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# Seroprevalence of varicella zoster antibodies among children with malnutrition, malignancies and HIV infection

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SEROPREVALENCE OF VARICELLA ZOSTER ANTIBODIES AMONG CHILDREN WITH MALNUTRITION, MALIGNANCIES AND HIV INFECTION
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# SEROPREVALENCE OF VARICELLA ZOSTER ANTIBODIES AMONG CHILDREN WITH MALNUTRITION, MALIGNANCIES AND HIV INFECTION

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## ABSTRACT

***Objective:*** **To determine the seroprevalence of varicella zoster in paediatric patients at a high risk of developing complications.**
***Design:*** **A cross-sectional study.**
***Setting:*** **Paediatric general wards at Kenyatta National Hospital.**
***Subjects:*** **Children with malignancies, severe malnutrition and were HIV positive.**
***Interventions:*** **The sample size was calculated at 147 subjects. Venous samples were tested for varicella zoster virus (VZV) antibodies using enzyme immunosorbent assay (ELISA) technique at Kenya Medical Research Institute (KEMRI) laboratories, The data were anaIysed using the SPSS software and presented in form of tables and graphs. The prevalence of VZV antibodies was determined and 95% confidence interval computed.**
***Results:*** **The overall seroprevalence of VZV antibodies in the three groups of children studied was 23.6% (95% CI= 17.4, 29.8), The seroprevalence of VZV antibodies in those with malignancies and severe malnutrition was 24.1 and 25.0% respectively. About 22% of HIV positive children had protective levels of VZV antibodies. Though the seroprevalence increased with age, it was not significantly associated with area of residence, size of residence, family size or income.**
***Conclusions:*** **The low prevalence of protective VZV antibodies among children with severe malnutrition, malignancies and HIV infection children at Kenyatta National Hospital warrants routine immunisation of the high-risk population.**

## INTRODUCTION

Varicella first became prominent in Europe during the sixteenth century and was called chickenpox in 1694 and varicella by Vogel in 1765 (1). Varicella zoster virus is the aetiologic agent of two human diseases, varicella and herpes zoster (2).

There is considerable interest in the disease due to epidemiological variations between geographic locations, especially between temperate and tropical regions of the world. Whereas in temperate countries, varicella is considered to be a childhood disease with almost universal seroconversion by early adolescence, in tropical countries, it is both a childhood and adulthood disease (3,4).

There is very scanty information on seroprevalance of VZV in Africa, and most of the information on tropical countries has come from Central America and South East Asia (4-6).

Immuno-compromised patients are at significantly higher risk of developing varicella-associated morbidity and mortality than their immuno-competent counterparts (7). Malignancies, malnutrition and HIV disease cause immuno-suppression, mainly affecting cell-mediated immunity. There appears to be some association between recovery from disease in the immuno-compromised and a brisk VZV-specific cell-mediated immune response, as indicated by lymphocyte blastogenesis or lymphocyte-mediated cytotoxicity at the time of initial evaluation. These patients have a mortality rate ranging from seven to 20% with a very high incidence of visceral dissemination (8-11).

An attack of varicella induces both cellular and humoral immune responses to VZV. Although the presence of either may be used to indicate immunity to varicella, this is most frequently determined by measuring the humoral response. The tests used

include complement fixation, neutralisation, immune adherence haemagglutination, fluorescent antibody to membrane antigen (FAMA), radioimmunoassay, and enzyme-linked immuno-sorbent assay (ELISA). The ELISA technique is relatively simple and the laboratory equipment required is minimal with sensitivity of about 97% and specificity of 94%. A live attenuated varicella vaccine has been developed and is immunogenic with a good safety profile in both healthy and high-risk individuals (12).

There are concerns about safety and efficacy in the use of live attenuated vaccines in immunocompromised patients particularly those with AIDS. Data from the 1999 Paediatric AIDS Clinical Trial Group indicated that the vaccine was immunogenic, effective and safe.

Chickenpox is thus an important cause of morbidity and mortality in immuno-compromised patients. Although this group of patients would benefit from the vaccine, the cost may make it impossible for all of them to be vaccinated. This study aims at determining the seroprevalence of varicella in the high-risk children population as an indicator of its susceptibility to the infection.

