Original Article

Birth Outcome and Maternal Risk Factors Associated with Childhood Leukemia in Rwanda: A case - Control Study

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Abstract

Background

Leukemia is the most common cancer affecting children and remains the top cause of death among children.

Objective

This study aimed at determining birth outcomes and maternal risk factors associated with childhood leukemia in Rwanda.

Methods

A case control study was conducted at Butaro Cancer Referral hospital. The sample of 103 cases and 103 controls was recruited using the records for children diagnosed with Acute lymphocytic leukemia (ALL) and Acute myelogenous leukemia (AML) and those who were hospitalized for non-cancer treatment as controls. Semi-structured questionnaire and phone calls were used to gather information. SPSS version 21.0 was used to analyze the data. Logistic regression analysis was used to assess the risk factors.

Results

The majority (56.8%) of children who participated in the study were aged 10-14 years. Overall 41.3% were born via C-Section. It was revealed that children who had had birth asphyxia had about three (3) times increased risk of childhood leukemia [AoR= 2.47, 95%CI: 1.167-5.262, P=0.018] compared to children that had not experienced birth asphyxia. Children who had suffered Neonatal Jaundice, had five (5) times increased risk of getting leukemia [AOR= 5.05, 95%CI: 1.738-14.664, P=0.003].

Conclusion

It is important that public and private stakeholders invest more in childhood oncology researches to enable the health system deliver effective management of the cases more efficiently.

Rwanda J Med Health Sci 2022;5(2):158-169

Keywords: Acute myelogenous leukemia, Acute lymphocytic leukemia, ALL, AML, Childhood cancer, Rwanda

Introduction

Globally, leukemia was found to be the most common cancer affecting children and remains the top cause of death among children. Acute lymphocytic leukemia (ALL) and Acute myelogenous leukemia (AML) are currently most diagnosed cancers in children from both developed and developing countries. The recent estimate show that 400,000 children and adolescents aged 0-19 years old develop cancer every year. [1,2]

The escalating evidence showed that childhood leukemia develops in utero, where ALL typically get the first of 2 key mutations in utero following the exposure of lymphoid cells in the bones (especially bone marrow) and liver that results from pre-differentiated state of leukemia cells .[3,4] Current data suggest that approximately 10% of all children with cancer have a predisposition because of genetic factors.[5] Several studies have reported some birth outcomes and maternal characteristics associated with childhood cancer.[6,7,8,9] For example, a study conducted in United stated observed that high birth weight, high birth order, young maternal age and inducted abortion were factors associated with risk of ALL.[6] In developing countries, the risk for leukemia in children seems to be connected with some factors like maternal reproductive elements as well as older maternal age.[7] Furthermore, it is was consistently found that high birth weight is among birth outcome factors which was found to be connected with the risk of leukemia in developed countries.[8,10]

A report from International Agency for Research on Cancer (IARC) show that over 20% of childhood cancer cases occur in Africa.[11] However, little is known about the risk of childhood cancer In Africa. Only one study confirmed birth weight to be a risk to childhood leukemia in Egypt.[7] The differences in risk factors for childhood leukemia may differ from low-income to high-income countries. For example, the high birth weight is increasing in developed countries while in developing countries like Rwanda, low birth weight and poor maternal nutrition remain among the serious public health problems. [12]

In Rwanda, there were found around 3,420 cases of cancer among which 320 cases were for children aged below 18 years recorded in the period between 2007 and 2011 though, it seems like many cases were unreported due to reasons like clinical workforce without formal specialty related training especially oncology but also there were some reasons like suboptimal pathology infrastructure. [13] In Rwanda, it was also shown that, leukemia was ranked the 9th of the top ten cancers with the 5-year prevalence of 5.90 %.[14]

But there is no available data about the risk factors associated to leukemia especially among children in Rwanda, yet it was reported to have the mortality rate of 3.6 /100000 in 2018.[14] The overall objective of this study was to determine birth outcome and maternal risk factors associated with childhood leukemia in Rwanda. Therefore, investigating the associations between birth outcome, maternal risks, and childhood leukemia, could pave the venue for further studies aimed to investigate other early life exposure and leukemia risks in Rwanda, hence the present study.

