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# RELATIONSHIP BETWEEN SELENIUM DEFICIENCY AND VULNERABILITY TO EBOLAVIRUS DISEASE IN BENI, DRC

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## ABSTRACT

In Ebola patients, selenium aids in regulating blood clotting and possibly assist in coagulopathy properties of the Ebola haemorrhagic fever. Therefore, the objectives of this study were to determine the Selenium levels of people living in Beni, DRC and whether there is an association between Ebola vulnerability and selenium deficiency.This was a case control study with cases being Ebola virus disease survivors and controls were their contact persons during the time of infection. Students t-test were computed to determine if there exist a significant difference in the population means selenium levels in the case group and control group. Logistic regression analysis model was fitted into the data to determine the association between selenium deficiency and vulnerability to EVD adjusting for demographic and socio-economic factors.The mean difference in selenium levels of non - survivors was higher than that of survivors. A t-test conducted suggested that this difference in mean was statistically significant with p-value less than 0.05 (0.00181). The odds of getting infected by Ebola while having normal selenium levels, is 3.47 (confidence interval, 1.30 - 10.21) times higher than when one has high selenium levels after adjusting for all other covariates as mentioned above.There was a statistically significant relationship between Ebola vulnerability and selenium deficiency.



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# INTRODUCTION

More than two billion people are affected by micronutrients deficiency (1). This is for both industrialized and developing countries and the main nutrients that are deficient are vitamins and minerals which are usually required in small (micrograms and milligrams) amounts for good health (2). A high-quality diet is characterized by micronutrients and will go a long way in ensuring good health. Micronutrients are required in very small amounts but acts as building blocks for healthy bones, brain and body and also a strong immune system (3). Some of the important micronutrients needed in the body include iron, iodine, zinc, selenium, fluorine, calcium and vitamins A, B6, B12, B1, B2,B3 and C (4). Great importance is given to selenium as it is necessary for the proper functioning of the immune, endocrine and cardiovascular system (5).Selenium aids body processes such as DNA synthesis, thyroid hormone metabolism, protection against infections and reproduction. The highest concentration of selenium in the body is found in the thyroid which is included in the endocrine system (6). Availability of selenium in the system supports growth, healthy muscle activity, immune system, reproductive organs, cuts the toxicity levels of some toxic elements including mercury and has been shown to reduce the spread of viruses such as influenza, HIV and Ebola (7). In Ebola patients, selenium aids in regulating blood clotting and possibly assist in coagulopathy properties of the Ebola haemorrhagic fever (Taylor *et al*, 2016). Increasing the amounts of selenium taken during illness is expected to decrease the bad effects of Ebola virus disease in the patient. On the other hand, selenium deficiency is predicted to increase the risk of death (8). However, less is known on whether vulnerability to the disease is associated with selenium deficiency Africa is reported to have a low supply of Selenium in the diet of its population (9). This is according to a Liberian study that reported that average selenium intake was estimated to be 23µg. Previous studies in the DRC has also shown high levels of malnutrition due to lack of food which owes to the frequent attacks by rebel movements, ethnic rivalry, attack from militias and armies, land disputes and demographic pressures (10). In 2018 for example, malnutrition was reported in 66/463 health zones (11). Furthermore, 5% Of the DRC population, in 2016 to 2018, fled from their homes due to lack of food with hunger in the area increasing by approximately 70% and 87% of the internally displaced persons surviving with only one meal a day(12). The DRC in general is living in condition that its population cannot have enough selenium in its dailydiet and Selenium deficiency remain less known and could be consideredin emergency supplementation.There fore, the objectives of this study were to determine the Selenium levels of people living in Beni, DRC and whether there is an association between Ebola vulnerability and selenium deficiency.

# METHODS

***Study design:*** This was a case control study with a treatment and control group. Cases were Ebola virus disease survivors and controls were their contact persons during the time of infection. The contacts were chosen as controls considering that they had high chances of infection but were not infected. The role of selenium in the vulnerability to EVD was investigated. Vulnerability to EVD was the dependent variable determined by whether one eventually got infected or not and the independent variable being the level of selenium in urine and accounting for demographicandsocio-economic factors.