## MATERIALS AND METHODS

The study objective was to determine the seroprevalence of varicella-zoster antibodies in children with malignancies, severe malnutrition and HIV infection at Kenyatta National Hospital.

This was a hospital based cross-sectional study carried out in paediatric general wards at Kenyatta National Hospital. KNH is the national tertiary hospital and teaching hospital for the University of Nairobi, Faculty of Medicine. It is also the main in-patient hospital for the low and middle - income society in Nairobi and its environments. There are four paediatric general wards at the hospital and each of these wards admits approximately 30-50 patients daily.

*Case definition:*

(i) *Malignancy:* based on bone marrow cytology for leukemia, fine needle aspirate or a biopsy for lymphoma and biopsy for solid tumours.
(ii) *Severe malnutrition:* defined using Wellcome classification as children less than 80% of the expected body weight with oedema or less than 60% of expected body weight with or without oedema.
(iii) *HIV positivity:* based on positive ELISA results for HIV infection.

*Study population:* All children who fulfilled the criteria outlined below were selected consecutively.

*Inclusion criteria:*

(i) Age between one to 12 years accompanied by either parent or guardian.
(ii) Diagnosed with malignancy using predefined criteria.
(iii) Diagnosed with severe malnutrition.
(iv) HIV positive children diagnosed using ELISA.
(v) Written consent by a parent or guardian before recruitment to the study.

*Exclusion criteria:*

Sample size was computed for each of the three groups, that is, children with malignancies, those with severe malnutrition and HIV positivity. This was done to give the study enough power to sub-analyse besides computing the overall prevalence.

The sample size was determined as follows

$n=(Z_{1-\alpha/2})^2P(1-P)/\delta^2$

Where:

n = minimum sample size

$Z_{1-\alpha/2}$ = the table value for standard normal distribution at 5% significance level = 1.96

$\delta$ = degree of precision = 10%

$\alpha$ = significance level set at 5%

p = estimated prevalence of children with VZV antibodies.
P was estimated from studies carried out in West Indies, Singapore, Phillipines and Western India where the prevalence of children with protective antibodies against varicella ranged from 10 to 20%, therefore a mean of 15% was used.

n = $1.96^2$ X 0.15 x 0.85/$0.1^2$
= 49 was the minimum sample size for each of the three groups involved.

*Study procedure:*

*Clinical procedures:* The investigator visited the paediatric general wards daily from 8:00am to 12:00pm and consequently identified eligible patients by going through the patients' clinical records. The primary diagnosis was confirmed to make sure it conformed to the case definition and the patient fulfilled the inclusion criteria.

After obtaining an informed written consent, a structured questionnaire, was then administered. Information collected included age, sex, previous admissions, size of family, number of rooms in the house and monthly family income. The patients were recruited consecutively in until they reached the minimum sample size for each of the three groups. A venous sample of 2ml was obtained in a sterile procedure and 30 minutes allowed for clotting.

Serum was then extracted and placed into plastic vacutainers. Serum samples were then transferred to KEMRI laboratories immediately where they were stored at -20°C until tested.

*Laboratory procedures:* VZV antibodies were measured by enzyme linked immuno-sorbent assay (ELISA) used to measure VZV specific IgG. This was done at KEMRI laboratories. A commercial kit by the name of Trinity Biotech Captia VZV IgG ELISA, which has a sensitivity of 97% and a specificity of 94% compared against fluorescent antibody to membrane antigen assay as the standard. For each serum sample tested, immune status ratio (ISR) value was calculated by a formula provided by kit manufacturers using optical density against the cut-off value. Value of greater than 0.9 were considered negative and indicated susceptibility to VZV infection.

*Ethical consideration:* Permission to carry out the study was sought from the KNH Research and Ethical Committee. There was no cost incurred by the parent or guardian in the transport or processing of the serum specimen. An informed written consent was taken from the parent/guardian of the children enrolled in the study and they were given an appointment when the results were to be made available to them. If the child was found to be susceptible to chickenpox, he/she was offered varicella-zoster vaccine at no cost to the parents.

