 – 55)
66+	19(48)	7.9	(1.1-56)	8.1	(1.1-59)
Vaccinated					
No	145 (71)	1			
Partially	21(10)	0.70	(0.23-2.1)		
Fully	38 (19)	0.90	(0.43-1.9)		
Comorbidity					
No	79(38)	1			
Yes	127(62)	1.3	(0.71-2.4)		
Multiple comorbidities					
0	79(38)	1			
1	72(35)	1.3	(0.65-2.5)		
2+	55(27)	1.3	(0.65-2.7)		
Hypertension					
No	116(56)	1		1	
Yes	90(44)	1.4	(0.82-2.5)	0.95	(0.55-1.63)
Diabetes					
No	169(82)	1			
Yes	37(18)	0.94	(0.73 -1.2)		
HIV					
No	187(91)	1			
Yes	19(9)	1.1	(0.44-2.7)		
Lung disease					
No	194(94)	1			
Yes	12(6)	0.85	(0.23-3.1)		
Kidney disease					
No	198(96)	1			
Yes	8(4)	0.64	(0.99-4.1)		
Heart disease					
No	194(94)	1			
Yes	12(6)	1.3	(0.47-3.7)		
Sickle Cell Disease					
No	200(97)	1			
Yes	6(3)	0.86	(0.14-5.3)		
Others					
No	188(91)	1			
Yes	18(9)	0.85	(0.29-2.5)		

Continued from page 20

Discussion

We investigated the factors associated with death among COVID -19 hospitalized patients in Mulago Hospital. Our findings showed that increasing age, starting with 41 years was associated with death. However, not being vaccinated, and having comorbidities were not associated with dying.

Similar to this study, increasing age has been found to be associated with death and severe outcomes in many studies globally [9, 14, 16]. This could be due to the age-dependent defects in B-cell and T-cell function and the excess production of type 2 cytokines which could lead to prolonged proinflammatory responses and deficiency in control of viral replication, predisposing the patients to poor outcomes including death [17]. Furthermore, there are many other risk factors in older patients like comorbidities and sarcopenia [18]. In addition, hypertension was found to confound age and this could be because mortality in patients with hypertension increases with advanced age [19].

In this study, there was no association between sex and death. This is contrary to other studies that have showed that males are more likely to have severe outcomes and death [9, 10, 14]. The male susceptibility has been associated to the differences in the levels and type of circulating sex hormones in males and females. This difference has been thought to influence the susceptibility of COVID-19 infection [20] and this has been supported by studies that show that adaptive and innate immunity responses are modulated by sex hormones [21]. Men have been showed to have an increased susceptibility to COVID-19 infection, susceptibility, higher viral spread, and more severe disease with worse outcome. This could be due to the increase in ACE2 expression in the lungs and the androgen stimulation of TMPRSS2 expression and/or the expression of TMPRSS2 variants among men [22] . Thus, it is important that male sex still be considered as a risk factor for death among COVID-19 patients.

Comorbidities were not associated with death in this study which is contrary to other studies that have showed that patients with comorbidities are more likely to die [9, 16]. This has been attributed to the high expression of angiotensin converting enzyme 2 (ACE2) receptor among patients with hypertension, diabetes, and cardio vascular disease especially in males [23, 24]. The reason for the lack of association of comorbidities and death in this study is unknown. However, comorbidities are still an important risk factor for severe disease and death among COVID-19 patients.

In this study, not being vaccinated was not associated with death. This is contrary to other studies which have showed that vaccination decreases hospitalization and severe outcomes due to COVID-19 [25, 26]. The lack of association between vaccination status and death could have been due to the low number of vaccinated patients in our study. Despite the lack of association between vaccination status and death among the patients, vaccination is known to have a big contribution to protection from severe COVID -19 disease. Thus, vaccination should still be considered protective against severe disease and death among COVID-19 hospitalized patients.

Limitations

We could not assess effects of use of chronic medications and respiratory support among the patients yet they have been reported to increase someone's risk for death. Our conclusions are based on a relatively small sample size of 206, which may have led to either led to an underestimation or overestimation of the study outcomes. Despite the limitation, our study ruled out the speculation of people vaccinated against COVID19 dying at the time.

Conclusion and recommendation

There was increased risk of death among older patients. There was no association of vaccination status, sex, and comorbidities with death among the patients. There is need to strengthen COVID-19 monitoring, and care among older persons.

Acknowledgement

We would like to thank the administration of Mulago National Referral Hospital for granting us permission to access patient information. We appreciate the COVID-19 Treatment Unit staff at MNRH for their support during data collections. We also appreciate the next of kin of the patients for giving us time to answer questions on phone.

Continues to page 22

References

1. World Health organization, *Coronavirus disease (COVID-19) Pandemic*. 2020.
2. World Health Organization, *https://covid19.who.int/region/afro/country/ug*. 2022.
3. file:///C:/Users/HP/Dropbox/My%20PC%20(DESKTOP-7JPG7SD)/Downloads/COVID-19-Resurgence-Plan-June2021-June-2022.pdf, 2021.
4. https://www., W.C.-c.p., *worldometers.info/coronavirus (accessed April 8, 2021). 2 Israel Ministry of Health. COVID-19 database (in Hebrew)*. 2021.
5. https://observer.ug/news/headlines/70361-delta-variant-driving-up-covid-19-infections-in-uganda-drc, *Delta variant driving up Covid-19 infections in Uganda, DRC*. 2021.
6. https://healthpolicy-watch.news/the-time-bomb-in-ugandas-health-care-system-reflections-from-the-emergency-room/, *Can Uganda Contain Its COVID-19 Infection Spike? Reflections Of An Emergency Room Doctor*. 2021.
7. Kyeyune, H., *Uganda confirms 1st cases of omicron coronavirus variant: Detection of new virus strain, growing list of new restrictions expected to affect travel plans ahead of Christmas*, in *AAA News Broadcasting System*. 2021.
8. Kiconco, A., *Uganda is out of COVID-19 third wave, says health minister*, in *KIU news*. 2022.
9. Silva, P.V.D., et al., *Risk Factors for Death Among 120,804 Hospitalized Patients with Confirmed COVID-19 in São Paulo, Brazil.* Am J Trop Med Hyg, 2021. **105**(1): p. 88-92.
10. Wang, D., et al., *Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China.* Jama, 2020. **323**(11): p. 1061-1069.
11. Williamson, E.J., et al., *Factors associated with COVID-19-related death using OpenSAFELY.* Nature, 2020. **584**(7821): p. 430-436.
12. Bongomin, F., et al., *High Mortality During the Second Wave of the Coronavirus Disease 2019 (COVID-19) Pandemic in Uganda: Experience From a National Referral COVID-19 Treatment Unit.* Open Forum Infect Dis, 2021. **8**(11): p. ofab530.
13. *Coronavirus (COVID-19) Vaccinations*.
14. *Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020.* MMWR Morb Mortal Wkly Rep, 2020. **69**(12): p. 343-346.
15. Samarasekera, U., *Feelings towards COVID-19 vaccination in Africa.* Lancet Infect Dis, 2021. **21**(3): p. 324.
16. *[The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China].* Zhonghua Liu Xing Bing Xue Za Zhi, 2020. **41**(2): p. 145-151.
17. Opal, S.M., T.D. Girard, and E.W. Ely, *The immunopathogenesis of sepsis in elderly patients.* Clin Infect Dis, 2005. **41 Suppl 7**: p. S504-12.
18. Wang, K., et al., *Clinical and Laboratory Predictors of In-hospital Mortality in Patients With Coronavirus Disease-2019: A Cohort Study in Wuhan, China.* Clin Infect Dis, 2020. **71**(16): p. 2079-2088.
19. Zhong, L., et al., *Effects of hypertension on the outcomes of COVID-19: a multicentre retrospective cohort study.* Ann Med, 2021. **53**(1): p. 770-776.
20. Parohan, M., et al., *Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies.* The Aging Male, 2020. **23**(5): p. 1416-1424.
21. Jaillon, S., K. Berthenet, and C. Garlanda, *Sexual Dimorphism in Innate Immunity.* Clin Rev Allergy Immunol, 2019. **56**(3): p. 308-321.
22. Pivonello, R., et al., *Sex Disparities in COVID-19 Severity and Outcome: Are Men Weaker or Women Stronger?* Neuroendocrinology, 2021. **111**(11): p. 1066-1085.

Continued from page 22

23. Patel, S.K., et al., *From gene to protein -experimental and clinical studies of ACE2 in blood pressure control and arterial hypertension.* Front Physiol, 2014. **5**: p. 227.
24. Patel, S.K., E. Velkoska, and L.M. Burrell, *Emerging markers in cardiovascular disease: where does angiotensin-converting enzyme 2 fit in?* Clin Exp Pharmacol Physiol, 2013. **40**(8): p. 551 -9.
25. Tenforde, M.W., et al., *Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity.* Jama, 2021. **326**(20): p. 2043-2054.
26. Lauring, A.S., et al., *Clinical Severity and mRNA Vaccine Effectiveness for Omicron, Delta, and Alpha SARS-CoV-2 Variants in the United States: A Prospective Observational Study.* medRxiv, 2022.

HIV Positivity Rate and Recent HIV Infections Among Adolescent Girls and Young Women 10-24 years, Uganda, 2017-2021

Authors: Patience Mwine[1], Benon Kwesiga[1,2], Richard Migisha[1,2] Steven Kabwama[1,2] Juliet Cheptoris[3], Peter Mudiope[3], Emmy Muramuzi[3], Daniel Kadobera[1.2], Lilian Bulage[1,2], Alex R. Ario[1,2]*
Institutional affiliations: [1]Uganda Public Health Fellowship Program, Kampala, Uganda [2]Uganda National Institute of Public Health, Kampala, Uganda [3]Ministry of Health, Kampala Uganda
**Correspondence: Email: pmwine@musph.ac.ug, Tel: +256-702-449-738*

Summary

Background: *New HIV infections still occur among adolescent girls and young women (AGYW) in Uganda despite HIV prevention programs. We described the HIV test positivity and recent infection (acquired in the past ~12 months) rates among AGYW from 2017 to 2021 to inform targeted planning for additional interventions among AGYW.*
Methods: *We analyzed routine HIV testing program data from 2017-2021 for AGYW (aged 10-24 years) reported through the District Health Information System 2 (DHIS2) and from the 600 clinical sites that test for HIV recency in Uganda. We evaluated trends in the positivity rate at national and district levels and used logistic regression to determine significance. We calculated the proportion of infections among AGYW newly diagnosed with HIV from November 2019-November 2021 that were recent and identified geographic clusters of infections (defined as ≥5 recent infections in a sub-county within 12 months).*
Results: *Of 8,532,992 HIV tests, 168,633 (2.0%) were positive. AGYW aged 20-24 had the highest rate (2.6%, 95%CI 2.5-2.6). There was a 5% (OR=0.95, 95% CI; 0.94-0.95) significant reduction in the trend of HIV positivity rate from 2.0% in 2017 to 1.7% in 2021. The district HIV positivity rate decreased in most districts but remained persistently >3% yearly in Mbarara, Sheema, Rwampala, and Kalangala districts. Among 2,672 newly -diagnosed AGYW aged 15-24 with a recency test, 359 (13.4%) had recent HIV infections. Most (276; 74.4%) were 20-24 years, 113(31.5 %) were first-time testers, and 47 (13.1%) were pregnant or breastfeeding. We observed clusters of recent HIV infections in sub-counties bordering the Democratic Republic of Congo (DRC), Western Uganda, and central divisions of Kampala Metropolitan.*
Conclusions: *HIV positivity rate among AGYW declined overall during 2017-2021, but specific Western Ugandan districts had comparatively elevated rates. Nearly one in seven HIV infections were acquired recently, and clusters of recent HIV infections were in some sub-counties. The Ministry of Health could strengthen HIV prevention and scale-up testing among AGYW in the most affected districts and initiate outbreak investigations in communities with clusters of recent HIV infections.*

Introduction

Worldwide, 3.9 million young people aged 15- 24 are estimated to be living with HIV/AIDS; seventy per cent of these are in Sub-Saharan Africa (1). According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020 report, around 4,200 new HIV infections occur among Adolescent Girls and Young Women (AGYW) 15-24 years every week; and six in seven new HIV infections were among adolescent girls 15-19 in Sub-Saharan Africa (2).

