Patterns of Eye Diseases among Children Visiting Two Tertiary-Level Facilities in Zimbabwe: A Retrospective Records Review (2018-2020) at Sekuru Kaguvi and Richard Morris Eye Hospitals in Harare and Bulawayo

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Abstract

Approximately 19 million children worldwide present with visual impairments resulting from eye diseases and physical causes and, 1.4 million are estimated to be totally blind. Visual impairment among children continues to be a growing public health concern globally with low-income and middle-income countries (LMICs) being disproportionately affected. In Zimbabwe, prevalence of blindness, frequency and types of eye conditions children present with are not known. The purpose of this study was to determine the patterns of eye disease among children attending the two tertiary facilities in Zimbabwe (Sekuru Kaguvi, Harare and Richard Morris, Bulawayo) and identifying the major eye conditions that children who attend the Harare and Bulawayo paediatric hospitals present with. A retrospective study design was conducted where hospital records containing patient data about age, gender, visual acuity and clinical diagnosis was retrieved and reviewed. The study had a sample size of 10066 children aged 15 years and below analysed between January 2018 and September 2020. Descriptive statistics were run using Stata statistical software and SPSS version 23. The study was approved by the Medical Research Council of Zimbabwe (MRCZ). Study results showed that the most frequent eye conditions are allergic conjunctivitis, eye injuries, lid pathology and refractive error while the least prevalent eye conditions included retinoblastoma, anterior segment disease and uveitis. The most affected age group was children between 0 to 5 years and 6
to 12 years respectively. Males had higher eye disease frequencies than females. Results show a downward trend in the number of children who present with eye conditions per year under study. In 2018, frequency of eye conditions was 56.1% while in 2019, it was 33% and lastly, 10.9% in 2020.

Keywords
Blindness, Visual Impairment, Childhood, Visual Acuity

1. Introduction and Study Background

Childhood blindness refers to a group of diseases and conditions which occur during childhood or early adolescence, and, if left untreated, may result in blindness or severe visual impairment [1]. Globally, 36.0 million people are blind which translated to a crude prevalence of blindness of 0.48% in 2015 [2]. It is further estimated that 1.4 million children in the world are blind [3]. Therefore, visual impairment among children continues to be a growing global public health concern with low-income and middle-income countries (LMICs) being disproportionately affected. Most LMICs lack effective screening programmes and interventions for children presenting with eye conditions and there is need to expand services to marginalized groups. It is increasingly difficult to estimate the burden of childhood blindness and severe visual impairment in Zimbabwe. This is mainly due to scarce data and heterogeneous data collection methods used. Thus, prevalence estimates are imprecise in much of southern Africa.

In Zimbabwe, the causes of blindness according to the Zimbabwe National Eye Health Strategy (2014 to 2018) are congenital cataracts, glaucoma, eye trauma, measles and retinoblastoma [4]. The strategy also reported a strong correlation between the prevalence of childhood blindness and under-five mortality rates, which raises the need to constantly interrogate the associations between these variables. Furthermore, paediatric eye services are lacking in Zimbabwe with most of the cases being attended at the two tertiary level paediatric eye hospitals, Sekuru Kaguvi Eye Hospital and Richard Morris Hospital located in Harare and Bulawayo respectively. As a result, only the most severe cases end up being given attention and priority while the majority are missed at primary care level which brings to the core of the importance of community screening for visual impairment among children in the country. However, there have been efforts to improve eye care among children in Zimbabwe. Two non-governmental organizations, the Christian Blind Mission (since 1974) and Council for the Blind (since 1955) have been supporting Ministry of Health and Child Care (MoHCC) in the provision of eye care services at tertiary eye units in the two major cities of Harare and Bulawayo, situated in the northern and southern parts of the country respectively. This report documents details of a study conducted by the Zimbabwe Council for the Blind to determine the patterns of eye conditions among children presenting at the two major eye hospitals, Sekuru Kaguvi Eye Hospital
and Richard Morris Hospital.