Methods

Research Design

An observational case control study with quantitative research methods was used in this study to get the information about birth outcome and maternal factors which are risks to childhood leukemia both in cases and controls. Case control designs classify people or subjects by outcome status at the beginning of the research. After that identification, some subjects are classified as cases whilst others are classified as controls (subjects with and without the outcome of interest but from the same population). Following this classification activity,

the information about exposure to a certain risk factor or many risk factors was then collected in a retrospective way.

Target population

The target population for the present study was all children aged 14 and below who were diagnosed at Butaro Cancer Referral Hospital with AML and ALL from July 2012 up to October 2020 as cases. At the same hospital, the study targeted children aged 14 and below who were receiving treatment for non-cancer diseases during the time of data collection as controls. The study excluded all children with coexisting medical conditions as the only targeted types of leukemia are AML and ALL as cases.

Sample size

The sample size for this study was 103 for cases which were drawn from Butaro Cancer Referral Hospital records. The desired sample size was determined using the formula of Casagrande et al.[15]

$$\delta = |P_2 - P_1|, \quad \bar{P} = \frac{P_1 + rP_2}{r+1} \quad \bar{Q} = 1 - \bar{P}$$

$$m = \frac{m'}{4}\left[1 + \sqrt{1 + \frac{2(r+1)}{rm'\delta}}\right]^2$$

$$m' = \frac{\left[z_\alpha \sqrt{(r+1)\bar{P}\bar{Q}} + z_\beta \sqrt{(rP_1Q_1 + P_2Q_2)}\right]^2}{r\delta^2}$$

N=(r+1)m=206
α: Significance level (=0.05)
1-β: Power of the test (=0.2)
P1: Success proportion in case (=0.3)
P2: Success proportion in control (=0.5)
r: Ratio of control to case (=1)
m: sample size for a case (=103)
n: Total sample size for case and control (=206)

Sampling technique

Systematic random sampling technique was used to recruit cases from children aged 14 years and below who had been diagnosed with AML and ALL from Butaro Cancer Referral hospital registries/records for the period starting from July 2012 up to October 2020. In case, there were more children with AML and ALL, the most recent cases were preferred just to reduce the recall bias and avoid missing information, which may result from old cases. After selecting the cases, the researcher randomly selected one control per case from the same hospital, but the controls were all children aged 14 years and below who were receiving a non-cancer treatment during the time of data collection or had received it before, but met the inclusion criteria.

Data Collection Instruments

A Semi-structured questionnaire adopted from the similar study conducted in Egypt [7] was modified and adapted to Rwandan context and was used to gather the information for the present study.The research tool consisted of a series of questions gathering information about respondents in order to answer research questions. The questionnaire had sections about socio-demographic characteristics, smoking, use of pesticides, parents' occupations, birth outcomes of the child, medical history of the mothers as well as reproductive aspects (including child's birth order, number of siblings as well as mode of delivery). This questionnaire provided indirect information about birth outcome and maternal factors associated to leukemia.

Procedures of Data Collection

Once potential cases and controls were identified, the researcher reviewed the completed inpatient and outpatient medical records of each study participant to confirm the diagnosis of AML or ALL. The researcher and/or researcher assistants administered the questionnaire to the caregivers of the cases and controls but for those who were

not at the hospital during the time of data collection or whose information was incomplete in the medical records, telephone calls were used to gather the additional information.

Data Analysis

After gathering the data, the researcher entered, cleaned, arranged, and analyzed them as follows:

Data were first entered in Excel, then coded in order to clean and classify them in the usable format in the excel spreadsheet. Proportion of cases and controls was obtained using descriptive statistics. Binary logistic regression analysis was used to determine adjusted odds ratios to estimate birth outcomes and maternal factors that constitute risks to childhood leukemia. Data were analyzed using SPSS version 21 and presented in tables. Variables with adjusted odd ratio above 1.0 and p-value less than 0.05 were considered as risks to childhood leukemia.

Ethical Consideration

Ethical clearance was received from Mount Kenya University ethical review board and permission to conduct this study was obtained from Butaro Cancer Referral hospital. The participants were assured that participation in this study was voluntary and that they had full right to withdraw at any stage of study without any consequences. Participants were also assured that the information they provided would be safely kept, with privacy and anonymity of the source being observed; and to be used just for the purpose of this study. Only oral consent from the caregivers/parents and assent from their children who were able to speak on phone was obtained before collecting the data from the respondents. After reading and explaining the purpose and the procedure of this research to the caregivers/parents, they were asked without coercion to consent for the study. Study information sheet and consent forms were both in Kinyarwanda. Precautions were set forth to ensure respect, dignity, value, and autonomy for the participants who took part in this study.