*Analysis and data management:* Data obtained were entered into the computer and analysed using the statistical package for social sciences software (SPSS). The seroprevalence of VZV antibodies was determined and 95% confidence interval levels (CI) computed, to get the proportion of children with protective antibodies, that is, immune status ratio of greater than 0.9, for both the overall study population and each of the groups defined by the primary diagnosis. Descriptive statistics including age, sex, area of residence, size of family, size of houses, monthly income and previous admissions were determined and used to describe the socio-demographic characteristics of the study population. For categorical variables the chi-square test was used and $P<0.05$ was used for significance.

## RESULTS

Data were collected in August and September 2003. The study population consisted of 182 children whose age ranged from one to 12 years with a mode of 1-4 years. The demographic characteristics of the study population are shown in Table 1.

*Seroprevalence of VZV:* The overall prevalence of protective varicella zoster antibodies was found to be 23.6% (95% CI; 17.4-29.8). The prevalence of protective VZV antibodies in children with malignancies was found to be 24.1 % (95% Cl; 13.3- 34.9), whereas in those with severe malnutrition it was 25.0% (95% CI; 14.1- 36.0). HIV positive children had a seropositivity rate of 21.9% (95% Cl 11.8-32.0). Seropositivity of VZV increased significantly with age, with 17.5% of one to four year old children being seropositive as compared to 38.3% in children between the ages of eight and 12 years ($p = 0.012$), (Table 2 and Figure 1).

**Table 1**
*Socio-demographic characteristics of study population*

| | | Primary diagnosis | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | | Severe malnutrition | | HIV positive | | Malignancy | | |
| | | No. | (%) | No. | (%) | No. | (%) | |
| Sex | Male | 31 | 52 | 35 | 54.7 | 38 | 65.5 | 104 |
| | Female | 29 | 48 | 29 | 45.3 | 20 | 34.5 | 78 |
| | Total | 60 | 64 | 58 | 182 | | | |
| Age (years) | 1-4 | 42 | 70 | 26 | 40.6 | 19 | 32.7 | 82 |
| | 4-8 | 18 | 30 | 19 | 29.7 | 16 | 27.5 | 53 |
| | 8-12 | - | 19 | 29.7 | 23 | 39.7 | 42 | |
| | Total | 60 | | 64 | | 58 | | 182 |
| Area of residence | Within Nairobi | 44 | 73.3 | 37 | 57.8 | 19 | 32.8 | 100 |
| | Outside Nairobi | 16 | 26.7 | 27 | 42.2 | 39 | 67.2 | 82 |
| | Total | 60 | | 64 | | 58 | | 182 |
| Monthly income per month (ksh) | <2000 | 44 | 73.3 | 52 | 81.3 | 35 | 60.3 | 144 |
| | 2000-5000 | 16 | 26.7 | 11 | 17.2 | 21 | 36.2 | 35 |
| | >5000 | - | 1 | 1.6 | 2 | 3.4 | 3 | |
| | Total | 60 | | 64 | | 58 | | 182 |

*Continuation of Table 1*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Number of siblings | 1 | 8 | 13 | 16 | 25 | 7 | 12.1 | 31 |
| | 2 | 20 | 33.3 | 35 | 54.7 | 31 | 53.4 | 86 |
| | 3 | 18 | 30 | 4 | 6.3 | 9 | 15.5 | 31 |
| | 4 | 9 | 15 | 6 | 9.4 | 7 | 12.1 | 22 |
| | >4 | 5 | 8.3 | 3 | 4.7 | 4 | 6.9 | 12 |
| | Total | 60 | | 64 | | 58 | | 182 |
| Previous hospital admission | Yes | 13 | 21.7 | 22 | 34.4 | 17 | 29.3 | 52 |
| | No | 47 | 78.3 | 42 | 65.6 | 41 | 70.7 | 130 |
| | Total | 60 | 64 | 58 | 182 | | | |
| Number of rooms | 1 | 40 | 66.7 | 44 | 68.8 | 45 | 77.6 | 129 |
| | 2-4 | 16 | 26.7 | 19 | 29.7 | 10 | 17.2 | 45 |
| | >4 | 4 | 6.7 | 1 | 1.6 | 3 | 5.2 | 8 |
| | Total | 60 | | 64 | | 58 | | 182 |

