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Hepatitis A seroprevalence in Western Cape Province, South Africa: Are we in epidemiological transition?

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Background. Hepatitis A virus (HAV) is the most common cause of viral hepatitis worldwide. Hepatitis A vaccine is not included in the Expanded Programme on Immunisation in South Africa (EPI-SA), as the country is considered to be highly endemic for hepatitis A.
Objectives. To determine the seroprevalence of hepatitis A infection in Western Cape Province (WCP), South Africa.
Methods. We conducted a cross-sectional seroprevalence study in the 1 - 7-year age group in WCP. Our samples (*N*=482) were blood specimens left over after laboratory testing obtained from referral hospitals between August and October 2015. A Siemens enzyme immunoassay was used to test for total hepatitis A antibodies. We also analysed hepatitis A immunoglobulin G antibody results from the National Health Laboratory Service (NHLS) Disa*Lab database at Groote Schuur Hospital from 2009 to 2014, and included 2009 - 2014 acute hepatitis A (immunoglobulin M-positive) surveillance data from the National Institute for Communicable Diseases to look at trends in notified acute infections over the same period.
Results. Our cross-sectional study showed 44.1% seroprevalence in the 1 - 7-year age group. Hepatitis A data from the NHLS database indicated a seroprevalence of <90% up to age 10 years, indicating intermediate endemicity. The surveillance data showed that a substantial number of symptomatic hepatitis A infections occurred in the 7 - 40-year age group, suggesting that an increasing proportion of the population is susceptible to HAV infection.
Conclusions. These results suggest an urgent need for detailed evidence-based considerations to introduce hepatitis A vaccine into the EPI-SA.

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Hepatitis A virus (HAV) is responsible for ~1.4 million new infections each year worldwide.[1-3] Transmission of HAV is via the faecal-oral route, either through an infectious person or by ingestion of contaminated food or water.[4-6] Risk factors for infection with HAV include low socioeconomic status, larger household size and overcrowding, particularly in rural areas, limited access to clean water sources and inadequate sanitation facilities.[1,7]

Globally, the epidemiology of hepatitis A is changing owing to improved sanitation and living standards in some regions.[8,9] A decrease in HAV prevalence has been noted in modern urban populations, whereas in populations with poor or no sanitation and overcrowded living conditions, infection occurs at an early age. In this context, close to 100% of children acquire infection in the first decade of life.[8]

In the past, it was thought that South Africa (SA) was highly endemic for HAV infection. However, significant improvements in water sources and sanitation facilities over the past 2 decades may have had a significant effect on the epidemiology of the disease, and the country could be in an epidemiological transition. SA may therefore qualify for introduction of hepatitis A vaccine as per the World Health Organization (WHO) position paper,[10] which recommends vaccination for children ≥1 year of age in countries of intermediate or low endemicity.

Objectives

To investigate whether SA is experiencing an epidemiological transition from high to low hepatitis A endemicity.

Methods

We chose Western Cape Province (WCP) as a study site for convenience, and conducted an observational cross-sectional study to examine the seroprevalence of hepatitis A in children between 1 and 7 years of age. Serum samples sent for routine haematology, chemistry and virology diagnostic testing were collected from three referral laboratories in the province, and were tested for antibodies against HAV. The study population was stratified into three age groups: 1 - 2 years, 3 - 4 years and 5 - 7 years.

We also conducted a retrospective review of hepatitis A laboratory results from two sources: hepatitis A immunoglobulin G (IgG) age-specific prevalence from routine diagnostic samples submitted to the Groote Schuur Hospital (GSH) National Health Laboratory Service (NHLS) virology laboratory from 2009 to 2014, and surveillance data on acute HAV infections in WCP between 2009 and 2014 collected by the National Institute for Communicable Diseases (NICD). The hepatitis A IgG data included individuals who were being screened for hepatitis A immunisation status, e.g. children who were vaccinated and awaiting liver transplants.

Seroprevalence study

Routine specimens from 1 - 7-year-old patients resident in WCP and collected during the period August - October 2015 from primary- and tertiary-level healthcare facilities in the province were used for the study. Based on an expected prevalence of ~50% in the study population and a margin of error of 5% (0.05), a sample size of 384 was deemed sufficient.[11,12] Samples from patients with liver

disease were excluded, and the HIV status of the patients was not known. We decided to use the 482 specimens available for testing to accommodate for any potential equivocal results. Hepatitis A total antibody testing was performed at the NHLS diagnostic virology laboratory at GSH.