Results

Socio-demographic characteristics of cases and controls

The child characteristics for both cases and controls are presented in the Table 1

Table 1. Child characteristics

Variables	Cases		Control		Total n (%)	P-value
	Frequency	Percentage	Frequency	Percentage		
Child age group						
0-5	16	48.5	17	51.5	33 (16.0)	<0.001
6-10	29	51.8	27	48.5	56 (27.2)	
10-14	58	49.6	59	50.4	117(56.8)	
Sex						
Boys	58	50.4	57	49.6	115(55.8)	
Girls	45	49.5	46	50.5	91(44.2)	
Birth weight (kg)						
<2.5	16	57.1	12	42.9	28(13.6)	
≥2.5	87	48.9	91	51.1	178(86.4)	

Table 1. Child characteristics

Variables	Cases		Control		Total n (%)	P-value
	Frequency	Percentage	Frequency	Percentage		
Gestational Age						
Full term	98	49.5	100	50.5	198(96.1)	
Pre-term	5	62.5	3	37.5	8(3.9)	
Cancer among relatives						
Yes	40	48.8	42	51.2	82(39.8)	
No	63	50.8	61	49.2	124(60.2)	
APGAR						
6-8	10	50.0	10	50.0	20(9.7)	
9-10	93	50.0	93	50.0	186(90.3)	
Congenital abnormalities						
Yes	11	47.8	12	52.2	23(11.2)	
No	92	50.3	91	49.7	193(88.8)	
Asphyxia						
Yes	28	68.3	13	31.7	41(19.1)	
No	75	45.5	90	54.5	165(80.1)	
Neonatal Jaundice						
Yes	20	80.0	5	20.0	25(12.1)	
No	83	45.9	98	54.1	181(87.9)	
Oxygen administration						
Yes	27	45.8	32	54.2	59(28.6)	
No	76	51.7	71	48.3	147(71.4)	

Note: Mean age was 10.21 for both cases and controls.

Findings presented in Table 1 indicate the child characteristics for both cases and controls. A total of 206 children participated in the study. Within age group, respondents aged from 0-5 years were 16 (48.5%) for cases and 17 (51.5%) for controls, followed by those aged between 6-10 years, 29 (51.8%) for cases and 27 (48.5%) for controls. The last and majority of the respondents were aged between 10-14 years, 58 (49.6%) for cases and 59 (50.4%) for controls. Generally, the majority (56.8%) of children who participated in the study were 10-14 years old.

Overall, the majority (55.5%) of children who participated in the study were boys being 58 (50.4%) for cases and 57 (49.6%) for controls.

There was a total of 28 (13.6%) of children born with low birth weight, the findings also revealed that children who had relatives with cancer were 40 (48.8%) among the cases, and 42 (51.2%) among the controls. Most children (90.3%) had the APGAR of 9-10 at birth, 47.8% cases and 52.2% controls had congenital abnormalities. It was also shown that, 28 (68.3%) cases and 13 (31.7%) controls had had asphyxia as birth outcome. Fifty-nine (28.6%), nearly a third of the children, had been administered oxygen, of whom 27 (45.8%) were from cases and 32 (54.2%) were from controls. Overall, 19.1% of children who participated in the study had birth asphyxia. This study revealed that 12.1% of children had neonatal Jaundice of 20(80%) for the cases and 5(20%) for the controls.