Continues to page 24

In 2017, about 1.4 million persons were living with HIV/AIDS in Uganda, according to Uganda's Population-Based HIV Impact Assessment (UPHIA) (4). Over the last decade, HIV prevalence among 15-60 years has progressively reduced from 7.3% to 5.6% (5). According to the United Nations International Children's Emergency Fund (UNICEF) report, Uganda registered 53,000 new HIV infections in 2019, and two-thirds were among AGYW (6). AGYW are four times more affected than their male counterparts (5); in 2017, an estimated 250 AGYW got infected weekly compared to 90 male counterparts (4). The high incidence of new HIV infections among AGYW is due to poverty, gender-based violence, lack of access to education, health care services, social protection, and information on HIV prevention (8). These have led young women and adolescents to be less likely to negotiate for safer sex and engage in risky sexual behaviours that predispose them to HIV infections.

In 2016, Uganda implemented a multisectoral AGYW HIV prevention approach to reduce the new HIV infections (9). Program activities aim to empower young girls who are not HIV positive to remain negative and link those already positive to care through the Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe (DREAMS) project (10). These strategies include behavioural change communication, keeping girls in school, use of condoms, use of Pre Exposure Prophylaxis (PrEP) among the risk groups, reducing gender-based violence, and many others (9). To monitor the progress and impact of these program activities to reduce new HIV infections among AGYW, we analyzed HIV testing services data in the District Health Information System 2 (DHIS2). We described the HIV positivity rate (2017-2021) and recent infections (November 2019-December 2021) among AGYW in Uganda to inform targeted planning for additional interventions among AGYW.

Methods

Study setting

For this study, we considered HIV Testing Services (HTS) data reported from all health facilities across the country. Uganda has a total of 146 districts, including the cities, and as of 2022, the estimated population is 44.2 million people. According to the Ministry of Health, Uganda has 6,937 health facilities (public, private and private not-for-profit). Of these, 3,133 (45.2%) are Government-owned, 1,002 (14.4%) are Private and Not For Profit (PNFP), while the remaining 2,795 (40.3%) are Private For-Profit (PFP) and 7 (0.1%) community-owned facilities (11). All health facilities provide HIV testing services according to the national HIV testing algorithm (12). In 2019, Uganda rolled out recency testing in 35 five sites (health facilities), which increased gradually to 600 recency sentinel sites at the end of 2021 (13). Recent HIV Infections surveillance system was established in the routine HIV testing to identify recent infections (acquired in the past ~12 months) among newly identified HIV-positive clients above 15 years of age. This system is meant to inform HIV epidemic control on the subpopulation most affected, map host spots for recent HIV infections, identify clusters of recent HIV infections and guide HIV prevention interventions (14).

Study design and data source

We conducted a descriptive analysis of surveillance data on HTS among AGYW (10-24 years) recorded from January 2017 to December 2021 in the DHIS2). The DHIS2 is an integrated data collection system used by the Ministry of Health to support planning, management, and decision-making in health facilities and organizations. Clients access HIV testing services at different points of care, including; outpatient departments (OPD), laboratory, antenatal care (ANC), and HIV/AIDS clinics. Health workers record HTS patient data in various HTS registers (HMIS 105), and health facility data clerks compile monthly summary reports submitted to the district. At the district, the Biostatistician uploads all health facility HTS aggregated data into the DHIS2 under data element "105-HT18j" and can be accessed at the national level.

We also analyzed the HIV recency data of AGYW from Nov 6, 2019, to Nov 22, 2021, reported from 600 Recency sentinel sites where a recency testing program was being implemented in Uganda at the time (13). We accessed these data from the Uganda Electronic Medical Records (EMR) system with permission from the Monitoring and Evaluation Technical Support Program (METS). Recency testing is done

Continued from page 24

among newly-identified HIV-positive clients aged 15 years and above as one of Uganda's National HIV Surveillance frameworks to monitor and control the epidemic. Recency testing uses a rapid testing kit known as Asante HIV-1 Rapid Recency Assay (ARRA). Asante is a simple, quick antibody test that distinguishes recent (most likely acquired within the past 12 months) from long-term infections (most likely acquired earlier than 12 months prior) using antibody avidity (15).

Study variables, data extraction, and analysis

From the DHIS2, we extracted data on HIV testing results from 2017 to 2021 for AGYW 10-24 under data element "105-HT18j". We obtained information on the district, age, total AGYW tested, and positives. We also extracted the average national reporting rates for HTS results for 2017-2021 to compare them with the positivity rate. We determined the HIV positivity rate as a proportion of AGYW who tested HIV positive through the national testing program from 2017 to 2021. We described the HIV positivity rate among AGYW in terms of place using the district variable, person by age, and time by year trends. We demonstrated the national trend of HIV positivity rate among AGYW 10-24 years as line graphs. We compared the average annual national reporting rates using the same line graphs with the HIV positivity rate trend to determine if they affected the positivity rates. We described the district trends as choropleth maps drawn using the Quantum Geographic Information System (QGIS 3.22). We carried out logistic regression to determine the significance of the trend and summarized the results as an odds ratio at a 95% Confidence Interval.

We applied a similar analysis to the HIV recency data on AGYW in Uganda to determine the proportion of recent HIV infections by person and geographic distributions of recent HIV infections (acquired within the past 12 months) among AGYW. We described the proportions of recent infections by other variables, including age, first-time testing, special category, and reason for testing. Using choropleth maps, we demonstrated the spatial distribution of the number of recent infections as clusters at the sub-county level (≥5 recent infections in a sub-county within 12 months).

Ethical Considerations

We used secondary data with no identifiers; hence, ethical approval was not required. We obtained permission to access data from METS, which manages recency testing data, and the Ministry of Health (MOH). In addition, a non-research determination form was submitted to US CDC for clearance before the commencement of the project as a requirement. The Office of the Associate Director for Science, U.S. Centers for Disease Control and Prevention, determined our project as non-human subjects research; this was in response to a public health problem with the primary intent of public health practice (epidemic disease control).

Results

Trends of HIV Positivity rate among Adolescent Girls and Young Women 10-24 years, Uganda, 2017 -2021

Overall, 8,532,992 Adolescent Girls and Young Women 10-24 years tested for HIV between January 2017 to December 2021. Of these, 168,633 (2.0 %) tested HIV positive during the five years (Table 1). Overall, there was a significant 5% [OR=0.95 CI 0.94-0.95] decline in HIV positivity among AGYW who accessed HIV testing services. There was a significant initial 16% increase in the positivity rate from 2017 to 2019, which later declined significantly in 2020 and 2021 (Table 1 and Figure 1).

Table 1: HIV positivity rate among Adolescent Girls and Young Women 10-24 years, Uganda, 2017-2021

Year	Total tested	Tested Positive	Positivity rate (%)	OR	95% CI
2017	1,697,614	34,357	2.0	Ref	-
2018	1,750,841	36901	2.1	1.04	(1.03-1.06)
2019	1,326,172	31035	2.3	1.16	(1.14-1.18)
2020	1,948,826	36200	1.9	0.92	(0.90-0.93)
2021	1,809,539	30140	1.7	0.82	(0.81-0.83)
Total	8,532,992	168633	2.0	0.95	(0.94-0.95)

Continues to page 26

The number of HIV tests increased over the years, except for the observed sharp decline of 21% in 2019. The HIV positivity rate initially rose from 2.0 % in 2017 to 2.3 % in 2019 and then decreased to 1.7% in 2021 (Figure 1). The reporting rates for HIV testing services were about 75% between 2017 and 2019 but sharply increased to above 95% in 2020 and 2021 (Figure 1).

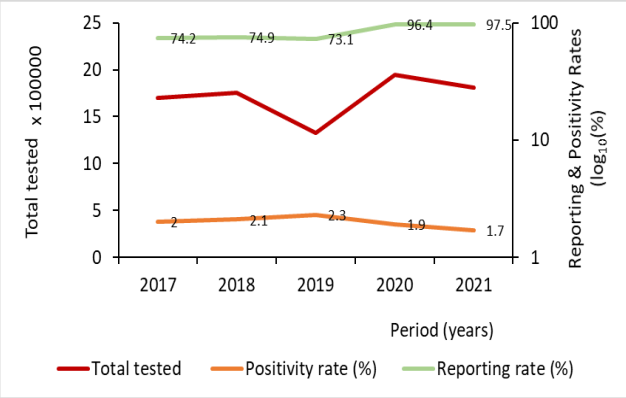


Figure 1: National trends of HIV positivity rate among Adolescent Girls and Young Women 10-24 years, Uganda, 2017-2021

HIV positivity rate among Adolescent Girls and Young Women by age group, Uganda, 2017-2021

The HIV positivity rate varied among the different age categories, and young women 20 -24 years had the highest HIV positivity rate of 2.55% (Table 2). Additionally, the positivity rate increased with age (Figure 2).

Table 2: HIV positivity rate among Adolescent Girls and Young Women by age groups, Uganda, 2017-2021

Age Category	Total Tested	Tested Positive	HIV positivity rate (%)	95% Confidence Interval
10-14	732,433	5,972	0.82	(0.80-0.84)
15-19	3,204,505	45,381	1.42	(1.40-1.43)
20-24	4,596,054	117,280	2.55	(2.54-2.57)

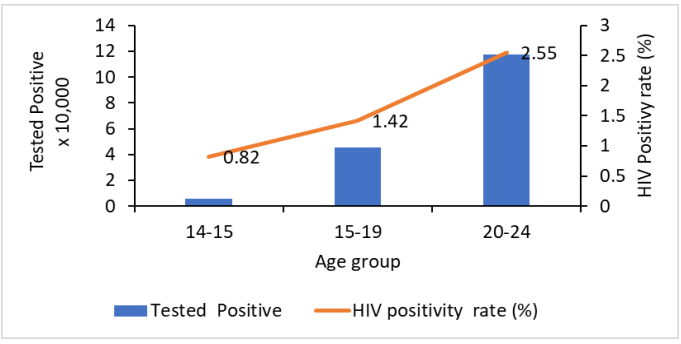


Figure 2: HIV positivity rate among Adolescent Girls and Young Women by age groups, Uganda, 2017-2021

Spatial distribution of HIV positivity rate among Adolescent Girls and Young Women 10-24 year, Uganda, 2017-2021

Overall, we established a variation in the HIV positivity rate among the different districts. The Western and Central districts demonstrated high HIV prevalence, and the Eastern region had the least. Furthermore, Mbarara, Sheema, Rwampala, and Kalangala districts had an elevated five-year positivity rate of >4% (Figure 3).