The following demographic details on the patients from whom the serum samples were obtained were also collected: age, gender, and residential location or referring clinics. It was not necessary to obtain informed consent, as there was no direct contact with the patients and the results of the study did not affect patient treatment.

Procedure

Samples were retrieved from the −80°C freezer and thawed at room temperature. Testing was performed according to the manufacturer's instructions.[13] Serum samples were tested for anti-HAV total antibodies (IgG and immunoglobulin M (IgM)) using a manual enzyme immunoassay (Siemens Enzygnost anti-HAV), as per Siemens protocol.[13]

Test samples with equivocal results were retested in duplicate, and the remaining samples were stored at −80°C. Anti-HAV total antibody results were entered on an Excel spreadsheet version 15.31 (Microsoft, USA) and stored on an access-controlled computer located at the NHLS virology laboratory at GSH.

Retrospective review

- Routinely collected hepatitis A anti-IgG antibody test results were extracted from the GSH NHLS database from January 2009 to December 2014. These results were analysed to provide a retrospective review of hepatitis A seroprevalence during that period.
- Acute hepatitis A surveillance data (anti-HAV IgM antibody results) routinely collected from public sector hospitals and clinics in WCP by the NICD between 2009 and 2014 were also analysed.

No patient identifiers were available from the routinely reported data that we used for our retrospective review analysis. Only basic demographic data for these samples are therefore reported.

Data analysis

All data were first entered on an Excel spreadsheet version 15.3 (Microsoft, USA) and stored on an access-controlled computer at Groote Schuur Hospital (NHLS server). Equivocal test results were excluded from analysis. SPSS version 23 (IBM, USA) was used for all the analysis. Descriptive statistics were generated from the cross-sectional seroprevalence data, the GSH NHLS laboratory database (anti-HAV IgG results, January 2009 - December 2014) and the hepatitis A surveillance data provided by the NICD (anti-HAV IgM results, 2009 - 2014).

For both the NHLS and NICD data sets, we evaluated the hepatitis A trends from 2009 to 2014.

Ethical considerations

Ethics approval was obtained from the University of Cape Town Human Research Ethics Committee (ref. no. HREC/REF:227/2015) and the Stellenbosch University Human Research Ethics Committee (for samples collected from Tygerberg Hospital) (ref. no. S15/08/173). Permission to conduct a study using samples from Red Cross War Memorial Children's Hospital (RCWMCH) was also obtained.

Results

Seroprevalence study

One serum sample test was equivocal (male, age 1 year) and remained equivocal even on repeat testing in duplicate. This sample was excluded from analysis, so only 481 samples were analysed. Seroprevalence, defined as the proportion of the serum samples that tested positive for anti-HAV total antibodies, was 44.1% (212/481). As expected, seroprevalence increased with age: 22.2% (45/203) for 1 - 2-year-old children, 51.7% (31/60) for 3 - 4-year-old children and 62.4% (136/218) for 5 - 7-year-old children. Of the total samples tested, 231/481 (47.9%) were from females (Table 1).

Positive and negative results as well as the median age distribution for the 482 tested samples are shown in Fig. 1.

Retrospective study

Hepatitis A seroprevalence from the NHLS GSH laboratory database, 2009 - 2014

We analysed and displayed the NHLS data from GSH as a heat map (Fig. 2). The total numbers of samples tested for the years 2009 - 2014 were 2 456, 2 207, 2 182, 2 287, 2 244 and 2 318, respectively. Seroprevalence is displayed for the following age categories: 1 - 2 years, 3 - 4 years, 5 - 7 years, 8 - 10 years, 11 - 15 years, 16 - 20 years, 21 - 25 years, 26 - 30 years, 31 - 35 years, 36 - 40 years and >40 years. A three-colour scale was used: purple to white to green to indicate increasing seroprevalence, with the minimum (lowest value) purple, the midpoint (50th percentile) white and the maximum (highest value) green. Seropositive percentages <50% are displayed in white font, as are percentages ≥90%. A seroprevalence of ≥50% by age 15 years, but <90% by age 10 years, was noted in all years (intermediate endemicity as defined by the WHO), with the exception of 2010, where the seroprevalence in the 16 - 20-year age group was 93%. Of note, seroprevalence was consistently <90% under the age of 10 for all calendar years. This finding suggests that hepatitis A infection is not as endemic in this population as it is thought to be.