Table 2. Maternal Characteristics

Variables	Cases		Control		Total n (%)
	Frequency	Percentage	Frequency	Percentage	
Maternal residence					
Rural	75	48.1	81	51.9	156 (75.7)
Urban	28	56.0	22	44.0	50 (24.3)
Maternal age					
< 22 years	17	53.1	15	46.9	32 (15.5)
23-29 years	45	50.6	44	49.4	89 (43.2)
> 30 years	41	48.2	44	51.8	85 (41.3)
Antenatal visit					
Yes	98	53.6	85	46.4	183 (88.8)
No	5	21.7	18	78.3	23 (11.2)
Mother education					
Not educated	6	46.2	7	53.8	13 (6.3)
Primary	55	48.7	58	51.3	113 (54.9)
Secondary /University	42	52.5	38	47.5	80 (38.8)
Maternal smoking					
Yes	5	45.5	6	54.5	11 (5.3)
No	98	50.3	97	49.7	195 (94.7)
Maternal exposure to tobacco from husband					
Yes	42	52.5	38	47.5	80 (38.8)
No	61	48.4	65	51.6	126 (61.2)
Maternal exposure to tobacco smoke from others					
Yes	32	50.8	31	49.2	63 (30.6)
No	71	49.7	72	50.3	143 (69.4)
Maternal use of HDSC					
Yes	61	53.0	54	47.0	115 (55.8)
No	42	46.2	49	53.8	91 (44.2)
Gestational age					
<36 weeks	5	62.5	3	37.5	8 (3.9)
≥36 weeks	98	49.5	100	50.5	198 (96.1)
Maternal exposure to pesticides					
Yes	50	45.5	60	54.5	110 (53.4)
No	53	55.2	43	44.8	96 (46.6)
Maternal exposure to antibiotics					
Yes	65	50.4	64	49.6	129 (62.6)
No	38	49.4	39	50.6	77 (37.4)
Mode of delivery					
Vaginal	65	53.7	56	46.3	121 (58.7)
C-section	38	44.7	47	55.3	85 (41.3)

Source: Researcher (2022)

The findings from Table 2 show maternal characteristics of both cases and controls. The majority (75.7%) of study population were from rural area of them 75 (48.1%) were from cases and 81 (51.9%) were from controls group. A good number 89(43.2%) of mothers were aged between 23 to 29 years old. The majority of mother's attended ANC (88.8%) more than a half of mother (54.9%) had completed only primary education. Maternal smoking (5.3%), exposure to secondhand smoke from husband (38.8%) or form others (30.6%) were less common among mothers who participated in this study.

The finding revealed that 115(55.8%) of mothers had used hair dyes and straightening cosmetic during pregnancy and while breastfeeding, specifically 61(53 %) were from cases and 54(47%) were from controls. The findings also revealed that 50 (45.5%) for cases and 60 (54.5%) for controls were the mothers who got exposed to pesticides during pregnancy. Overall, 62.6% of mothers had been exposed to antibiotics during pregnancy; half of them (50.4%) were from cases. Regarding the mode of delivery, the study revealed that 41.3% of the mothers delivered by C-Section.

Birth outcomes associated with childhood leukemia

Table 3. Child related risk factors associated with leukemia

Variables	Crude Odd Ratio			Adjusted Odd Ratio		
	CoR	95%CI	P-value	AoR	95%CI	P-value
Age groups						
0-5	0.95	0.442-2.074	0.912	1.02	0.452-2.325	0.953
6-10	1.09	0.578-2.066	0.785	1.00	0.488-2.050	1.000
10-14	Ref.			Ref.		
Sex						
Boys	1.08	0.600-1.803	0.888	1.01	0.537-1.866	0.999
Girls	Ref.			Ref.		
Birth weight						
<2.5 kgs	1.39	0.624-3.117	0.417	1.34	0.569-3.159	0.502
>2.5	Ref			Ref.		
Gestational age						
Pre-term	1.70	0.396-7.310	0.475	1.75	0.317-9.640	0.521
Full term	Ref.			Ref.		
Cancer among relatives						
Yes	0.92	0.528-1.611	0.922	0.84	0.457-1.542	0.574
No	Ref.			Ref.		
APGAR						
6-8	1.00	0.398-2.515	1.00	0.96	0.346-2.708	0.951
9-10	Ref.			Ref.		
Congenital abnormalities						
Yes	0.91	0.381-2.160	0.907	1.22	0.471-3.184	0.678
No	Ref.			Ref.		
Asphyxia						
Yes	2.58	1.251-5.340	**0.010**	2.47	1.167-5.262	**0.018**
No	Ref.			Ref.		
Neonatal Jaundice						
Yes	4.72	1.699-13.132	**0.003**	5.05	1.738-14.664	**0.003**
No	Ref.			Ref.		
Oxygen administration						
Yes	0.788	0.430-1.445	0.441	0.72	0.375-1.409	0.345
No	Ref.			Ref.		