**Sampling Technique and Sample Size Determination:** The following formula was used for sample size calculation (13):

$$n = \frac{r+1}{r}\frac{p_1(1-p_1)+p_2(1-p_2)*(Z_{\alpha/2+}Z_\beta)^2}{(p_1-p_2)^2}$$

$n =$ Desired sample size
$r$ = Ratio of control to cases: 1:1 = 1
$p_1$= Assumed average proportion in case arm: 0.5
$p_2$= Assumed proportion in control arm: 0.3
$Z_\beta$= Power of the study: 80% = 0.84 from standard normal table
$z_{\frac{\alpha}{2}}$= Level of significance: 5% = 1.96 from standard normal table

$$n = \frac{1+1}{1}\frac{0.5(1-0.5)+0.3(1-0.3)*(1.96+0.84)^2}{(0.5-0.3)^2}$$

$$= 2\frac{0.25+0.21*7.84}{0.04}$$

$\approx$ 95 per group

Therefore, 95 participants were sampled to the treatment group and 95 to the control group.

**Inclusion Criteria and Exclusion Criteria:** Respondents had to meet the following criteria in order to be included in the study

- Patients aged between 18 to 65 years and are registered with the EVD survivors association.
- People who had been exposed to EVD but not infected. These are basically those who came in contact with the infected.
- The person must have been a resident of Beni area six months before the study begun.
- Those who consent to participating in the study.
- Suspected EVD cases
- Those with active EVD infections.

**Below were the conditions for exclusion for the study:**

- People less than 18 years and those who are above 65 years.
- Those not registered with the EVD survivors association
- Those not infected or included in the contact list of the infected.
- Those who did not consent to participate in the study
- Non- residents of Beni area six months before the beginning of the study.
- Data Collection and analysis

**Both qualitative and quantitative data were collected using the following methods:**

1. **Questionnaires:** a questionnaire was developed and answered questions on demographic and socio-demographic status of the participant The structured questionnaires were given to study participants, health workers, laboratory technicians and nutritionists who have worked with EVD patients in Ebola treatment centers.
2. **Urine samples:** Samples of urine from study participants were collected and stored in 250 ml screwed caps. These were then frozen within one hour of collection and stored at a temperature of $20^0$for utmost eight hours before ferrying to the Catholic University of Graben central laboratory where it will be kept at $80^0$C temperatures. Barcodes were used to name the samples. The following procedures were used to collect urine samples from the patient:
   a) Consent was obtained from the patient after explaining all the procedures and why the sample is needed.
   b) Procedures of how to collect the sample without contaminating it were then outlined to the patient. Assistance was given to those experiencing difficulties.
   c) A suitable place where the sample could be collected was identified: a clean washroom that maintains the privacy of the participant.
   d) In cases where one was given company, there was use of gloves and washing of hands when handling the collected specimen.
   e) The patient was then asked to clean their hands with water and soap so as to avoid contamination.
   f) Patients who offered their specimen were asked to clean their genitals well using water and soap, disinfectant or 0.9% sodium chloride solution. Male patients who were not circumcised were asked to pull back the foreskin during cleaning. Females likewise separated the labia using fingers and wiped backwards using clean swabs.
   g) Men were advised to keep the foreskin back as they passed the urine and the first 15- 30 ml was directed to the toilet as this ensured that the bacteria in the urethra was washed out. Women did the same with the labia passing some urine to the toilet the rest to the container.
   h) It was during mid-urination that the sample was collected and the rest was allowed into the toilet
   i) Documentation of the specimen was then completed
   j) The specimen was then placed in a sterile container.
   k) Hands were thereafter sanitized and
   l) The specimen sent to the laboratory soon after collection

***Urine Analysis:*** Once the collected urine samples had been transported in cool boxes ($20^0$C) to the laboratory, measurement of selenium was done in Hydrogen to decrease polyatomic interferences resulting from 78Se. Internal standardization was achieved by simultaneously introducing tellurium (Te) through a T-piece (14). Selenium levels were then determined by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method. Determination of the element in the sample was determined following *10 dilution in 0.5% v/v HCL, 1% v/v $HNO^3$ by use of an Agilent 7500cx series ICP-MS machine.

***Statistical Data Analysis:*** Concentration of selenium in urine were compared to a standard selenium biomarker for status that is commonly used (14). The standard international units for selenium concentration in urine is µg $mL^{-1}$. All data and laboratory results were coded and entered into R statistical software for analysis. Students t-test were computed to determine if there exist a significant difference in the population means selenium levels in the case group and control group. Logistic regression analysis model was fitted into the data to determine the association between selenium deficiency and vulnerability to EVD adjusting for demographic and socio-economic factors.

***Ethics Consideration:*** Following preliminary acceptance given by Ministry of Health and agriculture, study procedures and implication were explained to selected respondents, verbal and written consent was be sought to carry out the study. Any concerns raised by the respondents were addressed and the researcher assured them that all information they gave were handled with care and used for study purposes only and no name would be written on the questionnaire. They were also assured that the data collected will be well kept by the researcher.

