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Adverse pregnancy outcomes among pregnant women with acute Rubella infections in Mwanza city, Tanzania

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ABSTRACT

Objective: This study investigated the adverse pregnancy outcomes among pregnant women with acute Rubella infections in the city of Mwanza, Tanzania.
Methods: A longitudinal study was conducted between 2014 and 2016 among pregnant women attending antenatal clinics. Women were screened for Rubella IgG and IgM antibodies using enzyme immunoassay (EIA). IgM seropositive pregnant women were followed up until the end of the pregnancy to determine Congenital Rubella Syndrome, congenital infections and other pregnancy outcomes.
Results: The median age of 685 enrolled pregnant women was 23 (IQR: 19–27) years. A total of 629(91.8%) were Rubella IgG seropositive while 61 (8.9%) were IgM seropositive. The IgM seropositivity was found to decrease significantly from first trimester to third trimester, $p < 0.001$. Forty six (83.6%) of 55 Rubella IgM seropositive women had adverse pregnancy outcomes and 6 (10.9%) delivered neonates with CRS, making the overall incidence of CRS to be 6/685 (0.87%). First trimester IgM seropositive women had significantly higher adverse pregnancy outcomes than those in second/third trimesters (70.4% vs. 35.7, $p = 0.01$).
Conclusion: There is one case of CRS in every 100 pregnancies necessitating additional strategies to reach a goal of elimination of CRS in developing countries.

Introduction

Rubella is an enveloped, single-stranded RNA positive sense virus of the genus *Rubivirus* in the family *Togaviridae* (Frey, 1994). The portal of entry of rubella virus is the respiratory epithelium of the nasopharynx possibly through myelin oligodendrocyte glycoprotein receptor (Cong et al., 2011). The virus invades the respiratory epithelium and then spreads hematogenously and replicates in the reticuloendothelial system. In the secondary viraemic phase, rubella virus can be detected in various body sites including lymph nodes, urine, cerebrospinal fluid (CSF), conjunctival sac, breast milk, synovial fluid, and lungs.

In susceptible pregnant women, especially when the virus is contracted during the first trimester, maternal viraemia frequently infects placental tissues and the foetus (Grillner et al., 1983). The virus then spreads through the vascular system of the developing foetus causing damage to blood vessels and developing organs. The teratogenicity of Rubella is due to several mechanisms such as direct cytopathic effects that trigger apoptosis and the arrest of the mitosis as the result of the derangements of the cytoskeleton, which lead to the arrest of the organ development. Another well described mechanism is the interactions of retinoblastoma (Rb) genes with viral products (putative replicase NSP90) which interfere with foetal cell growth (Lee and Bowden, 2000). These two mechanisms result into multiple organ defects referred to as Congenital Rubella Syndrome (CRS).

The disease is found worldwide with a seasonal distribution. However, little is known regarding the seasonality of Rubella cases especially in resource-limited countries. The data on confirmed cases by month of rash onset from different laboratories indicate that there are variations in Africa. In the Eastern African subregion, where Tanzania is located, there seems to be a biphasic seasonal pattern with peaks occurring in March–April and September–October (Goodson et al., 2011).

Rubella virus infection in early pregnancy has been associated with adverse pregnancy outcomes such as congenital Rubella syndrome (CRS), abortions, still birth etc. In high-income countries where strategic Rubella immunization has been implemented, the

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number of CRS cases have been extensively reduced and most of these countries are in the Rubella elimination phase (Noah and Fowle, 1988; Ukkonen and von Bonsdorff, 1988). However, Rubella remains a public health problem in most of resource constrained countries particularly in the sub-Saharan Africa (Binnicker et al., 2010; Katow, 1999).