**Table 2**
*Age related seroprevalence of VZV antibodies*

| Age (years) | Seropositive | | Seronegative | | Total | |
|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | No. | (%) |
| 1≤ 4 | 15 | 17.2 | 72 | 82.8 | 87 | 100 |
| 4≤ 8 | 11 | 20.8 | 42 | 79.2 | 53 | 100 |
| *8*≤12 | 17 | 40.5 | 25 | 59.5 | 42 | 100 |
| | Total | 43 | 139 | 182 | 100 | |

$X^2 = 8.816$; P = 0.012

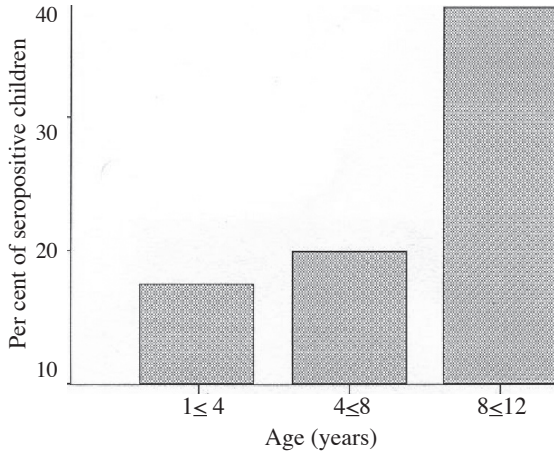
**Table 3**
*Relationship between seroprevalence and socio-demographic characteristics*

| Socio-demographic characteristic | | Seropositive | | Seronegative | | Total | P-value |
|---|---|---|---|---|---|---|---|
| | | No. | (%) | No. | (%) | | |
| Gender | Male | 24 | 23.1 | 80 | 76.9 | 104 | 0.840 |
| | Female | 19 | 24.4 | 59 | 75.6 | 78 | |
| | Total | 43 | | 139 | | 182 | |
| Previous hospital admissions | Yes | 16 | 30.8 | 36 | 69.2 | 52 | 0.151 |
| | No | 27 | 20.8 | 103 | 79.2 | 136 | |
| | Total | 43 | | 139 | | 182 | |
| Area of residence | Nairobi | 24 | 24 | 76 | 76 | 100 | 0.896 |
| | Outside Nairobi | 19 | 23.2 | 63 | 76.8 | 82 | |
| | Total | 43 | | 139 | | 182 | |
| Monthly family income | <2000 | 28 | 21.4 | 103 | 78.6 | 131 | |
| | 2000-5000 | 14 | 29.2 | 34 | 70.8 | 48 | |
| | >5000 | 1 | 33 | 2 | 67 | 3 | 0.519 |
| | Total | 43 | | 139 | | 182 | |

*Continuation of Table 3*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Number of siblings | 1 | 6 | 19.4 | 25 | 80.6 | 31 | 0.966 |
| | 2 | 20 | 23.3 | 66 | 76.7 | 86 | |
| | 3 | 8 | 25.8 | 23 | 74.2 | 31 | |
| | 4 | 6 | 27.3 | 16 | 72.7 | 22 | |
| | >4 | 3 | 25 | 9 | 75 | 12 | |
| | Total | 43 | | 139 | | 182 | |
| Number of rooms in the house | 1 | 29 | 22.5 | 100 | 77.5 | 129 | 0.847 |
| | 2-4 | 12 | 26.7 | 33 | 73.3 | 45 | |
| | >4 | 2 | 25 | 6 | 75 | 8 | |
| | Total | 43 | | 139 | | 182 | |

**Figure 1**
*Age related seroprevalence of VZV*




There was no statistically significant difference in the seroprevalence of VZV in children by gender, previous hospital admissions, area of residence, monthly family income, number of siblings and number of rooms in the houses they resided in (Table 3).

## DISCUSSION

This study revealed a very low overall prevalence of protective antibodies to VZV in all the three groups of children studied (23.6%), which mirrored that of many other countries in the tropics and less than those in the temperate countries. Various studies carried out in Thailand and Philippines showed the seroprevalence of VZV antibodies ranging between 20% and 30% (3), while studies in West Indies, India (Velore) and Singapore showed a seroprevalence of less than 10% in children (13).

In temperate countries, the prevalence of protective VZV antibodies is much higher. In surveys carried out in the United States of America, seroprevalence of VZV antibodies in children was more than 90% (3). Similar results were seen in studies carried out in Germany (13).