# RESULTS

***Exploratory analysis:*** A total of 190 participants took part in the study with 95 falling in the treatment group and 95 in the control group. Majority of the survivors who were interviewed were between the age of 26 to 30 years old (29.5%) followed by those in the range of between 18 to 25 years (26.3%). For non-infected, most of the study participants were between the age of 18 to 25 years (30.5%) followed by 26 to 30 years (25.3%) as summarized in Figure 1.

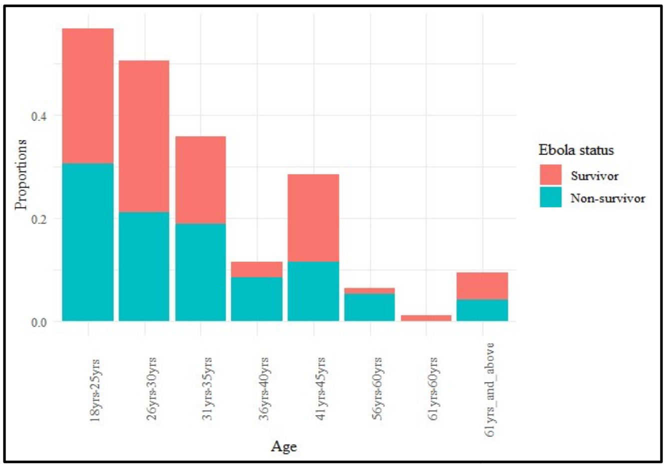
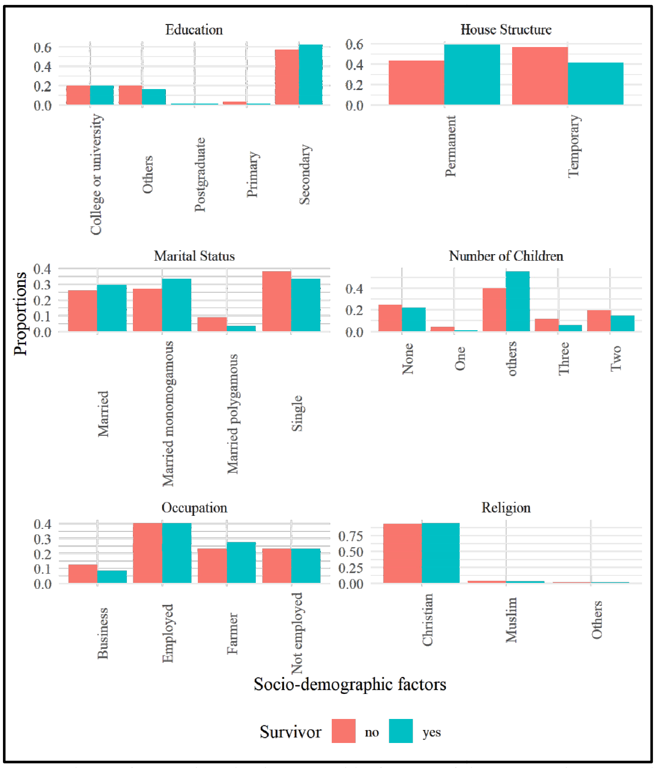



**Figure 1. Age distribution of survivor and non-infected**




A comparison of several socio-demographic factors of the two study groups is as shown in Figure 2.

**Figure 2. Comparison of socio-demographic factors among survivors and non survivors**

As visualized in Figure 2, most of the study participants from both groups attained secondary school education and only a few had primary and postgraduate education. More than 60% of the survivors had attained secondary education when compared to non survivors who were less. Forty three percent of non survivors lived in a permanent house structure compared to the 59% of survivors.

***Concentration of Seleniumin the Urine of Recovered andNon-Infected Patients in Beni, North-Kivu:*** Samples of urine were taken as described in previously and tested for selenium levels in the public health laboratory – Kivu Ami. Normal ranges of selenium content in urine were taken to be 10µg to 50µg/24 hours and any values above or below this range were considered high or low respectively. Summary statistics for selenium levels in the urine of both survivors and non-infected is as shown in Table 3.