1.1. Statement of the Problem

The prevalence of blindness among children in Zimbabwe is not known. The frequency and type of eye conditions that children present with in the eye units are also unknown. Knowing these, will help policy makers, programme managers and implementers to make evidence based decisions. It is against this background that Council for the Blind and MoHCC decided to do a quantitative analysis of the data that has been collected at two major paediatric eye units in the country over three years.

1.2. Study Justification

The study was deemed significant in the broader context of the Zimbabwe National Eye Health Strategy, because the country seeks to reduce avoidable blindness by 80% through the implementation of evidence-based eye health interventions. Furthermore, the study adds to the body of knowledge of the burden of childhood blindness in the country. The findings from this study will contribute to the development and design of appropriate and tailor-made eye health interventions and inform future paediatric eye health programming. This study also seeks to inform other broader community based studies which will measure the prevalence rate of childhood blindness.

1.3. Specific Study Objectives

The following were the specific objectives of the study:

- To identify the major eye conditions that children who attend Sekuru Kaguvi and Richard Morris Hospitals present with.
- To identify patterns of eye conditions that children who visit the Sekuru Kaguvi and Richard Morris Eye Hospitals present with.

1.4. Specific Research Questions

The study sought to answer the following research questions:

- What are the major eye conditions that children who attend the Sekuru Kaguvi and Richard Morris paediatric hospitals present with?
- What are the patterns of the eye conditions among children who visit the Sekuru Kaguvi and Richard Morris Hospitals?

2. Research Methodology

2.1. Study Design

A hospital-based retrospective study aimed at ascertaining the profile of childhood eye conditions was conducted in Harare and Bulawayo. Hospital archived data of patients aged 15 years and below presenting at Richard Morris Hospital in Bulawayo and Sekuru Kaguvi Eye Hospital in Harare between 1 January 2018 and 30 September 2020, were electronically retrieved and retrospectively re-
viewed. This review was quantitative in its orientation. The study protocol and ethical considerations were obtained and approved by the Medical Research Council of Zimbabwe, Regulatory Authority reference number MRCZ/E/291. All the data was anonymous to protect the identity of the patients in the study. In each of the study sites, data was extracted by ophthalmic nurses trained in data extraction and research ethics and the trained nurses were supervised by the ophthalmologists in their respective centres with a biostatistician and research methodologists from the University of Zimbabwe who provided technical back-stopping.

2.2. Study Setting

Data for this study was collected from patient registers kept at Sekuru Kaguvi (Harare) and Richard Morris (Bulawayo) eye hospitals. Sekuru Kaguvi Eye Hospital is located in the Northern part of Zimbabwe in the capital city of Harare. Sekuru Kaguvi Eye Hospital serves the northern provinces of the country and include Mashonaland provinces, Manicaland, parts of Midlands Province and parts of Masvingo. On the other hand, Richard Morris Hospital is located in the second largest city of Zimbabwe, Bulawayo and mostly serves the Matabeleland provinces, parts of Midlands and Masvingo provinces. The two hospitals were purposively sampled because they are the main referral centres for eye diseases and complications in Zimbabwe offering specialist eye services.

2.3. Study Population and Sample

The study population comprised of 10066 children (0 to 15 years) who were attended at Sekuru Kaguvi and Richard Morris during study timelines. From the two hospitals, a total of 10,066 children records for the period January 2018 to September 2020 were extracted and reviewed.

2.4. Data Extraction and Analysis

Information extracted from the patient records, included age of the patient at presentation, sex, visual acuity, and clinical diagnosis. Normally, one main diagnosis is reported for each individual consulting at the hospital and represents the main reason why the patient is seeking services. The clinical diagnoses were grouped according to the appropriate anatomical categories, for example, eyelid diseases, orbital diseases, neuro-ophthalmic diseases, refractive errors etc. Data was cleaned and descriptive statistics were run using Stata Statistical software.