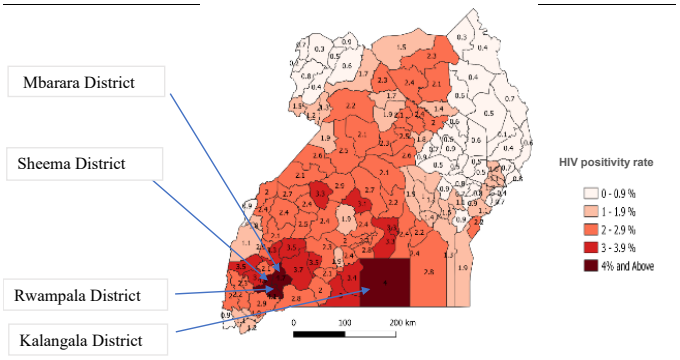


Figure 3: Spatial distribution of five-year HIV positivity rate among Adolescent Girls and Young Women 10-24 years, Uganda, 2017-2021

The trend of HIV positivity by district decreased with years as the number of districts with high prevalence reduced except in 2019. Despite the decreasing HIV trend, Mbarara, Sheema, Rwampala, and Kalangala districts remained with an HIV positivity rate of greater than 3% in all the years (Figure 4)

Continued from page 26

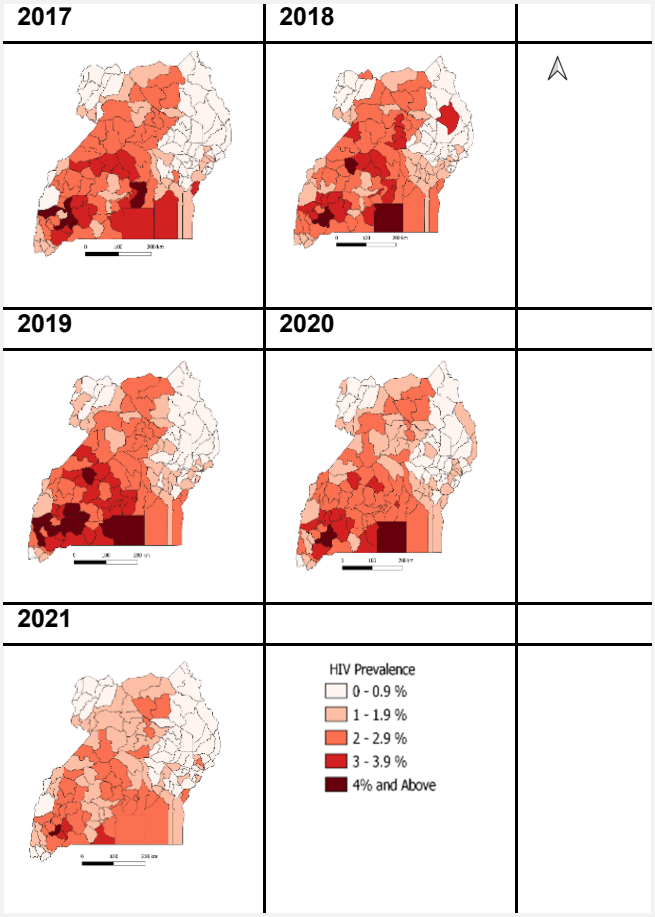


Figure 4: Trends of HIV positivity rate among Adolescent Girls and Young Women 10-24 years, Uganda, 2017-2021

Recent HIV infections among Adolescent Girls and Young Women 15-24 years, Uganda, 2019-2021

A total of 2,672 adolescent girls and young women 15-24 years who had newly tested HIV positive from Nov 6, 2019, to Nov 22, 2021, consented and received recency tests. Most (2018;76%) were young women 20-24 years, and 450 (16.8%) were pregnant or breastfeeding. The median age of all was 21 years [Range; 15-24]. Of those who tested, 359 (13.4 %) were recent infections. Of these, the median age was 22 years [Range; 15-24], most (267;74.4%) were 20-24 years of age, and 92(25.6%) were 15-19 years. Additionally, 113(31.5%) were testing for the first time, and 47 (13.1%) were pregnant or breastfeeding (Table 3)

Variable	Long term HIV infections n=2249		Recent HIV Infections n=359	
	n	(%)	n	(%)
Age				
15-19	525	(23.3)	92	(25.6)
20-24	1724	(76.7)	267	(74.4)
First time HIV test				
Yes	629	(27.9)	113	(31.5)
Special category				
Pregnant or Breastfeeding	403	(17.9)	47	(13.1)
Fisherfolk	43	(1.9)	7	(1.9)
Migrant	10	(0.4)	2	(0.6)
Others	1793	(79.7)	303	(84.4)
Reasons for testing				
APN	172	(7.6)	42	(11.7)
Index testing	40	(1.8)	7	(1.9)
PMTCT	491	(21.8)	65	(18.1)
Self-Initiative	710	(31.6)	119	(33.1)
Self-testing	33	(1.5)	5	(1.4)
Others	803	(35.7)	121	(33.7)

Table 3: Characteristics of Adolescent Girls and Young Women with long-term and recent HIV infections, Uganda, November 2019-November 2021

***APN-Assisted Partner Notification ** Prevention of Mother to Child Transmission *** Others-Were Adolescent Girls and Young Women not in any particular category**

We further described recency data by place at sub-county levels. Sub-counties with five or more recent infections were mainly in Uganda's western and central parts. We observed these clusters in Kyangwali sub-county in Kikube District, Ruteete sub-county in Kabarole District, Ruteete sub-county in Kagadi District, Kazo sub-county in Mbarara from the western region and Makindye division in Kampala District, Wakiso town council in Wakiso District from the Central region (Figure 5)

Continues to page 28

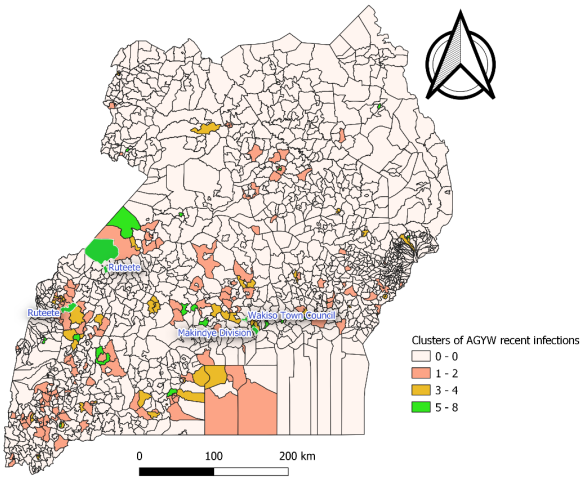


Figure 5: Spatial distribution of clusters of recent infections among Adolescent Girls and Young Women 15-24 years, Uganda, November 2019-November 2021

Discussion

Results from the analysis of DHIS2 data established a significant 5% decrease in HIV positivity among AGYW as HTS service uptake increased between January 2017 to December 2021. HIV positivity rate varied among age categories and districts. Nearly one in seven HIV infections (13.4%) was acquired recently among AGYW 15-24. We observed Variations of recent infections by age groups and sub-counties.

The decline in the HIV positivity rate could be due to the observed reduction in HIV prevalence among AGYW. According to the recent UPHIA 2020 results, HIV prevalence among AGYW 15-24 years declined from 3.3% in 2016 (4) to 2.9% in 2020 (16). Similarly, the national trend of HIV prevalence has been reducing over the last decade (5). We attribute this decline to the robust country-wide HIV prevention strategies, including the DREAMS program that targets HIV-negative AGYW girls to remain HIV negative, testing and treating all those HIV positive regardless of the CD4 count or WHO clinical stage, among others (17).

In addition, the decline could have also resulted from the effective HIV testing strategy as more AGYW accessed the HIV testing services. We established an increasing trend of HTS services, which was not affected during 2020-2021, the period of the COVID-19 pandemic. The high numbers tested during 2020 and 2021 differ from the known national decline in the HIV testing services in 2020 and 2021 due to COVID-19-related disruptions in the HIV testing and treatment services (18). Nevertheless, we observed a 24% drop in HTS services in 2019, a year with the highest HIV positivity rate. We attribute the high positivity rate to the efficient, targeted testing approach implemented at that time that prioritizes individuals at high risk and increases yield, according to the AIDS control program Ministry of Health 2019 annual performance report (19). This highlights the need to scale up the targeted testing approach to reach as many AGYW at high risk of HIV to achieve epidemic control.

Our analysis found that the HIV positivity rate increased with age, which was consistent with the 2016 and 2020 UPHIA survey reports (4,16). Also, the HIV positivity rate was different among the different age categories, and these findings were comparable with UPHIA 2020 estimates; (15-19 years: 1.4 % vs 1.7% UPHIA 2020) and (20-24 years: 2.6 % vs 4.9% UPHIA 2020) (16). The difference in the burden of HIV among the different age groups was further confirmed by the recency testing data, as most AGYW who had recent infections were 20-24 years old. These variations in the age category HIV burden suggest the need for age-appropriate and explicit HIV prevention strategies targeted at specific drivers of HIV infections among adolescent girls and young women. Such strategies may include scaling up pre-exposure prophylaxis (PrEP), condom use, behavioural change communication, sexuality education and targeted HIV testing (4,10).

Despite the reduction in HIV positivity rate over the five years, districts of Mbarara, Sheema, Rwampala, and Kalangala had comparatively elevated rates. These observations aligned with the 2016 UPHIA findings whereby the central (8%) and southwestern (7.9%) regions had the highest HIV prevalence (20). Elevated positivity rates in specific districts highlight the need to scale the DREAMS program to include the high

Continued from page 28

HIV-burden districts where this program is not being implemented, mainly in Sheema and Rwampala districts. Uganda is implementing the DREAMS program in only 44 districts due to limited funding; this leaves a gap for limited access to HIV prevention for all the girls in the country. Studies have shown this strategy effectively reduces new HIV infections among AGYW. For example, the DREAMS program reduced the incidence of HIV among AGYW in Lesotho by 71.4% in two piloted districts compared to a 48.4% decrease in those which didn't have the program (21).

Nearly one in seven HIV infections (13.4%) AGYW was acquired recently among AGYW 15-24. This analysis provided a clue on estimated HIV incidence among AGYW, implying that there may be several AGYW with recent HIV infections still undiagnosed; this may fuel the HIV epidemic. In addition, the high proportion of recent HIV infections could be due to gaps in the effective implementation of strategies to stop HIV transmission and prevent new HIV infections among AGYW in some parts of the country (10).

Nevertheless, we found a more considerable proportion (84.6%) of AGYW had long-term infections suggesting that most AGYW live with undiagnosed HIV, which puts them a risk of severe disease and HIV-related deaths. Moreover, a sizeable proportion (31.5%) was tested for the first time, suggesting a gap in timely HTS services. Despite the supporting HIV testing policy whereby a 12-year-old can test for HIV without a parents' consent, most are not utilizing the services (12). There is a need to scale up HIV testing services to reach out to undiagnosed HIV positive AGYW by strengthening mobile and self-testing HIV testing strategies, as these were found acceptable in a study done in Kenya (22).

Additionally, we observed clusters of recent HIV infections in Kyangwali and Ruteete subcounties in Kabarole district, Ruteete subcounty in Kagadi district, and Kazo subcounty in Mbarara district in western Uganda, trading Centres of Wakiso, Makindye, and central divisions of Kampala metropolitan. These are likely to be hotspots for HIV transmission. For example, the Kyangwali sub-county in western Uganda is a refugee settlement (23). Being a refugee puts adolescent girls more vulnerable to sexual gender-based violence and limited access to HIV prevention services (24). Also, some of these sub-counties were located in districts with high HIV prevalence, like Kabarole and Mbarara (4). Therefore, there is a need to strengthen HIV prevention interventions targeting the most affected districts and the hotspots for recent HIV infections. In addition, there is a need to investigate these clusters of recent infections to identify the risk factors and implement evidence-based prevention strategies.