In recent years, there have been increasing reports of congenital anomalies in most African countries with unidentified causes (Bickler and Sanno-Duanda, 2000; Mashuda et al., 2014; Ndibazza et al., 2011). Maternal infections such as syphilis and Rubella are a significant cause of congenital anomalies in low- and middle-income countries. By the year 2016, only 12 African countries had introduced Rubella vaccination in their national immunization programs to reduce incidences of acute Rubella virus infections and CRS cases (WHO, 2000). In Africa, the level of Rubella natural immunity has been found to be as high as 97.9% while in Tanzania particularly it has been found to be 92.6% among pregnant women and 93% among children and adolescents (Mirambo et al., 2017; Mwambe et al., 2014). Despite the reported high level of natural immunity, a significant proportion of child bearing aged women in Tanzania are still susceptible to acute Rubella virus infection that can lead to CRS (Mirambo et al., 2015; Mwambe et al., 2014). Previous studies in Africa (Mirambo et al., 2015) reported pregnant women with positive Rubella IgM antibodies indicating acute Rubella virus infections, however no follow up studies have been done to establish the associated adverse pregnancy outcomes. Data regarding outcomes of acute Rubella virus infection are limited in most of the resource limited countries. Previous studies (Mirambo et al., 2016; Mwambe et al., 2014) in Tanzania did not ascertain the adverse outcome of acute Rubella virus among pregnant women. Therefore, this study was undertaken to investigate the magnitude of Rubella virus infection and adverse outcomes associated with acute Rubella virus infection during the course of pregnancy in Tanzania.

Material and methods

Study design, setting, data and specimen collection

A longitudinal study was conducted between 2014 and 2016 among pregnant women attending Karume and Makongoro antenatal clinics, in the city of Mwanza, Tanzania. Pregnant women were enrolled randomly. Sociodemographic and other relevant clinical data were collected using structured data collection tool. About 5 ml of blood sample was collected using plain vacutainer tube (BD®, Nairobi, Kenya) from each consented participant and transported to the Catholic University of Health and Allied sciences (CUHAS) multipurpose laboratory for further processing.

The sample size

Sample size was estimated by Kish Leslie formula using prevalence of 50% in order to obtain maximum sample size. In order to obtain at least 30 women required to have a significant proportion, a total of 685 pregnant women were enrolled. Regarding the outcome of pregnancy among Rubella IgM seropositive pregnant women, we intended to follow up at least 50% of positive women to provide description of the adverse pregnancy outcomes.

Detection of rubella antibodies

Sera were tested for specific Rubella IgG and IgM using commercially available indirect enzyme-linked immunosorbent assay (ELISA) (Chem Well® 2910-Awareness Technology Inc., USA) according to manufacturer's instructions. As per WHO standards, Rubella IgG titers of $\geq$10 IU/mL was considered as positive and a pregnant woman was presumed to be naturally immune; whereas the index value of $\geq$1.1 was considered Rubella IgM seropositive signifying recent or acute infection as per manufacturer guidelines. The sensitivity and specificity of IgG ELISA used was >99% (Field et al., 1988; Rawls and Chernesky, 1976) while for IgM, sensitivity was 97.6% with specificity of 99.3% (Chernesky et al., 1984). Randomly selected 300 positive samples and 30 negative samples were re-tested at Institute of Microbiology Gottingen, Germany using AxSYM rubella virus IgG/IgM-MEIA (Abbott, IL, USA) as quality control.

Follow-ups of the participants

Telephone numbers for each participant were taken and an orange coloured sticker was placed on antenatal card of each participant for easy identification when they come for delivery. In addition, they were also asked to report their participation to the study as soon as they come for delivery. After every 2 weeks telephone conversations and text messages were made to follow up the status of the pregnancy. Most of these women had a plan to deliver at Bugando medical centre (BMC), Karume health centre, Sekou Toure regional hospital and Nyamagana hospital. Daily communication was made to a study nurse in each of these hospitals to ensure data and samples were taken.

Outcomes measures

New-borns of pregnant women who were IgM seropositive were assessed and gestation age at delivery, birth weight, viability, presence or absence of obvious congenital anomalies and other clinical presentations such as jaundice (yellowish or greenish pigmentation of the skin and whites of the eyes) were noted. Data regarding abortion and stillbirth were also collected. Neonates suspected to have congenital heart diseases were referred to the Bugando Medical Centre where further clinical examination was done by paediatrician followed by echocardiogram.

Cord blood samples of the neonates were tested for the presence of specific Rubella IgM antibodies. The CRS and congenital Rubella virus infections were defined as per Centre for Disease Control and Prevention (CDC) guidelines (Roush et al., 2008); in which the presence of Rubella specific IgM antibodies and features such as cataracts or congenital glaucoma, congenital heart diseases, hearing impairment, or pigmentary retinopathy confirm the CRS while the IgM seropositivity without features suggestive of CRS confirms Rubella congenital infections.