The findings presented in Table 3 show that birth asphyxia and Neonatal jaundice are birth outcome factors associated with Leukemia in both bivariate and multivariate analysis. No statistical significance observed within other birth outcomes and Leukemia in both bivariate and multivariate analysis. For asphyxia, it was revealed that for children who had had asphyxia during birth had about 3 times increased risks of getting childhood leukemia [AOR= 2.47, 95%CI: 1.167-5.262, P=0.018] compared to children without birth asphyxia. It was also shown that children who had suffered from Neonatal Jaundice were 5 times more at risk of getting leukemia [AOR= 5.05, 95%CI: 1.738-14.664, P=0.003]. Children with lower birth weight had 34% increased risk of childhood leukemia but no statistical significance observed in multivariable analysis. Similar findings were observed for children born with congenital abnormalities with 22% of increased risk of Leukemia compared to those without born without birth defects but no statistical significance observed. Despite, absence of statistical significance, pre-term babies had 75% increased risk of having childhood Leukemia compared to full term babies.

Maternal Factors associated with childhood leukemia in Rwanda

Table 4. Maternal related factors associated with childhood leukemia

Variables	Crude odd ratio			Adjusted odd ratio		
	AoR	**95%CI**	**P-value**	**AoR**	**95%CI**	**P-value**
Maternal residence						
Rural	0.728	0.383-1.381	0.330	0.88	0.392-2.005	0.773
Urban	Ref.			Ref.		
Maternal age						
≤ 22 years	1.21	0.539-2.746	0.637	0.99	0.390-2.527	0.787
23-29 years	1.09	0.606-1.989	0.759	1.27	0.634-2.550	0.498
30+ year	Ref.			Ref.		
Antenatal visit						
<4	0.24	0.086-0.677	**0.007**	4.97	1.703-14.505	**0.003**
≥4	Ref.			Ref		
Maternal education						
Not educated	0.77	0.239-2.512	0.672	0.59	0.154-2.257	0.441
Primary	0.85	0.484-1.522	0.600	0.82	0.402-1.664	0.578
Secondary and above				Ref		
Maternal smoking						
Yes	1.21	0.358-4.105	0.757	0.67	0.179-2.505	0.552
No	Ref.			Ref		
Maternal exposure to smoking from husband						
Yes	0.85	0.485-1.488	0.568	1.26	0.691-2.308	0.449
No	Ref.			Ref		

Source: Researcher (2022)

Table 4. Maternal related factors associated with childhood leukemia

	Crude odd ratio			Adjusted odd ratio		
Variables	**AoR**	**95%CI**	**P-value**	**AoR**	**95%CI**	**P-value**
Maternal exposure to smoking from other sources						
Yes	0.955	0.528-1.728	0.880	0.89	0.442-1.800	0.748
No	Ref.			Ref		
Maternal use of hair dyes and hair straightening cosmetics						
Yes	0.75	0.437-1.317	0.326	1.33	0.703-2.501	0.384
No	Ref.			Ref		
Exposure to pesticides						
Yes	1.48	0.853-2.564	0.163	0.62	0.333-1.159	0.135
No	Ref.			Ref		
Exposure to antibiotics						
Yes	0.95	0.546-1.687	0.885	1.04	0.533-2.012	0.918
No	Ref.			Ref		
Mode of delivery						
C-Section	1.43	0.822-2.506	0.203	0.58	0.310-1.076	0.084
Vaginal delivery	Ref.			Ref		

Source: Researcher (2022)

The findings presented in the Table 4 revealed that children born of mothers who did not attend recommended antenatal care visits had 5 times more likelihood to develop Leukemia [AoR= 4.79, 95% CI: 1.703-14.505, P=0.003] compared to those whose mothers had attended recommended ANC visits. The results from bivariate analysis showed that children born from mother who smoked during pregnancy had 21% risk of developing leukemia even if no statistical significance was observed. The results from multivariable analysis showed that children born to mothers who had been exposed to second hand smoke from their husbands during pregnancy had 26% increase risk of developing leukemia, but no statistical significance observed. Maternal use of hair dyes and hair straightening cosmetics increased the risk of childhood leukemia at 33% despite no statistical significance. In bivariate analysis, children born via C-section had 43% risk of developing leukemia compared to those born vaginally, however no statistical significance observed.