Limitations

Our analysis was limited due to the aggregated data in the electronic HMIS system; we could not explore other variables. Also, there is a possibility of underreporting or double reporting of clients due to limitations of patient identification. Nevertheless, the variables obtained provided adequate information useful in targeted HIV prevention.

Conclusions

The HIV positivity rate among AGYW reduced significantly from 2017 to 2021. However, were found variations among the different age categories and specific districts. At least one in seven AGYW had recent HIV infections. We observed clusters of recent HIV infections in specific subcounties bordering the Democratic Republic of Congo (DRC), Western Uganda and Central Kampala. The Ministry of Health could initiate outbreak investigations in communities with clusters of recent HIV infections. Additionally, MoH should consider strengthening the HIV prevention interventions among AGYW, which are age-specific in the most affected districts, and scale-up targeted HIV testing services to ensure early diagnosis and treatment of HIV positive AGYW.

Acknowledgments

We would like to thank the Ministry of Health Division of Health Information and the Monitoring and Evaluation Technical Support (METS) Program for permitting us to use these data.

References

1. Young people, HIV and AIDS [Internet]. Avert. 2015 [cited 2021 Apr 6]. Available from: https://www.avert.org/professionals/hiv-social-

Continues to page 30

issues/key-affected-populations/young-people

2. UNAIDS. Global HIV & AIDS statistics — Fact sheet [Internet]. 2022 [cited 2022 Apr 4]. Available from: https://www.unaids.org/en/resources/fact-sheet

3. UNAIDS. UNAIDS HIV Prevention Among Adolescent Girls and Young Women | PDF | Hiv/Aids | Adolescence [Internet]. Scribd. 2022 [cited 2022 Apr 4]. Available from: https://www.scribd.com/document/543853218/UNAIDS-HIV-prevention-among-adolescent-girls-and-young-women

4. Ministry of Health, Uganda. S. Uganda Population-based HIV Impact Assessment (UPHIA) 2016-2017: [Internet]. Uganda AIDS Commission. 2017 [cited 2022 Apr 4]. Available from: https://uac.go.ug/index.php

5. Ministry of Health, Uganda. S. HIV Fact Sheet 2020 [Internet]. Uganda AIDS Commission. 2020 [cited 2022 Apr 4]. Available from: https://uac.go.ug/index.php

6. HIV and AIDS [Internet]. [cited 2021 Oct 19]. Available from: https://www.unicef.org/uganda/what-we-do/hiv-aids

7. UPHIA Uganda factsheet.pdf.

8. HIV and AIDS in Uganda [Internet]. Avert. 2015 [cited 2021 Apr 1]. Available from: https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/uganda

9. Uganda AIDS commission S. National HIV and AIDS Strategic Plan 2020/21 – 2024/25: Ending the HIV and AIDS epidemic: Communities at the forefront: Kampala: Uganda AIDS Commission; 2020. [Internet]. Uganda AIDS Commission. 2020 [cited 2022 Apr 4]. Available from: https://uac.go.ug/index.php

10. DREAMS: Partnership to Reduce HIV/AIDS in Adolescent Girls and Young Women [Internet]. 2020 [cited 2021 Apr 6]. Available from: https://www.usaid.gov/global-health/health-areas/hiv-and-aids/technical-areas/dreams

11. Ministry of Health, Uganda. List of Hospitals, Ministry of Health Uganda [Internet]. Ministry of Health | Government of Uganda. [cited 2022 Jun 15]. Available from: https://www.health.go.ug/hospitals/

12. Ministry of Health, Uganda. S. National HIV Testing Services Policy and Implementation Guidelines Uganda | Ministry of Health Knowledge Management Portal [Internet]. 2010 [cited 2022 Apr 4]. Available from: http://library.health.go.ug/publications/hivaids/national-hiv-testing-services-policy-and-implementation-guidelines-uganda

13. HIV Recency Testing in Uganda | Mets [Internet]. [cited 2022 Jan 1]. Available from: https://mets.or.ug/hiv-recency-testing-in-uganda/

14. Disease Surveillance, UCSF team. HIV Recency Testing in Uganda | Mets [Internet]. 2019 [cited 2022 Jun 17]. Available from: https://mets.or.ug/hiv-recency-testing-in-uganda/

15. Biosciences S. Asanté™ HIV-1 Rapid Recency® [Internet]. Sedia Biosciences. [cited 2022 Jun 14]. Available from: https://www.sediabio.com/asante-hiv-1-rapid-recency/

16. Ministry of Health Uganda. Release of Preliminary Results of the 2020 Uganda Population-Based HIV Impact Assessment Uganda [Internet]. 2022 [cited 2022 Feb 25]. Available from: https://www.mediacentre.go.ug/media/release-preliminary-results-2020-uganda-population-based-hiv-impact-assessment

17. Consolidated Guidelines for Prevention and Treatment of HIV in Uganda | Ministry of Health Knowledge Management Portal [Internet]. [cited 2022 Mar 18]. Available from: http://library.health.go.ug/publications/hivaids/consolidated-guidelines-prevention-and-treatment-hiv-uganda-1

18. 2020 Uganda HIV -AIDS fact sheet, Sept 6 2021. pdf.

19. Ministry of Health, Uganda. Annual Health Sector Performance Report Financial Year 2019/20 | Ministry of Health Knowledge Management Portal [Internet]. 2020 [cited 2022 Apr 4]. Available from: http://library.health.go.ug/publications/performance-management/annual-health-sector-performance-report-financial-year-201920

Continued from page 30

20. UNAIDS. 2020 Uganda HIV -AIDS fact sheet, Sept 6 2021. pdf. 2020.

21. Pelletier AR, Derado J, Maoela L, Lekhotsa T, Sechache M, Nkuatsana K. Impact of the DREAMS Program on New HIV Diagnoses in Adolescent Girls and Young Women Attending Antenatal Care — Lesotho, 2015–2020. MMWR Morb Mortal Wkly Rep. 2022 Jan 14;71(2):48–51.

22. Wilson KS, Mugo C, Katz DA, Manyeki V, Mungwala C, Otiso L, et al. High Acceptance and Completion of HIV Self-testing Among Diverse Populations of Young People in Kenya Using a Community-Based Distribution Strategy. AIDS Behav. 2021 Sept 1;1–11.

23. Kikuube Local Government. Kikuube District Population [Internet]. KIKUUBE DISTRICT LOCAL GOVERNMENT. [cited 2022 May 6]. Available from: https://kikuube.go.ug/

24. CDC Immigrant and Refugee Health. Refugees HID and AIDS [Internet]. Refugee Health TA. [cited 2022 May 6]. Available from: https://refugeehealthta.org/physical-mental-health/health-conditions/infectious-diseases/hiv/

Trends and spatial distribution of neonatal sepsis, Uganda, 2016-2020

Authors: Stella M. Migamba[1], Esther Kisaakye[1], Miriam Nakanwagi[1], Allan Komakech[1], Petranilla Nakamya[1], Benon Kwesiga[1,2], Lilian Bulage[1,2], Robert Mutumba[3], Deogratius Migadde[3], Alex R. Ario[1,2]*

Institutional Affiliations

[1]Uganda Public Health Fellowship Program, Kampala, Uganda, [2]Uganda National Institute of Public Health, Kampala, Uganda, [3]Ministry of Health, Reproductive and Infant Health Department, Kampala, Uganda

**Correspondence: Email: smigamba@musph.ac.ug, Tel: +256-774-662-488*

Summary

***Background**: Neonatal sepsis is the third-leading cause of neonatal deaths in Uganda. The infection can be acquired perinatally (early-onset sepsis (EOS) occurring within seven days postpartum) or nosocomially or in the community (late-onset sepsis (LOS) occurring 8-28 days postpartum). We described trends and spatial distribution of neonatal sepsis in Uganda, 2016-2020.*

***Methods**: We analysed routinely-reported surveillance data on in-patient neonatal sepsis from the District Health Information Software version 2 (DHIS2) during 2016-2020. We analysed sepsis distribution by district and calculated incidence rates for EOS, LOS, and total sepsis at district, regional, and national levels as cases per 1,000 live-births (LB), as well as total sepsis incidence by health facility level. We determined significance of national and regional trends using logistic regression and the corresponding odds ratios. We demonstrated the spatial distribution using choropleth maps.*

***Results**: During 2016-2020, 95,983 neonatal sepsis cases were reported and of these, 71,262 (74.2%) were EOS. Overall incidence of neonatal sepsis was 17.4/1,000 live-births. Nationally, incidence of sepsis was generally highest at the Regional Referral Hospital (RRH) level (68/1000 live-births) and lowest at the Health Centre II level (1.3/1000 live-births). The change in total sepsis during 2016 to 2020 was not statistically significant (P=0.133). However, EOS increased from 11.7 to 13.4 cases/ 1000 LB, with an average yearly increase of 3% (p<0.001) and late-onset sepsis declined from 5.7 to 4.3 cases/1000 LB with an average yearly decrease of 7% (p<0.001). Regionally, early onset sepsis as well as total sepsis increased in Central (15.5 to 23.0/1000 live-births (p<0.001)) and Northern regions (15.3 to 22.2/1000 live-births (p<0.001) but decreased in Western (23.7 to 17.0 (p<0.001)) and Eastern (15.0 to 8.9 (p<0.001) Uganda. Three districts had incidences of >50/1000 live-births.*

***Conclusion:** Increase in incidence of EOS na-*

Continues to page 32

tionally points to a need to urgently address the quality of care for pregnant women and the quality of preventive measures for neonatal sepsis through timely maternal infection management across the country. Clean delivery and hospital environments should be emphasized. The heterogenous distribution of the incidence of neonatal-sepsis requires tailored root cause-analysis by health authorities in regions with consistently high neonatal -sepsis incidence. Prevention and treatment interventions in Central and Northern regions, as well as in the most affected districts should be strengthened.

Background

Neonatal sepsis caused 15% of neonatal deaths globally in 2018 and this impacts negatively on attainment of the Sustainable Development Goal to end preventable child deaths. There are approximately 1.3 million cases of neonatal sepsis annually, the bulk of which is in low-income countries especially those in Africa. Global data indicate a 3.5 times higher incidence in low-income countries and 1.8 times higher incidence in middle -income countries compared to high-income countries.

Although there is currently no concensus definition for neonatal sepsis, it is commonly referred to as a clinical syndrome that includes pneumonia and meningitis and characterised by bacterial infection in the first month of life (1, 2). Neonatal sepsis is categorized as either early-onset sepsis (EOS) if it occurs in the first seven days of life, or late-onset (LOS) sepsis if the infection occurs from 8 to 28 days of life. EOS is caused by intrapartum transmission of bacteria from the mother to the neonate (3-5), while LOS is usually acquired postnatally from the hospital or community environment (3). Risk factors for neonatal sepsis include: prematurity, low birth weight (below 2.5 kg), premature rupture of membranes, prolonged labour, caeserean section delivery, maternal infection, and lack of antenatal care (6-9). It is characterised by: temperature instability, inability to breastfeed, seizures, respiratory distress, jaundice, vomiting, diarrhoea, abdominal distention, and diminished activity (10). Although the gold standard test for neonatal sepsis is a blood culture, in resource limited settings, cases are often diagnosed clinically.