3. Results

3.1. Demography of the Participants

All the 10,066 patient records between January 2018 to September 2020 were extracted from Sekuru Kaguvi and Richard Morris eye clinic registers and subsequently reviewed.
There were 4785 (47.5%) from the Bulawayo records and 5281 (52.5%) from the Harare records. The median age of the children attending both eye hospitals was 5 years old and the range was 2 to 15 years old. The demographic profile of the patients in the study is presented in Table 1 below.

3.2. Frequency of Eye Conditions

The study sought to identify the eye conditions that were common amongst the study population. After reviewing the data from the two sources mentioned above, the frequencies of the eye conditions were as follows.

Table 1. Demographic details of study participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Center</strong></td>
<td></td>
</tr>
<tr>
<td>Bulawayo</td>
<td>4785 (47.5)</td>
</tr>
<tr>
<td>Harare</td>
<td>5281 (52.5)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4360 (43.3)</td>
</tr>
<tr>
<td>Male</td>
<td>5706 (56.7)</td>
</tr>
<tr>
<td><strong>Age, median (IQR) years</strong></td>
<td></td>
</tr>
<tr>
<td>5 (2 - 10)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number of patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 5</td>
<td>5060 (50.3)</td>
</tr>
<tr>
<td>6 - 12</td>
<td>3924 (39.0)</td>
</tr>
<tr>
<td>13 - 15</td>
<td>1082 (10.8)</td>
</tr>
</tbody>
</table>

Figure 1. Disease frequency by condition.
From Figure 1 above, it can be noted that allergic conjunctivitis was the most frequent eye condition totaling 2422 and constituted 24.1% of the study population. This was followed by eye injury, 1499 (14.9%), lid pathology, 911 (9.1%) and refractive error, 827 (8.2%). The most frequent eye conditions found in children seeking hospital care were allergic conjunctivitis, eye injuries, lid pathology, refractive error, ocular surface disease, corneal disease, cataract, ophthalmia neonatorum, squint, and aphakia.

The frequency of retinoblastoma was 99/10,066 (0.098%). When compared by site, SKH had more patients who were diagnosed with retinoblastoma (72 SKH; 27 RM). However, Richard Morris had more patients diagnosed with ophthalmia neonatorum (8 SKH; 469 RMH) conditions.

The study also sought to subclassify the eye conditions in relation to the laterality of the eye involved. The results for these trends are presented on Table 2 below. Data was grouped according to the nature or pattern of the condition.

From Table 2 below, almost half 4969 (49.4%) of the patients’ data was recorded as missing and thus, did not reveal the exact eye that was affected. 2959 (29.5%) had both eyes affected, while 1102 (11%) had the right eye affected and 1036 (10.3%) had the left eye affected.

### 3.3. Frequency of Eye Condition by Gender

The study also sought to determine the frequency of the eye conditions by gender. Figure 2 below illustrates this distribution.

Generally, males were shown to suffer more from eye conditions than females (allergic conjunctivitis, diseases with lid pathology; cataract, orbit, uveitis, diseases of the optic nerve) as illustrated in Figure 2 below. More males diagnosed with allergic conjunctivitis (1467/2422) compared to females (955/2422). However, the difference on prevalence of eye conditions by gender for this variable was not statistically significant with a p-value being greater than 0.05. Moreover, a similar pattern was also observed in eye injury condition in which the majority of the affected (1008/1499) were males. Results however, indicated a female preponderance for some conditions such as corneal and squint which were more prevalent among females than in males. These differences appear to be consistent over time, specifically in 2019 and 2020 with the data suggesting that there were no statistically significant differences in the presentation of eye problems according to gender.

<table>
<thead>
<tr>
<th>Affected eye</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both eyes</td>
<td>2959</td>
<td>29.4</td>
</tr>
<tr>
<td>Left eye</td>
<td>1036</td>
<td>10.3</td>
</tr>
<tr>
<td>Right eye</td>
<td>1102</td>
<td>11.0</td>
</tr>
<tr>
<td>Missing</td>
<td>4969</td>
<td>49.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10,066</td>
<td>100</td>
</tr>
</tbody>
</table>
3.4. Diagnosis by Age Group

In order to profile eye conditions by age group, patients with different eye conditions were grouped against three age groups, the 0 - 5 age group, 6 - 12 age group and the 13 - 15 age groups. Figure 3 below illustrates the results that were obtained.