**Table 3. Summary statistics for selenium levels in survivors and non-infected**

| | | non-infected (n = 95) | non survivors (n = 95) |
|---|---|---|---|
| Mean selenium levels (standard deviation) | Male | 28 µg(17.2) | 40.3 µg (14.6) |
| | Female | 28.4 µg (15.1) | 40.1 µg (11.8) |
| | Total | 28.2µg (16.1) | 40.2µg (12.9) |
| Number with normal selenium levels | Male | 42/85 (50.6%) | 27/71 (38.0%) |
| | Female | 43/85 (49.4%) | 44/71 (62.00%) |
| | Total | 85/95 (86.7%) | 71/95(77.2%) |
| Number with high selenium levels | Male | 7/13 (53.8%) | 9/21 (42.9%) |
| | Female | 6/13 (46.2%) | 12/21 (57.1%) |
| | Total | 13/95 (13.3%) | 21/95 (22.8%) |

From Table 3, the mean difference in selenium levels of non - survivors was higher than that of survivors. A t-test conducted suggested that this difference in mean was statistically significant with p-value less than 0.05 (0.00181).

**Selenium deficiency and vulnerability to Ebola virus:** A logistic regression model fitted to determine the relationship between selenium deficiency and vulnerability to Ebola yielded results summarised in Table 5. There was a statistically significant relationship between selenium deficiency and vulnerability to Ebola virus after adjusting for socio demographic, demographic, environmental and type of food eaten. Precisely, the odds of getting infected by Ebola while having normal selenium levels, is 3.47 (confidence interval, 1.30 - 10.21) times higher than when one has high selenium levels after adjusting for all other covariates as mentioned above. In addition, the odds of getting infected while being polygamous and when the education level was primary is respectively 0.15 (confidence interval, 0.01 - 0.99) and 0.24 (confidence interval, 0.05 - 0.88) times lower than when one is married to one wife and when one had their education level being university.

**Table 5. Logistic regression model for selenium deficiency and vulnerability to Ebola and adjusted for other covariates**

| | | Odds ratios | 95% CI | P-value |
|---|---|---|---|---|
| | (Intercept) | 0.8 | 0.09 – 6.31 | 0.8337 |
| Gender | Male | 1.03 | 0.48 - 2.20 | 0.934212 |
| Marital status | Polygamous | 0.15 | 0.01 - 0.99 | 0.061183 |
| | Single | 0.76 | 0.30 - 1.85 | 0.546347 |
| Education | Primary | 0.24 | 0.05 - 0.88 | 0.037554 |
| | Secondary | 0.56 | 0.22 - 1.38 | 0.214456 |
| Occupation | Employed | 1.05 | 0.25 - 4.44 | 0.944694 |
| | Farmer | 1.58 | 0.38 - 6.69 | 0.527506 |
| | Not employed | 1 | 0.22 - 4.61 | 0.995834 |
| Religion | Muslim | 7.53 | 0.83 - 92.19 | 0.08161 |
| | Other religions | 8.12 | 0.59 - 152.82 | 0.119965 |
| House structure | Temporary | 0.53 | 0.23 - 1.20 | 0.135207 |
| Selenium content | Normal | 3.47 | 1.30 - 10.21 | 0.016515 |

Among the key informants who were interviewed were two nurses, two lab technicians and one medical doctor. They described selenium as a mineral whose deficiency occurs when the levels in urine is less than the normal ranges (10 - 50 micrograms per 24 hours).

Selenium was termed as important as any other mineral as it strengthens the immune system, protects against diseases and aids in the development of organs. Specific to the Ebola virus, selenium was identified as important in the prevention of bleeding as it aids to prevent coagulopathy, a condition that results in excess bleeding. According to the key informants, selenium deficiency in the human body and the amounts available in food is determined by a lab test. In humans, the levels are determined by taking urine samples to the lab and getting them tested by a qualified lab technician. Once a person has been infected with the Ebola virus, the key informants pointed out that selenium helped by strengthening the patient's immune system and promoted treatment. Selenium works along other minerals that fortifies the body during illness and also ensures that different elements in the body are well balanced. In Ebola treatment centres, patients received a balanced diet comprising of proteins, carbohydrates, vitamins, minerals and water. Foods were majorly served three times a day during breakfast, lunch and super. The key informants who were interviewed identified some of the common characteristics of Ebola patients as: vomiting, fever, fatigue, asthenia, headache, trauma, stress, articular pain, diarrhoea, bleeding, abdominal pain, anxiety among others. Selenium was agreed to be important in the prevention of Ebola and its deficiency implied an unbalanced diet which could contribute to many other diseases. Among the factors that were identified to determine vulnerability to Ebola includes: poverty and lack of food, contact with Ebola patients, non-adherence to the preventive measures that are in place, stress, and war which prevented people from living healthy lives. Ebola patients faced rejection and stigma from family members and the community as a whole.