In Uganda, neonatal sepsis is among the top three contributors to high neonatal mortality rate alongside other causes such as birth asphyxia, preterm birth complications, intrapartum related events, and other infections such as meningitis and pneumonia (11, 12). The recommended first -line treatment of neonatal sepsis in Uganda is administration of intravenous ampicillin and gentamycin and cephalosporins as second-line drugs (2, 13). Worryingly, despite new born health interventions, neonatal mortality rate (NMR) persisted at approximately 27/1,000 live births between 2002 and 2016, according to three successive demographic health survey reports (11) . It is important that neonatal deaths decrease so that the 2030 national target of 12 or less new born deaths per 1,000 live births is met (14). There is paucity of epidemiological data on neonatal sepsis in Uganda. However, the Maternal Perinatal Death Surveillance and Response report for FY 2019/2020 attributed 12% of new born deaths in Uganda to neonatal sepsis (15) and a study done at Mulago National Referral hospital reported the case fatality rate from neonatal sepsis as 9.5% (16) . We describe the trends and spatial distribution of neonatal sepsis in Uganda between 2016 and 2020 so as to provide information that will guide interventions to reduce incidence of neonatal sepsis and sepsis related deaths.

Methods

Continued from page 32

Study setting

This study was done in Uganda, a country located in Sub-Saharan Africa. Uganda has a population of 34.6 million persons and a population growth rate of 3 percent according to the 2014 National Population and Housing Census (17). Uganda's fertility rate is 5.4 children per woman, one of the highest in the world, and the crude birth rate is 38.7 per 1,000 population (11). There are 6, 937 health facilities in the country; Of these, 45.2 % are government owned, 14.4 % are private and Not for Profit (PNFP), 40.3 % are Private For Profit (PFP) and 0.1% (7) community-owned facilities. These health facilities are classified into seven levels; maternity services are provided at facilities from level 3 upwards (18). The recommended intravenous antibiotics for the management of neonatal sepsis are available at health facilities from level 3 and above (19).

Study design, neonatal sepsis surveillance, and data source

We performed a descriptive analysis of routinely reported surveillance aggregate data on in-patient neonatal sepsis using the District Health Information System version 2 (DHIS2) from 2016 to 2020. The DHIS2 is an electronic version of data from the Health Management Information System (HMIS). The HMIS is a paper-based reporting system where integrated health unit data on several conditions including neonatal sepsis are reported on a weekly and monthly basis. In the DHIS2, neonatal sepsis is categorised as in-patient and out-patient sepsis, which are further classified into early-onset (0-7 days) and late-onset (8-28 days) sepsis. Specifically, for the data extracted in this analysis, the flow of the data was from health units at level 3 to the health sub-district (level 4) and then to the district. At the district, data are entered by the district biostatistician by health facility level into DHIS2. Regional and national referral hospitals send data directly to the Ministry of Health. At the Ministry of health, data from all health facilities are collated and the national performance on each indicator is determined.

Study Population

The study population comprised of all records of new born babies aged 0-28 days (neonates) delivered at health facilities in Uganda between January 2016 and December 2020.

Study variables and data abstraction

For this analysis, we downloaded data elements on: Neonatal Sepsis at 0-7 days, Neonatal Sepsis at 8-28 days, and deliveries in a health unit (live births) from HMIS 108 which aggregates in-patient data. In-patient cases were considered because the computation of sepsis incidence would be more accurate since the denominator of live births is more readily available for health facility deliveries than home deliveries .We also downloaded data on the national reporting rate on neonatal sepsis for the years 2016 to 2020 from DHIS2 to determine whether fluctuations in reporting rates could have affected sepsis incidence. These data were then exported from DHIS2 to Microsoft Excel and then into Epi Info 7 for analysis.

Data Analysis

We calculated incidence rates of early-onset (0-7 days), late-onset (8-28 days), and total (0-28 days) neonatal sepsis from 2016 to 2020 at district, regional, and national levels. Incidence rates for total sepsis were also calculated at health facility level. Incidence rate was the number of sepsis cases divided by total live births per 1,000 live births. We demonstrated regional and national trends on line graphs and determined the significance of the change in trend using logistic regression in Epi-info version 7. We interpreted the odds ratios as the odds of increase or decre

Continues to page 34

crease in in-patient neonatal sepsis cases per 1,000 live births per year. Choropleth maps were drawn using QGIS version 3.6.3 to show the regional and district-level distribution of neonatal sepsis at district level.

Ethical considerations

This study utilized routinely reported surveillance data that did not have personal identifiers. We obtained permission to use the HMIS data from the Ministry of Health Resource Centre which is responsible for collating and storing health information. We stored the data in password-protected computers. The US Centers for Disease Control and Prevention (CDC) Center for Global Health determined this study was non-research with a main aim improving data use to guide health planning and practice.

Results

Trends of incidence of in-patient neonatal sepsis nationally, Uganda, 2016- 2020Nationally, a total of 95,983 cases of in-patient total neonatal sepsis (early-onset plus late-onset sepsis) were reported from 2016 to 2020. Seventy five percent (71,262) of them were early-onset cases (0-7 days). On average, 1.7% of all live born neonates experienced sepsis (Table 1).

Year	LB†	Total sepsis	% among LB*	EOS[π]	% among LB[¶]	LOS[β]	% among LB[§]
2016	959,078	16,717	1.7	11,249	1.2	5,468	0.6
2017	1,040,265	18,096	1.7	13,301	1.3	4,795	0.5
2018	1,123,279	19,328	1.7	14,838	1.3	4,490	0.4
2019	1,176,931	20,515	1.7	15,674	1.3	4,841	0.4
2020	1,205,995	21,327	1.8	16,200	1.3	5,127	0.4

Table 1: Neonatal sepsis cases and total live births, Uganda, 2016-2020

LB- Live births. *Percentage of total sepsis among live births. [π]EOS- Early-onset sepsis. [¶]Percentage of EOS among live births. [β]LOS- Late-onset sepsis. [§]Percentage of LOS among live births

Overall incidence of total sepsis increased during 2016 to 2020 by an average of 0.004/1,000 live births per year (Figure 1), which was not statistically significant (P=0.133). This was on the backdrop of an almost constant reporting rate, which only increased in 2020 (Figure 1).

Continued from page 34

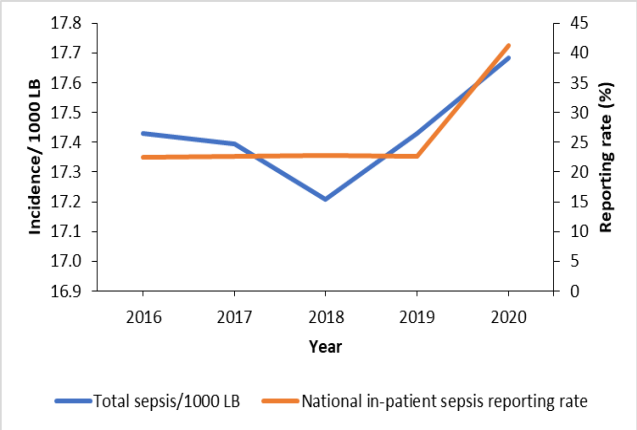


Figure 1: Total neonatal sepsis national incidence rates in Uganda, 2016-2020

Early-onset sepsis increased from 11.7 to 13.4 cases/ 1,000 LB, with an average yearly increase of 3% (OR: 1.03, CI: 1.02- 1.03, p<0.0005) and late-onset sepsis declined from 5.7 to 4.3 cases/1000 LB with an average yearly decrease of 7% (OR: 0.93, CI: 0.92-0.94, p<0.0005) (Figure 2).

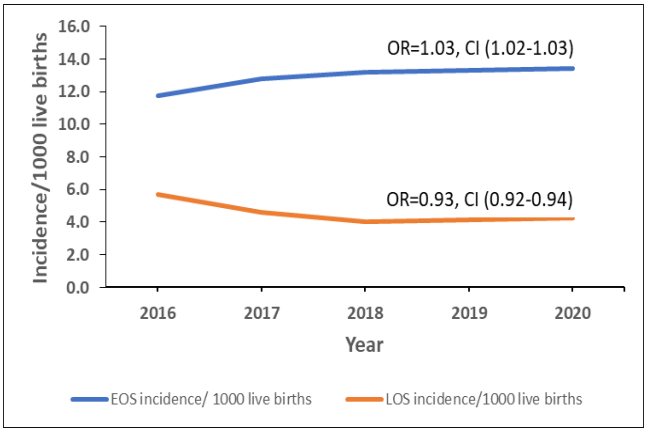


Figure 2: Early-onset and late-onset neonatal sepsis trends, Uganda, 2016-2020

Trends of incidence of in-patient neonatal sepsis at regional level, Uganda, 2016-2020

At regional level, early onset sepsis as well as total sepsis increased in Central and Northern regions but decreased in Western and Eastern Uganda. However, LOS only increased in Central region during the period while other regions registered decreases. These changes were statistically significant (Table 2).

Table 2: Significance of trends of neonatal sepsis incidence rates at regional level, Uganda, 2016-2020

Variable	IR§ 2016	IR 2020	OR	95% CI	P-value*
Total sepsis					
Central	15.5	23	1.5	1.4- 1.6	<0.001
Northern	15.3	22.2	1.2	1.2- 1.3	<0.001
Western	23.7	17	0.7	0.7- 0.7	<0.001
Eastern	15	8.9	0.6	0.6- 0.6	<0.001
Early-onset sepsis					
Central	11.8	16	1.4	1.3- 1.4	<0.001
Northern	8.3	16.8	2	1.9- 2.2	<0.001
Western	15.4	14.1	0.9	0.9- 0.9	<0.001
Eastern	10.9	7.3	0.7	0.6- 0.7	<0.001
Late-onset sepsis					
Central	11.8	16	1.9	1.8-2.0	<0.001
Northern	8.3	16.8	0.8	0.7-0.8	<0.001
Western	15.4	14.1	0.3	0.3- 0.4	<0.001
Eastern	10.9	7.3	0.4	0.4-0.5	<0.001

*Significant association at p-value < 0.05

§IR= Incidence rate

Spatial distribution of neonatal sepsis incidence rates at district level, Uganda, 2016-2020

Despite Central and Northern regions having the highest early-onset sepsis across the years, the districts with the highest early-onset sepsis were not concentrated only in those regions. In 2017, districts generally showed much lower EOS incidence compared to rates in 2016 and other years. From 2018 to 2020, increasingly more dis-

Continues to page 36

tricts had high EOS incidence in the range 17.5-50 cases/ 1,000 live births. The highest number of districts (5) with incidences of > 50 cases/1,000 live births occurred in 2020, and they included Gulu, Hoima and Kapchorwa (Figure 3).

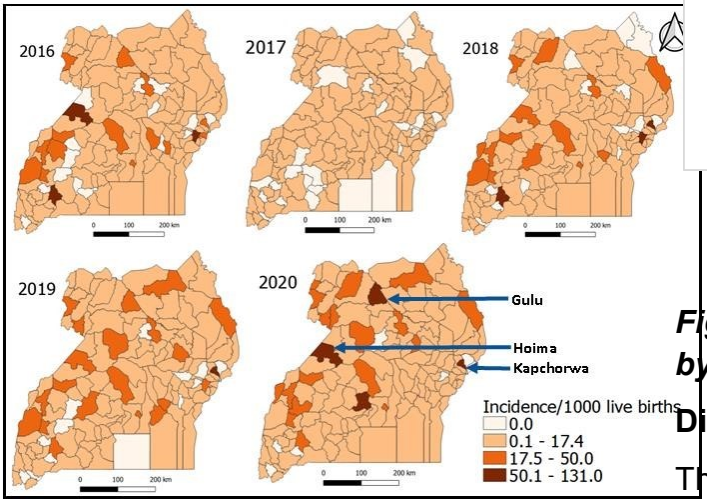


Figure 3: Spatial distribution of early-onset neonatal sepsis incidence rates, Uganda, 2016-2020

Incidence rate of in-patient neonatal sepsis at health facility level, Uganda, 2016- 2020

Incidence of sepsis was generally highest at the Regional Referral Hospital level (the highest level of health care) and decreased at each successive level (general hospitals, Health Centre 4, Health Centre 3) up to the lowest level of health facilities (Health Centre 2) (Figure 4).