Review of acute hepatitis A surveillance data from WCP, 2009 - 2014

The results analysed and displayed in Fig. 3 are a summary of the

Table 1. Participant gender, age groups and anti-HAV total antibody results

	Age groups (years)			
	1 - 2	3 - 4	5 - 7	Total
Gender,* *n* (%)				
Female	91 (44.8)	36 (60)	104 (47.7)	231 (48.0)
Male	112 (55.2)	24 (40)	114 (52.3)	250 (52.0)
Total	203 (42.2)	60 (12.5)	218 (45.3)	481 (100)
Results, *n* (%)				
Negative	158 (77.8)	29 (48.3)	82 (37.6)	269 (55.9)
Positive	45 (22.2)	31 (51.7)	136 (62.4)	212 (44.1)

HAV = hepatitis A virus.
*Fisher's exact test showed no significant statistical difference between males and females.

surveillance data provided by the NICD, and reflect hepatitis A IgM-positive tests from 2009 to 2014. The total numbers of results analysed per year for the years 2009 - 2014 were 475, 637, 711, 526, 656 and 879, respectively, showing a peak of positivity around the age of 6 years.

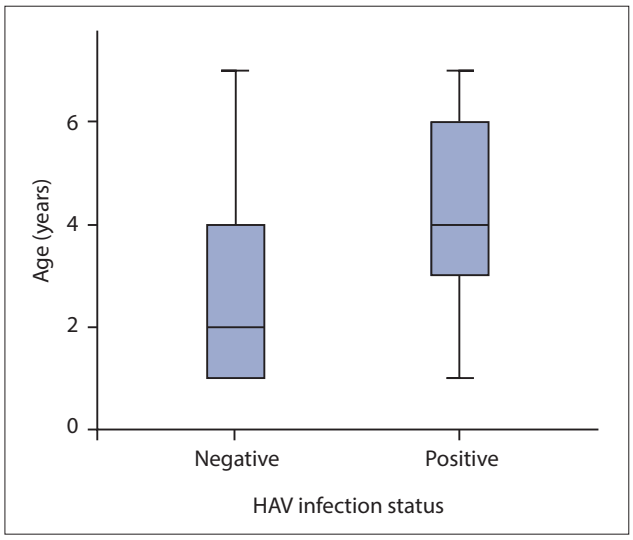

Fig. 1. Median age distribution of anti-HAV total antibody-positive and negative individuals. The box plot demonstrates the negative and positive results, as well as the median age distribution of the 482 tested samples. The median age of positivity in the sample population was ~4 years, and no statistical difference was noted between the positive and negative samples at this age. (HAV = hepatitis A virus.)

The positive hepatitis A IgM results that were recorded from hospitals in WCP from 2009 to 2014, provided by the NICD, are also displayed in Fig. 4. We grouped the results into three categories: 1 - 6 years, 7 - 40 years and >40 years, and plotted them according to each calendar year. In the past most children in SA were infected with HAV by age 6 years, hence the reason for the selection of 1 - 6-year-old category, and we wanted to assess whether this has shifted to the 7 - 40-year age group, as well as to assess the burden of disease in the >40-year-old age group. Across all years, the highest number of clinical hepatitis A cases was in the 7 - 40-year age group. Cases in the >40-year age group were very few, accounting for only 4.2% of the total positives in 2009, 2.5% in 2010, 3% in 2011, 6.5% in 2012, 3.4% in 2013 and 4.7% in 2014.

Discussion

Our cross-sectional study, for which the samples were collected between August and October 2015, indicates a seroprevalence of 44.1% in the 1 - 7-year age group. The retrospective study using the NHLS GSH data also reflects intermediate endemicity, while analysis of the NICD data displays an increase in symptomatic hepatitis A infection in all groups, but mostly in the 7 - 40-year age group. Taken together, the results indicate a possible epidemiological change of HAV infection in WCP. We propose that better-designed studies be prioritised in the future to generate quality data that can guide the development of a vaccination policy against HAV infection in SA.