In the current study low birth weight was defined as weight at birth of less than 2,500 grams. Abortion was defined as pregnancy termination prior to 28 weeks gestation and stillbirth was defined as a baby born with no signs of life at or after 28 weeks gestation.

Data analysis

All data collected from this study were entered in the Microsoft Office Excel 2007 and later transferred and analysed using STATA version 13 (StataCorp LLC, College Station, Texas USATexas.co). Categorical variables such as residence, marital status, occupation, education level, gravidity and trimesters were summarized as proportions while age and gestation age were summarized as median and its interquartile range. Pearson chi^2 was used to test statistical difference of adverse outcomes between IgM seropositive pregnant women in the first and second/third trimesters while Fisher's exact test was used to compare the difference of parity and IgM seropositivity. The Kruskal–Wallis equality-of-populations was used to compare the median age in different trimesters and

Ranksum–Mann Whitney test was done to compare median gestation age of women with normal baby and those with adverse pregnancy outcomes/Rubella congenital infections. The 95% confidence interval was determined using Two-sample test of proportion. A p value of less than 0.05 was considered statistically significant.

Results

Socio-demographic characteristics

The median age of 685 pregnant women enrolled in this study was 23 (IQR: 19–27) years with median gestation age of 20 (IQR: 13–27) weeks at enrolment. The majority of participants 465 (67.9%) were residing in rural areas with the majority 490 (71.6%) having primary education (Table 1). About half of the women, 331 (48.3%) were in the second trimester while 315 (46%) were multigravid. The median age of pregnant women in the first trimester was 23 (IQR: 20-27) years, 22 (IQR: 19–27) years for the second trimester and 24 (IQR: 2.5–28) years for the third trimester. On Kruskal–Wallis equality-of-populations rank test the differences of median ages by gestation ages were statistically significant (P = 0.019). The median gestation age of seronegative pregnant women at the time of IgG testing was 19.5 (IQR: 12–25.5) weeks.

Seroprevalence of Rubella virus specific antibodies

In 685 pregnant women enrolled and investigated, 629 (91.8, 95% CI: 89–94) were Rubella IgG seropositive while 61 (8.9%, 95% CI: 6–11) were seropositive for Rubella IgM antibodies. A total of 572 (83.5%) were IgG seropositive only, while 4 were IgM seropositive only. Fifty seven (8.3%) pregnant women had both Rubella IgM and IgG while 52 (7.5%) were seronegative (no detectable IgG and IgM) and thus susceptible to Rubella virus infection.

IgG seropositivity was 154/174 (88.5%), 305/331 (92.2%) and 170/180 (94.4%) among women in the first, second and third trimester, respectively ($Chi^2 = 4.244$, p = 0.120). Regarding the IgM seropositivity in relation to trimesters; 33/174 (18.9%), 22/331 (6.6%) and 6/180 (3.3%) of pregnant women in the first, second and third trimester, respectively ($Chi^2 = 30.6794$, $p < 0.001$) were seropositive for Rubella IgM antibodies.

Table 1
Sociodemographic and obstetrics characteristics of the enrolled antenatal attendees in Mwanza city.

Characteristics	Frequency/median	Percentage
Age (years)	**Median 23 (IQR: 19–27)**	
Gestation age (weeks)	**Median 20 (IQR: 13–27)**	
Residence		
Rural	465	67.9
Urban	220	32.1
Education		
Tertiary/secondary	153	22.3
Primary	490	71.6
Illiterate	42	6.1
Marital status		
Single	91	13.3
Married	594	86.7
Occupation		
Small scale business women	452	66.0
Housewife	187	27.3
Employed	46	6.7
Gravidity		
Primagravid	286	41.7
Multigravid	315	46.0
Grandmultigravid	84	12.3
Trimester		
First	174	25.4
Second	331	48.3
Third	180	26.3

Bold highlighted cases with confirmed CRS and those with loss to follow up.