This study showed a seroprevalence of 24.1% in children with malignancies. A study conducted in Yaounde, Cameroon on immunity to VZV in children with leukemia showed a seropositivity rate of 34%, whilst in Denmark; a seropositivity rate of 37% was found. A study in Israel to compare antibodies to VZV in children with Hodgkin's disease and healthy children found the difference not to be statistically significant (14).

The seroprevalence of VZV antibodies in children with HIV was found to be 21.9%. This correlates well with other studies conducted in Eritrea where and overall seropositivity rate was 44% (5). This difference was thought to be due to the fact that the Eritrean study included adults as well. Other studies on children with HIV in Connecticut, USA showed 28% of the children were susceptible to varicella (7). In Madrid, Spain, a study conducted on HIV positive children admitted at a hospital showed 20% of the children were susceptible to VZV (10). There seems to be no significant difference in the prevalence of varicella infections between HIV positive children and their healthy counterparts. This was confirmed by a comparative study on the prevalence of VZV in conjunctiva of HIV positive and healthy children in Canada, which showed no significant difference (15).

In severely malnourished children the seroprevalence of VZV antibodies was found to be 25%. No studies have been conducted elsewhere to compute the susceptibility to varicella in this population, though it is postulated to reflect that in the general population.

The differences in seroprevalence of VZV antibodies in temperate and tropical countries have been thought to be due to the weather differences. The year long high temperature, humidity, and absence of human clustering during winter are thought to reduce transmission rate (13). It is thought that high ambient temperature and humidity in the tropics decreases VZV transmission by inactivating the virus in the cutaneous lesions. Alternatively, it is possible that because of high prevalence of certain other childhood viruses in tropical countries, there is interference with the transmission of VZV and the age of varicella infection is postponed (16).

This study showed a seropositivity rate of 23.1% and 24.4% for males and females respectively. This difference between the seroprevalence of VZV antibodies between males and females was not statistically significant (p=0.840). This observation was in keeping with the findings of studies in Sao Paulo, Brazil and Thailand, which showed a seroprevalence of 49.4% and 55.2% in males and females respectively, a difference that was not statistically significant (16).

This study showed a gradual increase in the seropositivity rate of VZV antibodies in immunocompromised children between one year of age and 12 years, with seropositivity increasing from 17.2% to 40.5% in 1-4 years to 8-12 years respectively. This difference was statistically significant (p = 0.012). This observation was in keeping with other studies from West Indies, Singapore, and Thailand (3). In India, the age related seroprevalence rate of VZV antibodies was 29% in the age group of 1-5 years, 51.1% in 5-10 years and 71% in 11-15 years (4). A study in Thailand showed a seroprevalence of 20% in children aged between 1-4 years, which increased to 70% above the age of 15 years. In Singapore, VZV seroprevalence was noted to be 30% in children aged 1-5 years and 56.7% in children aged 11-15 years (3). A study in UAE showed a seroprevalence of 45.8% in children less than 10 years and 68% in those aged less than 20 years, a difference, which was statistically significant (17). These findings are thought to be due to the fact that as children grow, they tend to have more exposure to VZV thus more chances of developing the disease. Varicella is considered a pre-school disease in countries with temperate climates and a childhood and adulthood disease in tropical areas. This is attributed to the year long high temperature and humidity, and the absence of human clustering during winter.

There was a slightly increased albeit not statistically significant seropositivity of VZV antibodies in children who had been admitted previously (30.8%) as compared to those not previously admitted at KNH (20.8%) (p = 0.151). An increase in seropositivity in children with a history of previous hospital admissions was anticipated due to exposure to varicella whilst in the wards and the effects of human clustering as it happens in institutions.

In this study, children living within Nairobi, which is an urban area, had a seroprevalence of 24.0% and those living outside Nairobi had a seroprevalence of 23.2%. This difference was not statistically significant (p = 0.896). Epidemiological comparisons between rural and urban populations have been documented in West Bengal, India, where nearly all adults in the urban area were immune and all rural adults were susceptible to varicella infection (16). A study in Thailand showed no significant difference in the overall seroprevalence of VZV between rural and urban population, but in southern states of the country, the seroprevalence was significantly lower in rural areas (16). This finding was thought to be due to high population densities in urban areas, which may partially overcome the transmission-interrupting effect of a tropical climate. This phenomenon was not evident in our study probably due to the fact that the population density of Nairobi is much less than that of the city of Calcutta, West Bengal and the temperature and humidity in Nairobi is markedly lower than those encountered in Calcutta where the highest temperatures are about 38°C. These differences blunt the effect of urban living in the transmission of VZV as was seen in the northern states of Thailand.