# DISCUSSION

This was a case control study investigating the role of selenium in the vulnerability to Ebola Virus disease in Beni area. Study participants were 95 Ebola virus survivors and 95 who had been in contact with Ebola patients but were not infected. The study participants were probed to identify their demographic characteristics, environmental and socio-demographic features and the type of food that they ate. Analysis of the amount of selenium in the urine of study participants from both study groups showed a significantly higher level for non-infected compared to survivors. Normal ranges of selenium are expected to be between 10 and 50 µg per 24 hours. Mean selenium levels for non-infected were 40.2 µg while that of survivors was 28.2 µg per 24 hours as summarized in Table 4.1. Moreover, higher percentage of non-infected had high levels of selenium in their urine (22.8%) compared to survivors (13.3%). A high value is more than 50 µg per 24 hours. A difference in mean statistical test for the two groups confirmed it to be statistically significant. According to Hays and team in a paper written in 2014, selenium levels in human beings can be determined by testing its availability in urine (15).. This study took urine samples from participants and tested for selenium levels in the lab. This was then used to identify whether a person had high or low levels of the mineral. Normal levels of selenium were taken to be between 10 to 50 µg per 24 hours. This study found that the mean selenium levels of Ebola survivors was lower than that of non-infected and this suggests that selenium had a role to play in protecting the non-infected as was suggested by Lyon in 2014 (16). In their study, Lyon identified that having high levels of selenium would aid in the healing process and prevention of Ebola.

***Association between Selenium Deficiency and EVD:*** An interview was undertaken with key informants who were believed to be experts in matters Ebola and had vast experience in diagnosis, treatments and prevention of the disease. They all agreed on the importance of selenium in the prevention of Ebola as would later be confirmed by this study. According to them, a balanced diet was key to preventing any other ailment and, in the treatment thereof and this is why they provided a well-balanced diet to all their patients. This was also expected to improve the chances of survival and speed recovery. However, according to the key informants, Ebola patients received rejection from their families and the community from which they were coming from. This posed a great challenge in their healing process. The logistic regression model confirmed the results of the earlier analyses by establishing a statistically significant relationship between selenium deficiency and vulnerability to the disease. From the analysis, those who had normal levels of selenium had higher odds of infection than those who had high levels. Previous studies have also determined that the progression of many diseases including Ebola, is enhanced when selenium is low in blood (17). Moreover, these studies reveal that for timely and successful healing of viral diseases, selenium had to be in appropriate quantities in the blood. This is similar to our study as we found a positive association between selenium deficiency and vulnerability to Ebola disease. In other words, those who had high levels were less vulnerable. However, this study did not explore the role of selenium in the healing process of the survivors but is only limited to the protection of those who were not infected yet were in contact with patients. Furthermore, it is evident that those who were not Ebola survivors had higher levels of selenium in their bodies as evidenced by the results from urine analysis. This then, might explain their high resistance to the virus despite being in contact with patients. However, some of the foods that were commonly eaten by both study groups were low in selenium but there were others that had normal levels. There were foods that were not mentioned by either survivors or non-infected as being eaten despite having normal selenium levels. Among the sociodemographic factors that were analyzed, age, gender religion and occupation did not have a great impact on whether one was vulnerable to the disease. Survivors were however found to be very cautious on germ aversion as compared to non-infected. This could be attributable to the fact that they already knew how bad it was to be ill and would do anything to avoid being ill again. Among the study groups there appears that a larger proportion were employed. However, this doesn't imply well-paying formal employment. Finally, a statistically significant relationship was found between selenium deficiency and vulnerability to the Ebola virus and this suggest the importance of having people living in Ebola endemic areas to pay special attention to eating foods that had enough levels of selenium.

**Recommendation:** As it is now evident as suggested by this study that selenium is an important element in the prevention of the virus, people might want to now choose their foods wisely so as to get those that would avail selenium in their bodies. The government could also provide education to the members of society on the importance of having them choose the best foods for their families. During Ebola outbreaks, it is recommended that those infected have their urine tested for selenium levels and supplementation given to those whose levels are below the acceptable ranges. The entire population could also be boosted with the mineral by distributing it in form of tablets as this would strengthen their immune systems thus preventing further infections and fatalities. Health workers could also be educated on the importance of this mineral in the prevention of Ebola and the importance of choosing highly nutritious foods for their patients as this would reduce fatalities and speed up recovery. Suggestions for supplementation to ill and vulnerable patients could be given in a bid to improve outcomes.

**Recommendations for further study:** The study was limited to north Kivu area due to funding but could be expanded to cover larger geographic areas so as to increase generalizability of results. There is also a gap in exploring the relationship between selenium deficiency in Ebola patients and death. This could further assist in reducing deaths resulting from Ebola.

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