From the results shown above, it can be deduced that out of the 2422 diagnosed with allergic conjunctivitis, the majority, 1071 were among the youngest (0 - 5) age group followed by 1067 who were between the 6 - 12 age group and the minority, 284 being in the 13 - 15 age group. Eye injuries were most prevalent in children between ages 6 - 12, with a frequency of 700 out of the 1499 diagnosed with the condition. The age group 0 - 5 had 615 children diagnosed with the condition whilst the minority, 184 out of 1499 who had eye injury were between the ages of 13 - 15. With regards to lid pathology, the majority of children (537/911) who had the abnormality were between the 0 - 5 years age group followed by 298/911 who were between the 6 - 12 age group whereas the minority 76/911 were between the 13 - 15 age group.

Generally, conditions that were found to be very prevalent in the 0 to 5 age group are allergic conjunctivitis, ophthalmia neonatorum, retinoblastoma, diseases of lid pathology such as, glaucoma, ocular surface disease, posterior segment disease, optic nerve disease and squint.
Eye conditions that were most common in the ages 6 to 12 were uveitis, anterior segment disease, aphakia, corneal diseases, refractive error, and eye injuries. However, there were no conditions that were only peculiar to the 13 to 15 age group.

Table 3 below shows a 95% Confidence Interval falling between (1.46) lower bound and (1.49) upper bound for the 0 -5 age group on the diagnosis of eye conditions variable. On the 6 - 12 age group, the 95% CI is between (1.45) lower limit and (1.48) upper limit on the same variable. For the 13 - 15 age group, the 95% CI for diagnosis of eye conditions is between (1.46) lower bound and (1.52) upper bound.

Data on Table 3 below suggests that differences do exist in diagnosis of eye conditions across different age groups, but that there is no pronounced difference in diagnosis of eye conditions within each age group category.

3.5. Diagnosis by Region

Furthermore, the study also sought to determine diagnosis of the eye conditions amongst the participants by region. Figure 4 below shows the results that were obtained from the reviewed data.

Data on Figure 4 below shows that some of eye conditions were more prevalent and diagnosed in the Northern Region (SKH) compared to the Southern Region (RMH), save for eye injury, refractive error, ocular surface disease anterior segment disease and ophthalmia neonatorum which were mostly diagnosed...
Table 3. Statistical analysis showing diagnosis of eye conditions by age group.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Statistic</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 5</td>
<td>Mean</td>
<td>1.476</td>
</tr>
<tr>
<td></td>
<td>95% Confidence Interval</td>
<td>Lower Bound</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper Bound</td>
</tr>
<tr>
<td></td>
<td>5% Trimmed Mean</td>
<td>1.474</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>0.249</td>
</tr>
<tr>
<td></td>
<td>Std. Deviation</td>
<td>0.4995</td>
</tr>
<tr>
<td>6 - 12</td>
<td>Mean</td>
<td>1.470</td>
</tr>
<tr>
<td></td>
<td>95% Confidence Interval</td>
<td>Lower Bound</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper Bound</td>
</tr>
<tr>
<td></td>
<td>5% Trimmed Mean</td>
<td>1.467</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>0.249</td>
</tr>
<tr>
<td></td>
<td>Std. Deviation</td>
<td>0.4992</td>
</tr>
<tr>
<td>13 - 15</td>
<td>Mean</td>
<td>1.494</td>
</tr>
<tr>
<td></td>
<td>95% Confidence Interval</td>
<td>Lower Bound</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper Bound</td>
</tr>
<tr>
<td></td>
<td>5% Trimmed Mean</td>
<td>1.493</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>0.250</td>
</tr>
<tr>
<td></td>
<td>Std. Deviation</td>
<td>0.5002</td>
</tr>
</tbody>
</table>

in the Southern Region.