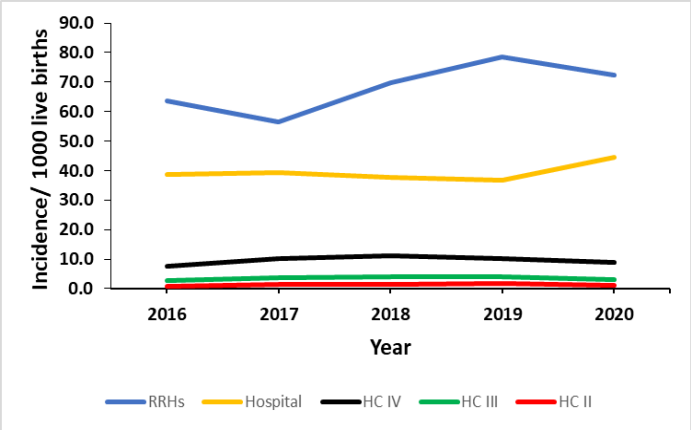


Figure 4: Total neonatal sepsis incidence rate by health facility level, Uganda, 2016- 2020

Discussion

This study revealed that 1.7% neonates of all live births that occurred in Uganda between 2016 and 2020 developed sepsis, which is a preventable cause of neonatal morbidity and mortality. In an interrupted time series study conducted at an urban private hospital in Central Uganda, whereas the case fatality rate from intrapartum hypoxia and prematurity decreased significantly, that from neonatal sepsis increased from 1.9% in 2006 to 5.7 % in 2015 (20). Another study done in Eastern Uganda showed that sepsis or pneumonia were the leading causes of all neonatal deaths accounting for 31% of such deaths and that these deaths are influenced by three delays. The delay by caretakers in identifying unwell neonates and seeking care contributed to 50% of neonatal deaths, delay in receiving quality care at the health facility contributed 30%, while transport delay to the health facility contributed 20% (21). Therefore, strategies that address the three delays could result in timely intervention for neonates with sepsis so as to prevent adverse outcomes such as death.

Nearly three quarters of sepsis cases in this study were early-onset, that is, they occurred

Continued from page 36

within the first 7 days of newborn life. This finding is similar to the 2.6 fold higher incidence of EOS than LOS that was reported globally and to the 80% EOS incidence of all sepsis that was found in South Western Uganda (22, 23). Sankar, Natarajan (24) showed that one-half of sepsis-related deaths in developing countries occur in the first week of life, whereas another study in Eastern Uganda revealed that 78% of neonatal deaths occurred in the first week (21). The early neonatal period represents a time when neonates born at health facilities are exposed to the health facility environment. Neonates are susceptible to sepsis from health care associated infections which occur more commonly in resource limited settings; health-care associated infections account for 1 in 4 sepsis cases in hospitals (25). Early onset sepsis reflects issues of quality of care which include infrastructure limitations that hinder adequate care of pregnant women and neonates, suboptimal use of preventive measures such as early diagnosis of maternal infection for prompt treatment before it spreads to the neonate, and poor management of maternal and neonatal infections and their complications (26). Since EOS usually results from infection acquired in utero or during the birth process, the period around birth represents an important time at which to intervene to control neonatal sepsis.

In this study, we observed mixed trends by region in neonatal sepsis with the Central and Northern regions showing increasing trends while declining trends were observed in Eastern and Western Uganda. The high incidence in Central region may possibly be due to the high population density and the region also has the highest concentration of health facilities (18). While total sepsis incidence appeared to increase, the reporting rate for neonatal sepsis remained almost constant from 2016 to 2019. However, in 2020, the reporting rate increased. The increase in total sepsis in 2020 might be due to the increased reporting rate in the same year. Increased sepsis in 2020 is also probably due to emergence of COVID-19 which increased home births hence sepsis. COVID-19 also caused delays in mothers reaching hospital hence prolonged labour which is a risk factor for infection. One of the attributable factors for the reduction in Eastern Uganda could be the prompt adherence by care takers of newborns to community health workers' facility referral advice. (27). Early identification of danger signs of infection presents an opportunity for timely interventions thus decreasing adverse outcomes. Health facility level analysis showed that regional referral hospitals had the highest incidence of neonatal sepsis which is expected given that lower level health facilities refer complicated cases of neonatal infections to them. Hospitals also have a higher availability of drugs for treating neonatal sepsis than lower level facilities (28). Four of the five high burden districts (Mbale, Gulu, Hoima, and Mbarara) each have a regional referral hospital. Presence of a referral hospital in these districts implies that they receive cases from neighbouring districts in their respective regions which could be an additional factor for high incidence rates observed in these districts.

The financial burden of neonatal sepsis in sub-Saharan Africa has been described (29). Investing in prevention and effective case management of neonatal sepsis has important benefits including the prevention of nervous system complications that result in serious permanent disability (30). There is need for health workers to scale up infection prevention and controls practices in the most affected settings including in Central and Northern Uganda, the most affected districts, and at regional referral hospitals. Guidelines to health workers to improve essential maternal and newborn care were launched in October 2021 by the Ministry of Health. Widespread roll out and implementation of these guidelines by the Ministry of Health to health facilities will likely improve maternal and neonatal outcomes. Routine care for

Continues to page 38

all pregnant women and neonates includes ensuring a clean delivery environment (31). Health workers should continuously strive to create a conducive environment for child birth by ensuring a clean delivery environment. Antenatal care visits should be harnessed as points of education of pregnant women on neonatal sepsis including its causes, danger signs, and prevention strategies. Mothers should be encouraged to identify signs of infection they may be harbouring especially towards term pregnancy so that they seek treatment early.

Study Limitations

The data in the district health surveillance system are aggregated data and can only be used to analyze data at aggregate level. Health care access bias where the numbers we see are only those who make it to the health facilities could have led to underestimation of the burden of neonatal sepsis. In addition, this analysis includes only in-patient DHIS2 sepsis data and excludes out-patient department data which would likely include a greater proportion of neonatal sepsis from home births. These factors could have led to underestimation of the burden of neonatal sepsis. Also, reporting rates for the study period were low so there is a possibility that neonatal sepsis cases were under represented. Moreover, for each of the years, some districts did not report neonatal sepsis cases (not even zero reporting). For such districts, incidence rate of neonatal sepsis per 1,000 live deliveries could not be computed. We studied in-patient cases and so have missed out on the true burden of late-onset cases in the community.

Acknowledgements

The authors would like to thank the Ministry of Health Division of Health information for permitting us to use these data, and the Reproductive Health Department of the Ministry of Health as well as the Uganda Public Health Fellowship Program for the technical support.

References

1. Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. Bmj. 2007;335 (7625):879-83.

2. Ministry of Health. Essential Maternal and Newborn Clinical Care Guidelines for Uganda. In: Department RaCH, editor. Kampala, Uganda: Ministry of Health; 2021.

3. Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatric Clinics. 2013;60(2):367-89.

4. Cortese F, Scicchitano P, Gesualdo M, Filaninno A, De Giorgi E, Schettini F, et al. Early and late infections in newborns: where do we stand? A review. Pediatrics & Neonatology. 2016;57(4):265-73.

5. Mukhopadhyay S, Puopolo KM, editors. Risk assessment in neonatal early onset sepsis. Seminars in perinatology; 2012: Elsevier.

6. Beletew B, Kassie A, Getu MA. Neonatal sepsis and its associated factors in East Africa: a systematic review and meta-analysis, 2019. 2019.

7. Chan GJ, Lee AC, Baqui AH, Tan J, Black RE. Risk of early-onset neonatal infection with maternal infection or colonization: a global systematic review and meta-analysis. PLoS Med. 2013;10(8):e1001502.

8. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392

Continued from page 38

Black Water Fever among children in Districts of Bugisu, Bukedi, and Busoga Region, Eastern Uganda, January 2019 – July 2021

Authors: Alice Asio[1], Veronicah Masanja[1], Andrew Kwiringira[1], Stella Martha Migamba[1], Esther Kisaakye[2], Lilian Bulage[1,2], Daniel Kadobera[1,2], Benon Kwesiga[1,2], Alex R. Ario[1,2]*
Institutional affiliations: [1]Uganda Public Health Fellowship Program, Kampala, Uganda, [2]Uganda National Institute of Public Health, Kampala, Uganda
**Correspondence: Email: aasio@musph.ac.ug, Tel: +256788006553*

Summary

Background: *In May 2021, districts in Eastern Uganda reported an increase in suspected black water fever (BWF) affecting children, most <12 years of age. We investigated to confirm the outbreak, generate information on the causative agent, and describe the case-patients in terms of person, place, and time.*
Methods: *A suspected case was an onset of dark/red urine with at least one of the following: fever >37°C, anorexia, fatigue, abdominal pain, abdominal distention, anemia, jaundice, headaches, or vomiting in a patient attending Mbale, Soroti or Jinja Regional Referral hospitals (RRHs) of Eastern Uganda during January 2019 to May 2021. To describe the case-patients, we abstracted medical record data for cases identified from January 2019-May 2021. To generate information on the possible causative agent and also rule out other conditions in the case-patients, we collected blood, stool, and urine samples from 20 case-patients and 20 randomly selected non-case-patients (children admitted in the same ward as the case-patients) matching them with the hospital and tested them for ten different tests per case-patient and per non-case-patient. We defined non-case-patients as* any patient with malaria admitted in pediatric wards of Mbale and Soroti RRHs who never passed out dark colored urine in their lifetime. *We tested non-case-patients to find out if there could be any differences in BWF case-patients and non-case-patients. We also conducted pathogen discovery to find out the causative organism. We described the case-patients in terms of age of onset of illness, number of episodes, and intervals between episodes.*
Results: *According to the records review, we identified 4,913 case-patients, including 26 who died (CFR=0.5%). All 4,913 presented with dark-coloured urine, 2,617 (53%) with high-grade fever, and 2,295 (47%) with anaemia. Most case-patients (65%) were reported from Soroti RRH. The attack rates were similar in 2019 (AR=2.3/10,000) and 2020 (AR= 2.5/10,000). Males [2019: AR=3.2/10,000, 2020: AR= 3.3/10,000, and 2021(Jan-May): AR=1.5/10,000] were more affected than females in all the years of the records review period.*
Among the 40 participants (20 cases and 20 non-cases-patients), the mean age was 4.5 (SD=2.4), ranging from 1 to 8 years. Case-patients and non-patients were nearly comparable in mean age (4.5 years among cases and 4.0 years among non-patients), and sex distribution (65% of case-patients and 55% of non-cases-patients were males). Among the case-patients, 20% (4/20), 20% (4/20), and 20% (4/20) developed the illness at the age of 2, 3, and 6-years respectively. 45% (9/20) of the case-patients had 1 to 3 episodes since the onset of the illness. 55.2% (48/87) of the case-patients experienced varying intervals between episodes and 70% (14/20) experienced the relapses of the illness after every 2-3 weeks. From the laboratory investigation, all the case-patients 100% (20/20) had low hemoglobin compared to the non-patients at 0% (0/20). None of the case and non-cases-patients tested positive for Hep B, syphilis, HIV, stool, and blood cultures never identified any organism in both stool and blood. Both case-patients (20/20) and non-case-patients (20/20) had malaria parasite seen on PCR and only 55% (11/20) of case-patients and 100%(20/20) of non-case-patients tested malaria positive by MRDT. Pathogen discovery findings are not yet out.
Preliminary conclusion: *BWF caused substantial morbidity among children in Eastern Uganda during our study period. Case-patients experienced repetitive episodes. Future studies should focus further of the causative agent(s), triggers of BWF, and expand case capture sites to identify geographic boundaries of this problem in Uganda.*

Introduction

Malaria is the leading cause of death in Uganda, accounting for 27% of the total deaths, of which

Continues to page 40

50% are among children under five years (*President's Malaria Initiative Uganda, Malaria Operation Plan FY 2018*). Blackwater fever (BWF) is thought to be a complication of either severe malaria or malaria treatment. Among patients with BWF, red blood cells burst in the bloodstream (haemolysis), releasing hemoglobin directly into the blood vessels and into the urine, frequently leading to haemoglobinemia, hemoglobinuria, jaundice, anuria, kidney failure, and sometimes death (4). Treatment for BWF includes blood transfusion, antimalarials, folic acid and fluids. Children are more commonly affected than adults with sickle cell (12).