Rubella adverse outcomes among 61 Rubella IgM seropositive women

A total of 61 pregnant women were found to have acute rubella virus infection in different gestation ages at the time of enrolment. The median gestation age at the time of IgM testing was 14 (IQR: 10–19) weeks. Out of 61 women 6 (9.8%) could not be reached during follow up; some provided wrong numbers, some were not answering the phones or text messages and some shifted to another residence for delivery (Figure 1). The remaining 55 women were followed until the end of the pregnancy; of the 55 women; 27 were in the first trimester while 28 were in the second/third trimesters. Six (10.9%) women were confirmed to have newborns with CRS out of 55 women followed, making the overall incidence of CRS as 6/685 (0.87%). All cases of CRS were from women who were Rubella IgM seropositive in the first trimester of the pregnancy. Overall, out of 55 women with acute rubella infections, 46 (83.6%) had adverse pregnancy outcome including low birth weight, congenital rubella infections or congenital abnormalities (Tables 2 and 3). The overall cumulative incidence of Rubella congenital infections was 29/55 (52.7%). The rates of Rubella congenital infection by trimesters were; 16/27 (59.1%) for the first trimester, 6/18 (33%) for the second trimester and 7/10 (70%) for the third trimester.

It was further observed that, the median gestation age at the time of Rubella diagnosis of IgM seropositive women with good pregnancy outcome was 18.5 (IQR: 12.5–28) compared to 12 (IQR; 10–15) weeks of IgM seropositive women with adverse pregnancy outcome (p = 0.001). Further analysis revealed that out of 27 IgM seropositive women in the first trimester, 19 (70.4%), 95%CI: 53–87, had adverse pregnancy outcomes compared to 10 (35.7%) 95% CI: 17.9–53.4; of 28 pregnant women in second/third trimesters (p = 0.01). The rate of rubella transmission during the first trimester was 76% while that in the second/third trimester was 56% ($Chi^2 = 1.8900$, p = 0.169).

A total of 49 women had term delivery and 6/55 (10.9%) had abortion. The median gestation age of the women who had term delivery was 39 (IQR 38–39) weeks. The median birth weight of neonates with rubella congenital infections was 2700 (IQR: 2500–2900) grams while that of neonates with no rubella congenital infections was 3300 (IQR: 2400–3700) grams; two-sample Wilcoxon rank-sum (Mann–Whitney) test, p = 0.031.

Discussion

In Tanzania, the Rubella vaccination in the national immunization programme was introduced in 2015, targeting only children with no community vaccination programme. Additionally, the coverage of Measles first dose vaccine was around 80% with some regions reported below 80% (Semali, 2010). It should be noted that the main prerequisite, prior to the introduction of the Rubella vaccine, is to achieve a first dose Measles vaccine coverage of not lower than 80% (Publication, 2011). Introducing the Rubella vaccine when the Measles vaccine coverage is low may result into a shift of average age exposure due to the presence of non-immune individuals and eventually increase the prevalence of CRS.

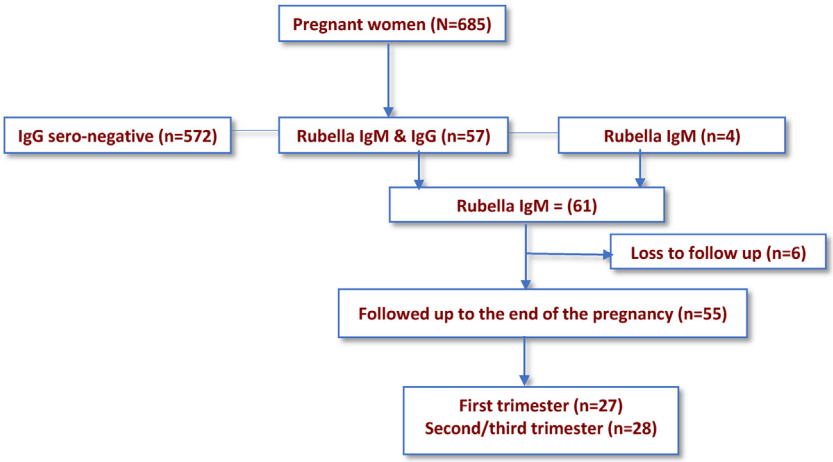

Figure 1. Flow chart regarding follow up.