3.5. Eye Condition by Year of Diagnosis

From Figure 5 below, it can be noted that most children with allergic conjunctivitis (1544/2422) were diagnosed in 2018 whilst 712 and 166 were diagnosed in 2019 and 2020, respectively. In addition, a total of 676 out of 1499 with eye injury were diagnosed in 2018 followed by 511/1499 who were diagnosed in 2019 with the minority, only 312 with condition having been diagnosed in 2020.

Table 4 below shows a pattern that was observed in all eye conditions, patients presented with, per year. Many children were diagnosed of various eye abnormalities in 2018, followed by 2019 and lastly, 2020.

A descriptive analysis of data on the prevalence of eye conditions by year of diagnosis (three years that fall under study 2018; 2019 and 2020) has shown that there was a decline in the number of school children presenting with or being diagnosed with eye conditions. As illustrated by Table 4 below, 56.1% of the total
Figure 4. Diagnosis by region: Harare & Bulawayo.

Figure 5. Eye condition by year of diagnosis.
population sample presented with eye problems in 2018 while only 33% did the same in 2019 and only 10.9% of the study population presented with eye problems in 2020.

4. Discussion

This study presented a cursory analysis into the frequency and patterns of common childhood eye conditions presenting in two major referral eye hospitals in a low-resourced setting. Hospital based data was used to show trends and patterns of eye conditions as reflected on the study sample and this data adds confidence in the results obtained because diagnoses were conducted by qualified eye health experts as opposed to having to elicit views from respondents which may have social desirability or recall biases. It must be noted at this point that there are few studies in Zimbabwe which have attempted to characterize the burden of eye conditions among children and that this study adds to the growing body of evidence on this important public health problem. Additionally, this study is important as it included the two major referral centres in Zimbabwe which are located at vantage sites, which geographically covers the whole country.

Results showed that more records were extracted and analysed from Harare, which can be attributed to the fact that the northern provinces of Zimbabwe are more populated than the southern regions. It may also be related to the perception that a lot more Zimbabweans may be inclined to seek services in Harare as it is perceived to have better services by virtue of it being the capital city. It is also important to note that Richard Morris Hospital refers some conditions to Sekuru Kaguvi, for instance, those requiring paediatric oncology services. Interestingly, results showed no differences on the types of eye diseases seen in the two hospital centres. Therefore, there were no geographical variations for most of the conditions that were reviewed.

By comparison, 469 Ophthalmia neonatorum cases were reported at Richard Morris whereas SKH only reported 3 cases. Ophthalmia neonatorum is a notifiable condition and treatment should be done at the local health centres. This might mean that the Northern region is managing the condition locally and the Southern region health centres were referring to Richard Morris. A standardised protocol of treatment should therefore be followed. Such discrepancies need to be explored in future research so that uniformity is maintained and that deserv-
ing cases are not missed.

Between 2018 and 2020, there were 99 retinoblastoma cases, an average diagnosis of 33 children were diagnosed annually. The condition did not feature among the top ten prevalent conditions and further analysis did not yield any statistical significant results.

Study findings revealed that there were more eye health problems among the younger age group (0 - 5 years) which affirms previous concerns raised by researchers in Zimbabwe where trachoma was found to be highly prevalent among those below 9 years [5]. This finding has a number of important implications in terms of the provision of both preventative and curative services for eye diseases targeting children in Zimbabwe. Focus should thus be put more on the population in terms of programming. There is additional need to promote preventive behaviours within the communities where the patients are coming from because there is evidence to suggest that over 90% cases of eye diseases are preventable [6].

Our findings also appear to suggest that the most common conditions which are frequent in referral hospitals in Zimbabwe include allergic conjunctivitis, eye injuries, lid pathology, refractive errors, ocular surface disease, corneal disease, cataracts among others. It is important to note, for instance, that allergic conjunctivitis was the most common eye condition and yet it is a condition that can be easily prevented and controlled if the patient is educated on avoiding those elements that irritate their eyes. In such instances, targeted health education should be fostered to help reduce the burden. Similarly, the second most frequent (eye injuries) is related to behaviour which could be easily targeted. Children are particularly at risk of ocular injury due to their decreased ability to detect and avoid potential hazards. Most childhood eye injuries are sustained during unsupervised play and domestic activities. It is worth mentioning that such findings are in tandem with those reported in other regions in Africa and beyond [7] [8] [9] [10].