The causes of BWF remain unclear, and it is not known why some children with malaria develop BWF while others do not. Previous studies have suggested a link between BWF and quinine treatment or other antimalarials (8), rainy seasons, and low parasitemia (13). Other studies have suggested possible genetic contributors, such as genotype AA or G6PD deficiency (8, 5,10). The persistence of PCR-detectable parasitemia after administration of artemisinin-combination therapy (ACT) is often observed in asymptomatic children from endemic areas. The development of resistance to chloroquine led to the reintroduction of quinine and the introduction of mefloquine and halofantrine, and this has previously been associated with a reappearance of BWF (16). Treatment requires prompt transfusion to replace lost red blood cells, and sometimes a change in antimalarial drugs. Some of the countries that have reported BWF are France (1990-1999), Niger, Sierra Leone in 1889, Congo, Burundi and others (9, 14,6,13, 15). In all these countries, BWF was suggested to be associated with quinine use.

Although BWF is linked to malaria, it is not present everywhere malaria is present. Starting in 2009, cases of BWF began being reported in Eastern Uganda in the districts of Manafwa, Soroti, Katakwi, Namutumba, and Namisindwa. Other areas of the country appear relatively unaffected. On May 29, 2021, a story ran in the Ugandan Newspaper New Vision about suspected BWF affecting children <12 years of age in Eastern Uganda. They reported that there were 13-16 admissions of children to Mbale Regional Referral Hospital from Mbale and the surrounding regions each day, and that some of the cases were fatal. The article noted that response to the conventional antimalarials – primarily artemether -lumefantrine - was poor. The Hospital Director reported that some of the cases were coming from outside their catchment area, i.e., Bukedea and Kumi both located in Bukedi region and Namutumba located in Busoga region. We investigated to confirm the outbreak, generate information on the causative agent, and describe the case-patients in terms of person, place, and time.

Methods

Outbreak setting

Cases were reported in the Eastern, is one of the four regions of Uganda. It has 37 districts with mixed tribes: Busoga, Bugishu, Bugweri, Samia, Teso, Jopadhola, and Kumam. The region has an approximate population of 13.6 million persons, representing approximately 14% of the country's population. The major economic activity in this region is agriculture; growing of rice, millet, coffee, groundnuts, millet among other activities. Additionally, the population practices fishing in the lakes and rivers including swamps found in eastern Uganda. Furthermore, the eastern region has natural features like Mt Elgon, and many rocks.

Case definition and finding

We defined a suspected case as any patient with onset of dark/red urine with at least one of the following: high-grade fever, loss of appetite, fatigue, abdominal pain, abdominal distention, anemia, jaundice, headaches, or vomiting who attended either Mbale, Jinja, and Soroti RRHs of Eastern Uganda from January 2019 to May 2021.

We conducted records review in Soroti, Mbale, and Jinja RRHs to understand the historical pattern, seasonality, geographical patterns, and case-patients' characteristics January 2019-May 2021. The current and past medical records were reviewed for the suspected cases including the deceased.

Continued from page 40

Laboratory investigations

To generate information on the possible causative agent and also rule out other conditions in the case-patients, we collected blood, urine, and stool samples from 20 case-patients and 20 non-patients from Mbale and Soroti RRHs. We considered Mbale and Soroti hospitals because they were the only hospitals receiving many case-patients, an average of 5-7 case-patients daily and Jinja RRH had no case-patients during the study period. A non-case-patient was any patient with any other condition admitted in pediatric wards of Mbale and Soroti RRHs who never passed out dark colored urine in their lifetime. We tested non-case-patients to find out if there could be any differences in BWF case-patients and non-case-patients. We tested for malaria parasites using both microscopy and PCR, Hep B using HBsAg test, sickle cell disease detect using HB electrophoresis, urinalysis using microscopy and ASTRA Care Dipsticks for proteins, Glucose, Ketones Leukocytes, Nitrites, Urobilinogen, Blood cells, Bilirubin, pH and Specific gravity, syphilis using T -pallidum Ab test, blood culture using ELISA (Giemsa staining and BD Bactec blood culture systems), HIV using HIV-1/2rapid test and CBC. We also conducted pathogen discovery to identify the possible causative agent.

We recruited cases sequentially and kept recruiting the cases until we reached the desired number. Non-case-patients were randomly selected from children admitted within the same ward. We administered a questionnaire to caretakers/parents.to collect information on socio-demographics, clinical presentation, natural history of the current suspected BWF episode, history of previous BWF episodes, medical history before the onset of the first episode of suspected BWF

Descriptive epidemiology

We analyzed data using Epi Info 7.2.2.6. Regarding the records review data, we generated epidemic curves, attack rates by year, sex, and age group using annual population estimates for the region by the Uganda Bureau of Statistics. We then generated proportions by number of episodes experienced by case-patients, distribution of case-patient by age group, age at onset of the illness, and number of intervals between the episodes. We also generated proportions to describe the case-patients by symptoms and signs experienced. We described the 20 case-patients and 20 non-case-patients by the laboratory investigation outcomes.

Ethical considerations

We obtained permission to conduct this this investigation from the Ministry of Health of Uganda through the office of the Director General Health Services. The Office of the Associate Director for Science, U.S. Centers for Disease Control and Prevention, determined that this activity was in response to a public health emergency with the primary intent of public health practice (epidemic disease control activity). It was determined therefore to not be human subjects research. Furthermore, we obtained permission from the hospital directors of Mbale RRH, Soroti RRH, and Jinja RRH to access the paediatric wards suspected BWF related records, case-patients, and non-case-patients. Since all our participants were below 18 years of age, we sought verbal consent from their parents or guardians to allow us interview them and collect samples.

Results

Descriptive epidemiology

Distribution of case-patients by signs and symptoms, age group, and sex at Mbale, Soroti, and Jinja regional referral hospitals, January 2019-May 2021

In total, 4,913 case-patients were identified, including 26(CFR=1%) for whom the hospital records recorded as dead. All the case-patients presented with dark coloured urine (100%), 2,617 (53.3%) with high grade fever, and 2,295 (46.7%) with anaemia (Figure 1).

Continues to page 42

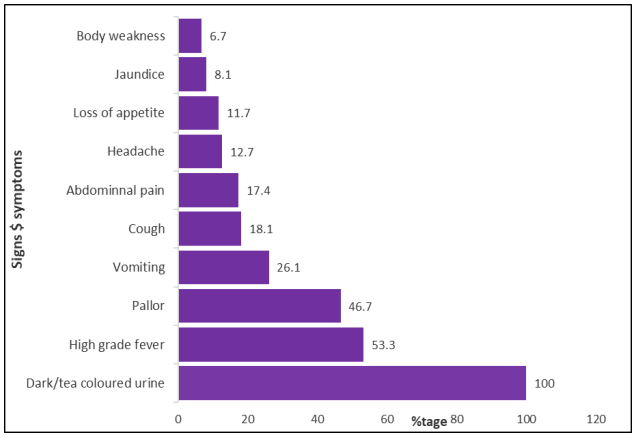


Figure 1: Distribution of case-patients by signs and symptoms (N=4,913) at Mbale, Soroti, and Jinja regional referral hospitals, January 2019-May 2021

Attack rates by age group and sex

The mean age of case-patient was 6 years (range, 21 days to 24 years). The most affected age group across the years was 5-9 years [2019: AR=4.7/10,000, 2020: AR= 5.0/10,000, and 2021(Jan-May): AR=2.5/10,000]. Males [2019: AR=3.2/10,000, 2020: AR= 3.3/10,000, and 2021(Jan-May): AR=1.5/10,000] were more affected than females in all the years of the assessment (Table 1).

Table 1: Attack rates by age group (n= 4,729) and sex (n=4,695)

Year	Age group (yrs.)	Cases	Population <24yrs	Attack rates/10,000
2019	0-4	637	2,022,728	3.1
	05-9	827	1,747,861	4.7
	10-15	323	1,798,804	1.8
	16-24	1	2,022,094	0.005
2020	0-4	712	2,097,700	3.4
	05-9	875	1,747,428	5
	10-15	400	1,910,296	2.1
	16-24	4	2,087,638	0.02
2021 (Jan-May)	0-4	305	2,173,868	1.4(5Months)
	05-9	430	1,746,995	2.5 (5Months)
	10-15	212	2,021,788	1.0(5Months)
	16-24	3	2,153,182	0.01 (5Months)
	Sex (n=4,695)			
2019	Female	619	3,541,080	1.7
	Male	1,166	3,636,670	3.2
2020	Female	748	3,623,140	2.1
	Male	1,219	3,742,580	3.3
2021 (Jan-May)	Female	359	3,705,200	1.0 (5 months)
	Male	584	3,848,490	1.5 (5 months)

Distribution of case-patients by regional referral hospital admitted and address of residence

Out of 4,913 case-patients, most case-patients were reported from Soroti RRH (64.9%), 21.3% were from Jinja RRH, and 13% from Mbale RRH. Among the 4,433 (90%) patients who had a known address, 95% were from the Eastern Region; 4% were from Central Region, and 1% were from Northern Region.

Distribution of case-patients by date of admission and attack rates over time

The number of case-patients admitted at health facilities have been increasing over years from 2019 to date (Figure 2). Case-patients admitted at health facilities increased gradually over years from 2019 [2019: AR=2.3/10,000, 2020: AR= 2.5/10,000, and 2021(Jan-May): AR=1.2/10,000].

Continued from page 42

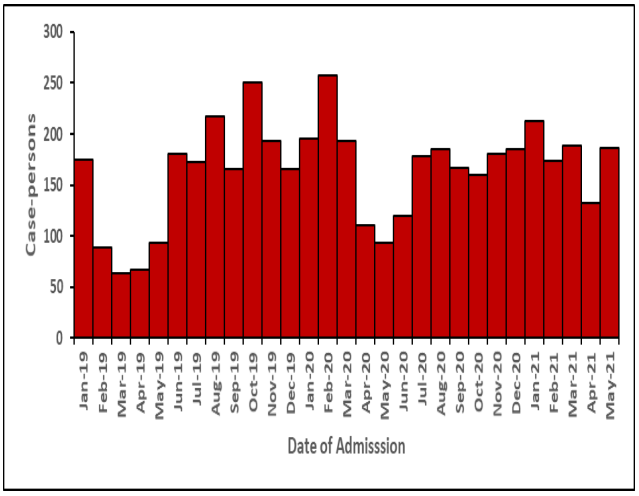


Figure 2: BWF cases by date of admission to Jinja, Soroti, and Mbale RRH, 2019-2021 (N=4,747 cases with admission dates)

Attack rates of black water fever cases by district, eastern Uganda, January 2019-May 2021

District-specific attack rates varied over the eastern region, with Soroti District being the most affected across the years.