Table 2
Outcome of pregnancy among 29 IgM seropositive pregnant women in their first trimester.

Age (years)	Gestation age at IgM testing	Neonatal pregnancy outcomes	Rubella IgM in cord blood at delivery	Gestation age at delivery (weeks)
20	10	Stillbirth, Abnormal baby	**Not done**	39
22	10	Congenital infections	**Positive**	38
25	11	Congenital infections	**Positive**	39
36	10	Congenital infections	**Positive**	40
25	7	Abortion	**Not done**	23
24	12	Low birth weight, Congenital infections	**Positive**	39
23	9	Low birth weight, Congenital infections	**Positive**	39
19	8	**Confirmed CRS** (CHD)	**Positive**	39
19	13	Low birth weight	**Negative**	40
20	12	**Confirmed CRS** (Cataract)	**Positive**	37
20	13	Congenital infections	**Positive**	38
27	9	Neonatal Jaundice	**Negative**	40
19	13	Normal baby	**Negative**	39
35	9	Congenital infections	**Positive**	38
28	10	**Confirmed CRS**(CHD)	**Positive**	40
28	10	Low birth weight, Congenital infections	**Positive**	38
30	10	**Confirmed CRS** (Cataract)	**Positive**	40
18	11	**Confirmed CRS** (CHD)	**Positive**	38
22	6	Abortion	**Not done**	18
25	12	*Loss to follow up*	**N/A**	NA
17	8	Neonatal Jaundice	**Negative**	38
21	12	Abortion	**Not done**	20
24	9	Neonatal Jaundice	**Positive**	38
30	11	Congenital infections	**Positive**	39
35	10	*Loss to follow up*	**N/A**	NA
22	10	**Confirmed CRS** (Cataract)	**Positive**	38
19	11	Stillbirth (spinal bifida)	**Not done**	39
19	8	Stillbirth (Omphalocele)	**Not done**	**38**
19	13	Low birth weight	**Negative**	**37**

Bold highlighted cases with confirmed CRS and those with loss to follow up.

This is the first study in Tanzania to document the outcomes of Rubella virus infection among pregnant women. In the present study, the IgM seropositivity was found to decrease significantly as gestation age increases. The higher Rubella IgM seropositivity in the first and second trimesters could be explained by the fact that women in the first and second trimesters were significantly younger than those in third trimester. Younger age has been associated with a high risk for acute Rubella virus infection, due to the fact that most of these women are still susceptible to Rubella virus infection as previously documented (Lawn et al., 2000).

Another important observation in the current study is that the majority (84%) of women who were Rubella IgM seropositive during pregnancy were found to have adverse pregnancy outcomes characterized by spontaneous abortion, stillbirths, congenital heart diseases, congenital cataracts and low birth weight with six of them confirmed to be CRS cases. Watson-Jones et al. (2007) observed various adverse pregnancy outcomes to range from 2.7% to 12% in a large cohort in Tanzania; therefore the overall adverse pregnancy outcomes in this cohort is significantly high. However; in relation to abortion (miscarriage) the observed prevalence is comparable to that of the general pregnant women population (Keogh et al., 2015). Apart from six cases of CRS which were confirmed in this study; it was difficult to directly link the presence of Rubella virus infections and other documented adverse pregnancy outcome such as low birth weight. Nevertheless, rubella infections during pregnancy can lead to varieties of pregnancy outcomes due to devastating teratogenic effects of the Rubella virus (Waldorf and McAdams, 2013). Previous reports documented low birth weight in about 23–85% of newborns with CRS (Feigin and Cherry, 2009; Reef et al., 2000), this could be

Table 3
Outcome of pregnancy among 32 IgM seropositive pregnant women in second and third trimesters.