Results have shown that although there are differences between males and females in the way they present different types of eye conditions, there were no statistically significant differences in the frequencies of eye conditions according to gender. It would be important for future research to explore this association using large sample sizes and also using community-based surveys.

From 2018 to 2020, there was a downward trend in the number of cases seen and this can be attributed to unavailability of health personnel in health institutions to screen, examine and diagnose the different eye problems that children present with because over the past four years, Zimbabwe has experienced a significant number of health staff migrating overseas for greener pastures [11]. Additionally, there have also been strikes by health staff over poor working conditions and remuneration, shortage of medication and other resources needed to screen and diagnose eye problems in children are some of the reasons for the decline in figures over the past three years. Another plausible explication for the
differences could be due to the effects of the COVID-19 pandemic which significantly altered access to health care services because schools closed and lockdowns restricted movement for many people, and thus may have hindered children from accessing eye screening and diagnosis services.

5. Study Limitations

The major limitation of the study was that it was conducted during the time of COVID-19 pandemic and thus could only be a retrospective review. Richer information could have been obtained from face-to-face interviews with caregivers. Moreover, the study was retrospective in nature and utilised data from patient registers from the hospitals. Reporting tools from the two hospitals were different rendering it difficult for some variables to be compared. In addition, some records at the hospitals were incomplete or missing data and this made data extraction and review difficult.

The study was hospital based and as such results cannot be generalized to the rest of the population outside this setting. The study did not conduct interviews or have any physical contact with participants. This limitation means that there might be some vital information that might have been missed from the caregivers and the patients. In addition, it was also noted that the two paediatric hospitals used slightly different data capturing tools which compromised merging of the datasets in some instances and therefore, some data may have been lost. Childhood blindness could not be calculated due to different data sets as one eye unit did not record the visual acuity for patients in the years that were under study.

6. Conclusions

The study sought to:

1) Determine the patterns of childhood blindness and severe visual impairment in children below the age of 15 years.

2) Identify the major eye conditions that children who attend the Harare and Bulawayo paediatric hospitals present with.

3) Identify patterns of the eye conditions that children who visit the Harare and Bulawayo Eye Units present with.

Results of the study underscore the urgent need to prioritize eye health for children in Zimbabwe and to institute interventions which would help reduce this growing burden presented by eye diseases. With regards to the pattern of the conditions, the study findings revealed that children are affected in different ways. Some have both eyes affected whilst others have either one eye affected by these different conditions. The challenge of managing childhood eye injuries is enormous with considerations ranging from late presentation to eye care centres and lack of facilities, the low socioeconomic status of the children involved, the special care required during examination, postoperative management and the risk of secondary vision loss. Prevention of ocular trauma in children remains a
priority in order to reduce ocular morbidity. This will involve the adequate education of children, parents and teachers to ensure adequate supervision during playtime.

7. Recommendations

1) The paediatric hospitals should have similar data capturing tools so as to ensure ease of merging data for programming purposes. In view of this more investment in data recording and storage should be encouraged especially using electronic database systems which are able to show real-time trends.

2) Integration of eye screening at Post Natal Units and Child Immunization Programmes is essential for early identification and treatment of the conditions that are found in the 0 to 5 age group.

3) Effective screening should be conducted especially at community level with the involvement of community health workers. This could also involve scaling up prevention, health education and early presentation of children to ophthalmic hospitals for treatment of eye disorders are also essential.

4) General nurses and community health workers should be given basic primary eye care training so as to reduce the number of conditions referred to the tertiary institution as some of these can be treated at the health centre (ophthalmia neonatorum).

5) More resources should be channeled towards the prevention and cure of allergic conjunctivitis, eye injuries and lid pathology especially in younger age groups which appear to more affected.

Acknowledgements

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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