There was a slight increase in the seropositivity of VZV antibodies in children who came from families with a higher monthly income (33.3%), as compared to those from a lower monthly income (21.4%). This difference was not found to be statistically significant (p= 0.519). These results mirrored those in Eritrea, where a tribe called the Rashaida, which has a low socio-economic status, was found to have a significantly lower seroprevalence than the rest of the population (5). In Israel though, in children with Hodgkin's disease, no statistical difference was found in the seroprevalence of VZV antibodies between those children from affluent backgrounds and those of a lower socio-economic status (14). These differences in the seroprevalence between children of different socio-economic backgrounds as seen in some studies is thought to be due to the fact that children from richer families tend to go to schools earlier, are then exposed to the virus earlier with clustering in classrooms making transmission easier.

This study showed that the number of rooms in houses the children living in did not make a significant difference in the seroprevalence of VZV (p = 0.847). This finding was surprising as children living in smaller houses were expected to have a higher seropositivity rate due to enhanced clustering and thus transmission of VZV.

This study showed a VZV seropositivity rate of 27.3% in children who lived in families with four children as compared to 19.4% in those with one child. This difference was not statistically significant (p = 0.966). It was thought that larger families would enhance early exposure and transmission of varicella, which is a highly infectious disease with secondary infection rate of 90-100%. In our set-up though, this factor does not seem to be playing a significant role in transmission mechanics of VZV.

Illnesses like severe malnutrition, malignancies, use of chemotherapy for the treatment and HIV infection cause immuno-suppression by affecting the cell-mediated immunity. A study conducted by Gershon *et al* (18) showed that there is an association between recovery from varicella infection in the immuno-compromised and a brisk VZV-specific cell-mediated immune response.

Patients with malignancies receiving anticancer therapy at St. Judes Children Research Hospital

were found to have visceral dissemination in 32% after VZV infection, and had a mortality rate of seven (7%). A study at Sizwe Tropical Hospital in Reinfontein, South Africa showed a mortality rate of 43% in children with HIV disease who developed chickenpox (18).

These complications could be prevented using a live-attenuated varicella vaccine. This is a highly immunogenic vaccine with a seroconversion rate ranging from 92.2% to 98.7% in healthy children and 83.7% to 92.1% in children with underlying disease (19, 20). It has also shown to have 98% vaccine efficacy.

The vaccine is indicated for all healthy individuals older than 12 months, who are susceptible to varicella, seronegative children who are at high risk of complications, such as patients undergoing chemotherapy, severe malnutrition and HIV positive children. It is also indicated for susceptible women of childbearing age to prevent foetal varicella syndrome and in closed societies like institutions.

In developing countries it is not feasible to recommend vaccination of all children. Since the cost of the vaccine is more than the average monthly income of majority of families in the study population, it would only be practical to vaccinate the immunocompromised patients since the risk of mortality and morbidity is the highest in this group. Given that the seroprevalence of VZV ranges from 17.2% to 40.5% in 1-4 years to 8-12 years old children respectively, it would be appropriate to vaccinate immunocompromised patients soon after one year of age or on first contact. It is hoped that this study will contribute to the prevention of chickenpox in this high-risk population.

In conclusion, we found overall prevalence of protective VZV antibodies (23.6%) among children with HIV infection, severe malnutrition and malignancies admitted at KNH paediatric wards to be relatively low. This was comparatively lower than the seroprevalence in countries with temperate climates and mirrors the situation in other tropical countries. The prevalence of protective VZV antibodies was not dependent on sex, area of residence, family size, family income, previous admissions but increases significantly with advancing age ($p = 0.012$).

Vaccination of children with malignancies, severe malnutrition and HIV infection at Kenyatta National Hospital against varicella-zoster is highly recommended so as to reduce morbidity and mortality from varicella in this high- risk population.

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