Age (years)	Gestation age at IgM testing	Neonatal Pregnancy outcome	Rubella IgM in cord blood at delivery	Gestation age at delivery
18	23	*Loss to follow up*	**N/A**	**N/A**
17	19	Normal baby	Negative	39
17	28	Low birth weight	Negative	38
19	30	Congenital infections	Positive	39
20	30	Congenital infections	Positive	40
21	16	Normal baby	Negative	38
22	15	Congenital infections	Positive	38
28	15	Omphalocele, Congenital infections	Positive	38
20	16	Abortion	Not done	20
21	24	Normal baby	Negative	39
19	30	Congenital infections	Positive	39
28	14	Low birth weight	Negative	37
24	14	*Loss to follow up*	**N/A**	**N/A**
21	15	Abortion	Not done	23
35	30	Normal baby	Negative	39
20	28	Congenital infections	Positive	38
27	32	Congenital infections	Positive	38
22	18	Normal baby	Negative	38
20	16	Low birth weight, Congenital infections	Positive	39
21	15	Low birth weight	Negative	39
23	18	Normal baby	Negative	40
35	16	Low birth weight, Congenital infections	Positive	38
22	26	Normal baby	Negative	38
30	28	Normal baby, congenital infections	Positive	39
22	14	Congenital infections	Positive	40
22	15	Abortion	Not done	24
18	23	Normal baby	Not done	39
17	19	*Loss to follow up*	**N/A**	**N/A**
17	28	congenital infections	Positive	40
19	30	Stillbirth, normal	Not done	41
20	14	Low birth weight, Congenital infections	Positive	38
36	27	*Loss to follow up*	**N/A**	**N/A**

explained by the fact that Rubella infection during pregnancy can lead to placental insufficiency (Waldorf and McAdams, 2013). Due to this limitation of the failure to establish attributable risk of the Rubella virus to the adverse pregnancy outcomes, there is a need for further studies to establish the attributable risk of infections in relation to pregnancy outcomes.

Comparing pregnant women in their first trimester and those in the second/third trimester, significantly more adverse pregnancy outcomes were observed in women in their first trimester with all six confirmed CRS cases coming from this group. Previous studies have documented that about 90% of women contracting Rubella infections in the first trimester will end up with adverse pregnancy (Miller et al., 1982; Peckham et al., 2006; Reese, 1944; Robertson et al., 2003; WHO, 2000). In the current study, this observation is further supported by the fact that women with adverse pregnancy outcome had significantly lower gestation age at the time of Rubella diagnosis than those with normal pregnancy outcomes. As documented previously, Rubella transmission rates were higher in the first trimester/third trimesters than in the second trimester (Miller et al., 1982).

The data from this study underscore the importance of screening and vaccinating child bearing aged women so as to reduce the Rubella associated adverse outcomes. This additional strategy in developing countries is highly needed due to the fact that management of CRS cases have been found to be more costly than preventing CRS (WHO, 2011). The cost of managing CRS case in upper and middle income countries has been found to range from 4261 to 57010 USD per year and is estimated to be high in resource limited countries (Babigumira et al., 2013). Combination of strategies that includes vaccinating children below five years of age, susceptible adolescent girls, and a strategy of screening and vaccinating pregnant women after delivery has been found to reduce CRS to a greater extent than vaccinating only children below five years of age (Bjerregaard, 1990; Gudnadóttir, 1985).

One of the major limitations in this study is underestimation of CRS cases due to the fact that these neonates were not tested for hearing impairment, as it is difficult to assess hearing impairment during infancy. Hearing impairment has been found to be the commonest feature in CRS cases (Duszak, 2009). In addition, the lack of follow-up of children after delivery might also contribute to the underestimation.

In conclusion, there is a high Rubella transmission rate in the studied population which contributes to the increased cases of congenital anomalies including CRS. Despite a good strategy of vaccinating children below five years of age in Tanzania, there is a paramount need to consider additional strategies to reach a goal of CRS elimination.

Contributions

MMM, SEM, SA and UG participated in the design of the work. MMM, MM participated in the collection of specimens and clinical data. MMM and SEM performed serological tests. MMM, MM and SEM analysed and interpreted the data. MMM wrote the first draft of the manuscript. SEM, SA, MM and UG did critical review of the manuscript which was approved by all authors.

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Ethical approval

The protocol for conducting this study was approved by a Joint Catholic University of Health and Allied Sciences/Bugando Medical Centre (CUHAS/BMC) research ethics and review committee with certificate no: CREC/043/2014. Permission was sought from

hospital/clinics administration. Written informed consent was obtained from each participant/parent/guardian/husband prior recruitment to the study.

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Conflict of interest statement

No conflict of interest to declare.

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