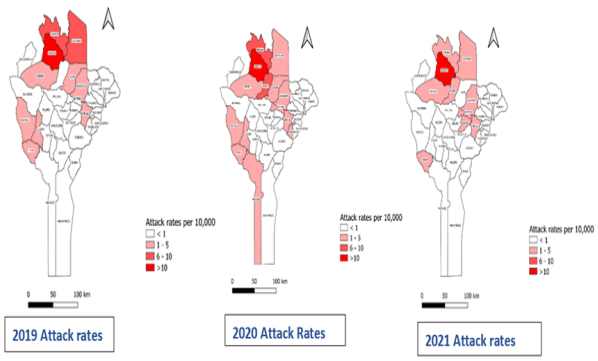


Figure 3: Attack rates by district per year during a black water fever outbreak, eastern Uganda, January 2019-May 2021

Description of 20 case-patients recruited for laboratory investigations

Age of onset and nature of episodes of black water fever

Twenty percent (4/20), 20% (4/20), and 20% (4/20) developed the illness at the age of 2, 3, and 6years respectively. 45% (9/20) of the case-patients had 1 to 3 episodes since the onset of the illness. 70% (14/20) of the case-patients experienced varying intervals between episodes and 70% (14/20) experienced the relapses of the illness after every 2-3week (Figure 4). All the case-patients had had recurrent episodes which subsides on treatment with anti-malarials, antibiotics, blood transfusion, and steroids and 30% (6/20) of the case-patients started getting episodes of the illness in 2018. 45% (9/20) of the case-patients had 1 to 3 episodes, 20% (4/20) had 7 to 9 episodes, 20% (4/20) had >10 episodes while 15% (3/20) had 4-6 episodes since the onset of the illness. 70% (14/20) of the case-patients experienced varying intervals between episodes, 25% (5/20) had an interval of 1-3weeks and 5% (1/20) had one-week interval between episodes.

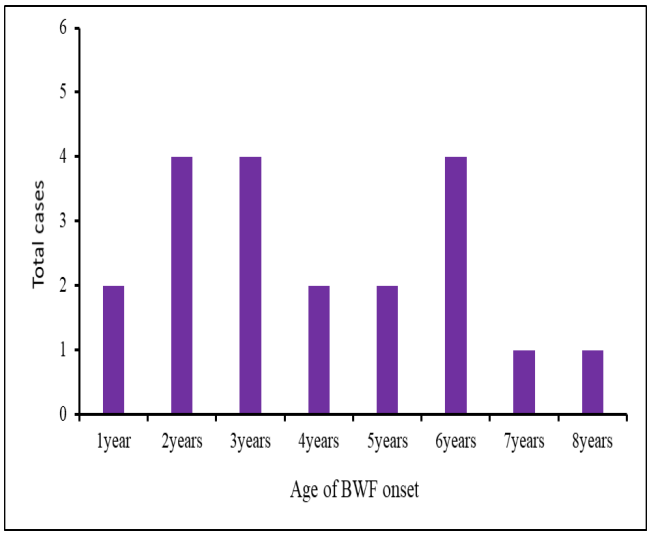


Figure 4: Distribution of case-patients by age at onset of illness (N=20)

Laboratory investigation findings

Laboratory investigation results as per records review

A total of 1,221 out of 4,913 case-patients were tested for malaria by RDT; 81.2% (991/1221) tested positive. Out of 4913, 775 were tested using microscopy; 61.5% (477/775) tested positive. A total of 682 out of 4,913 patients had their hemoglobin levels recorded. Among children less than 1 year, 95% (19/20) had low hemoglobin levels. For children aged 1-5 years and 6-11years, low hemoglobin levels were reported at 96.2% (378/393) and 95.6% (237/248) respectively. All those aged 12-24 years had low hemoglobin levels.

Laboratory investigation results for case-patients and non-case-patients

Continues to page 44

The case-non-cases-patients study included 40 participants (20cases and 20non-cases-patients) with a mean age of10.9(SD=11.2), ranging from 1 to 14 years. Case-patients and non-cases-patients were comparable in mean age (12.6 years among cases and 9.2 years among non-cases-patients), and sex distribution (65% of case-patients and 55% of non-cases-patients were males).

Hundred percent of the case-patients (20/20) had low hemoglobin while the non-case-patients had 20% (4/20) with low hemoglobin. 50% (10/20) of the case-patients had low platelet count compared to 40(8/20) for the non-case-patients (Table 2).

Table 2: Complete blood count findings for

		RBC (3.9 -5.3*12/l)	HB (11.5-14.5g/dl)	Heamacrite (0.35-0.44l/l)	MCV (73 -85f/l	MCH (73-89pg)	MCHC (30-37g/dl)	RDW (11 -16)	Platelets (150-450*10g/l
Case	Normal	3(15)	0	18(90)	16(80)	12(60)	12(60)	8(40)	8(40)
	Low	16(80)	20(100)	2(10)	2(10)	6(30)	8(40)	0	10(50)
	High	1(5)	0	0	2(10)	2(10)	0	12(60)	2(10)
Non-cases-patients	Normal	6(30)	16(80)	4(20)	17(85)	16(80)	9(45)	7(40)	10(50)
	Low	14(70)	4(20)	14(80)	0	2(10)	11(55)	0	8(40)
	High	0	0	2(10)	3(15)	2(10)	0	12(60)	2(20)

Hundred percent (20/20) of the case-patients had low basophils compared to 85% (17/20) of the non-case-patients. 25% (5/20) case-patients had high WBC count compared to 10% (2/20) non-case-patient (Table 3).

Table 3: White blood cell count results case-patients and non-case-patients

		WBC (515*10g/l)	Neutrophils (1.58*10g/l)	Lymphocytes (1.5-7*10g/l)	Monocytes (0.2-0.8*g/l)	Basophils (0-0.5*10g/l)	Eosinophils (0-0.3*10g/l)
Case	Normal	14(70)	12(65)	13(65)	10(50)	0	2(10)
	Low	1(5)	1(5)	5(25)	0	20(100)	18(90)
	High	5(25)	6(30)	2(10)	10(50)	0	0
Non-cases-patients	Normal	10(50)	11(55)	10(50)	13(65)	3(15)	1(5)
	Low	8(40)	3(15)	5(25)	2(10)	17(85)	19(95)
	High	2(10)	6(30)	5(25)	5(25)	0	0

Continued from page 44

Findings from other laboratory investigations

Blood cultures never identified any organism, no child turned positive for Hep B, none had syphilis, and all HIV test results were negative. Both case-patients (20/20) and non-case-patients (20/20) had malaria parasite seen on PCR and 55% (11/20) of case-patients and 100% (20/20) of non-case-patients tested malaria positive by MRDT.

Key findings

Based on our investigation, cases presented with signs and symptoms typical of BWF, a serious complication of severe malaria. Males were more affected compared to females across all the study period. Case-patients aged 5-9years were more affected. Soroti District registered the highest number of cases compared to all the districts in eastern Uganda. Case-patients developed illness at the age of 2, 3, and 6years with many experiencing between 1 to 3 episodes from the onset of the illness. Case-patients experienced varying intervals between episodes. The laboratory investigations showed significant difference in haemoglobin, and WBC count among the case-patients and non-case-patients.

Preliminary conclusion

BWF caused substantial morbidity among children in Eastern Uganda during our study period. Case-patients experienced repetitive episodes of illness. *Future studies should focus further of the causative agent(s), triggers of BWF, and expand case capture sites to identify geographic boundaries of this problem in Uganda.*

Acknowledgement

The authors would like to thank the management of Mbale, Jinja and Soroti RRH for allowing us carryout the investigation including the hospital staffs: Wandwasi Joseph (CO, Mbale RRH), Abeno Martha (Nurse, Soroti RRH) for helping in the recruiting the participants for the case-non-cases-patients study and collections of samples.

References

Pasvol G: The treatment of complicated and severe malaria. Br Med Bull. 2005, 75–76: 29-47

Rogier C, Imbert P, Tall A, Sokhna C, Spiegel A, Trape J-F: Epidemiological and clinical aspects of blackwater fever among African children suffering frequent malaria attacks. Trans R Soc Trop Med Hyg. 2003, 97: 193-197. 10.1016/S0035-9203(03)90116-7.

Buffet PA, Safeukui I, Deplaine G, Brousse V, Prendki V, Thellier M, et al. The pathogenesis of Plasmodium falciparum malaria in humans: insights from splenic physiology. Blood. 2011;117(2):381–392.

Ghosh JB. Black water fever. Indian J Pediatr. 2000;67(2):161–162.

Van den Ende J, Van den Ende J, Coppens G, Verstraeten T, Van Haegenborgh T, Depraetere K, et al. Recurrence of blackwater fever: triggering of relapses by different antimalarials. Trop Med Int Health. 1998;3(8):632–639.

Tran TH, Day NP, Ly VC, Nguyen TH, Pham PL, Nguyen HP, Bethell DB, Dihn XS, Tran TH, White NJ: Blackwater fever in southern Vietnam: a prospective descriptive study of 50 cases. Clin Infect Dis. 1996, 23: 1274-1281. 10.1093/clinids/23.6.1274.

Dondorp AM, Fanello CI, Hendriksen ICE et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet. 2010, 376: 1647-1657. 10.1016/S0140-6736(10)61924-1.

White NJ. Malaria. In: Cook GC, Zumla AI, editors. Manson's tropical diseases. XXI ed. Philadelphia: W.B. Saunders; 2003. p. 1205–95. [Google Scholar]

Bruneel F, Gachot B, Wolff M, et al. Resurgence of blackwater fever in long-term European expatriates in Africa: report of 21 cases and review. Clin Infect Dis. 2001; 32:1133–40. 10.1086/319743 [PubMed] [CrossRef] [Google Scholar]

Bisoffi Z, Marocco S, Montero G, Marsiaj M. Acute intravascular haemolysis (blackwater fever) after malarial treatment. Trop Med Int Health. 1999; 4:72–3. [PubMed] [Google Scholar]

Glanantonio CA, Vltacco M, Mendilaharzu F, Gallo GE, Sojo ET. The hemolytic-uremic syndrome. Nephron. 1973;11(2–4):174–192.

Djibo A, Souna-Adamou A, Brah Bouzou S, 2000, Blackwater fever in adults with sickle cell anemia. Two fatal cases

Bodi, J.M., Nsibu, C.N., Longenge, R.L. et al. Blackwater fever in Congolese children: a report of clinical, laboratory features and risk

Continues to page 46

factors. Malar J **12,** 205 (2013). https://doi.org/10.1186/1475-2875-12-205
Mahamadou D, Hassane DM, Zeinabou MTM, et al. A report of Four cases of Black water fever after quinine treatment at Zinder National hospital, Niger Republic, Case Rep Infect Dis. 2019 Aug 25.
Gobbi, Federico, et al. Blackwater Fever in Children, Burundi, Emerg Infect Dis, 2005 July.
Danis M, Nozais, et al, 1993, Black water fever after taking mefloquine. 3 observations.
Olupot-olupot, et al, The clinical spectrum of severe childhood malaria in Eastern Uganda, 2020
Olupot-Olupot, et al. Characterising Childhood Blackwater Fever and Its Clinical Care at Two Tertiary Hospitals in Eastern Uganda, 2021
Opoka et al, Blackwater Fever in Ugandan Children With Severe Anemia is Associated With Poor Postdischarge Outcomes: A Prospective Cohort Study,2020

End