Discussion

This case control study reported important factors associated with childhood leukemia, these factors are birth asphyxia, neonatal jaundice and not attending recommended ANC. However, risk factors such as birth weight and congenital abnormalities as birth outcomes did not show any statistical significance. The risk factors such as maternal smoking and exposure to different substances including pesticides, hair dyes and straightening cosmetics were not associated with childhood Leukemia.

In line with the current findings, a study conducted in Norway showed that children who had had postpartum asphyxia had about 3 times increased risks of getting leukemia especially ALL whereby the OR was 2.57 at 95% CI (1.21-6.82).[16] The same study also confirmed that children who had had physiological jaundice suffered increased risk of getting childhood leukemia mainly ALL, whereby OR was 1.8; 95%CI; 1.2-2.8.

For congenital abnormalities like Down Syndrome, the same study confirmed that it was a protective factor though it didn't eliminate the increased risk associated with children born with asphyxia who had to get supplemental oxygen exposure (OR=2.4; 95%CI=1,2-4.7) which is in line with what the current study found. It was previously reported that birth asphyxia followed by re-oxygenation can potentially lead to development of cancer'[17] This might be due to that asphyxia is characterized by hypoxia (mild or severe oxygen deficiency) and the pH-values reduced below 7. Depending on the grade of oxygen deficits perinatal asphyxia causes either severe brain injury or subtle perturbations affecting further development of the central nervous system (CNS).[18] We did not find an association between birth weight and childhood cancer; in contrast a study conducted in Egypt confirmed that compared with the children having normal birth weight, children with high birth weight had increased risk of ALL (OR=1.33, 95%CI=1.20-1.49) whilst low birth weight was associated with decreased risk of ALL (OR=0.83,95%CI=0.75-0.92). Nevertheless, the current study didn't confirm low birth weight or high birth weight as a high risk of developing ALL or AML . [7] This difference is due to that only the 13.8% of children were born with low birth weight and none of them born with high birth weight. It is well known that high birth weight is not common in developing countries like Rwanda.

Several studies confirmed that children whose mothers had an exposure to pesticides and antibiotics during pregnancy were at greater risk of developing leukemia than controls. The same studies also reported the same increase with leukemia risks among children whose mothers had frequent prenatal exposure to pesticides from the garden and homes.[19,20] However, the current study did not confirm any of those risks, may be due to methodological approach and sample size. The current study confirmed the association between not attending the recommended number of antenatal care visits with increased risk of leukemia.

The current study has had some limitations. However, the main limitation of this study was the recall bias for both cases and controls especially on birth outcomes like APGAR and some medications taken during pregnancy as a maternal factor. This study also had a limitation of insufficient sample size and incomplete data from the records whereby the data about birth outcomes were not all available.

Conclusion

Birth asphyxia and neonatal jaundice were observed as birth outcomes associated with childhood leukemia. The study also confirmed that not attending recommended antenatal care visits may lead to development of childhood leukemia. Ministry of health needs to continue strategically implementing maternal, newborn and child health programs to improve pregnancy and birth outcomes. This study showed that birth asphyxia and neonatal jaundice are strongly associated with childhood leukemia. It was also confirmed by the same study that not attending the recommended antenatal care visits for pregnant mothers is associated with childhood leukemia. It is important for public and private stakeholders to invest in research in the evolving sector of oncology especially in children.Hospitals like Butaro Cancer referral hospital and other hospitals that receive cancer patients should focus on research and ensure that Rwanda and the region has enough evidence that can guide treatment and prevention in the oncology area.

Acknowledgement

We would like to thank all mothers who accepted to provide information about their children. Authors thank the management of Butaro Hospital who assist us to get the files of all patients

Conflict of interest

I declare that this thesis entitled "Birth Outcome and Maternal Risk Factors Associated with Childhood Leukemia in Rwanda: A case- Control Study" is our original research.

It was written by the listed authors and has not been submitted for publication in any other journal. Authors declare no conflict of interest.

Authors' contributions

FT designed the study, collected, analyzed, interpreted the data and writes a manuscript, MH and ER supervised the study, contributed to data analysis and manuscript writing. All authors read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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