According to a WHO position paper on hepatitis A vaccines,[10] seroprevalence levels of endemicity are classified as follows: high (≥90% by age 10 years), intermediate (≥50% by age 15 years, with <90% by age 10), low (≥50% by age 30 years, with <50% by age 15) and very low (<50% by age 30 years). SA is currently considered

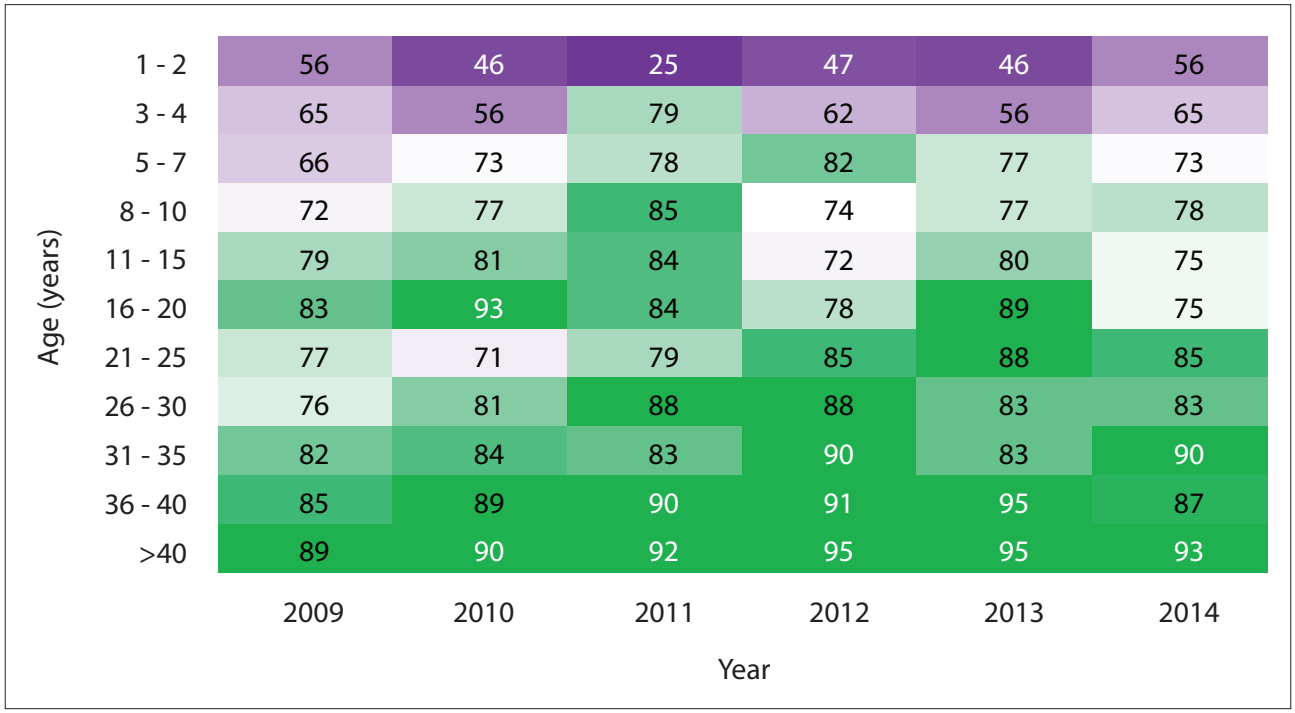

*Fig. 2. Heat map of the positive NHLS GSH hepatitis A IgG results, 2009 - 2014. The total numbers of samples tested in the years 2009 - 2014 were 2 456, 2 207, 2 182, 2 287, 2 244 and 2 318, respectively. Pearson's χ^2 test showed no statistical difference between samples tested per year. The positive hepatitis A IgG results that were extracted from the GSH NHLS database (Disa*Lab) from 2009 to 2014 are reflected as percentages and stratified into the following groups: 1 - 2 years, 3 - 4 years, 5 - 7 years, 8 - 10 years, 11 - 15 years, 16 - 20 years, 21 - 25 years, 26 - 30 years, 31 - 35 years, 36 - 40 years and >40 years. A three-colour scale was used (purple to white to green), with minimum (lowest value) purple, midpoint (50th percentile) white, and maximum (highest value) green. Seropositive percentages <50% are displayed in white font, as well as percentages ≥90%. Of note that is that the seroprevalence is <90% by age 10 from 2009 to 2014. (NHLS = National Health Laboratory Service; GSH = Groote Schuur Hospital; IgG = immunoglobulin G.)*

to be highly endemic for hepatitis A, as it is thought that most children are exposed to the virus by the age of 6 years.[4,14] Our cross-sectional data showed a seroprevalence of 44% among 1 - 7-year-olds. The moderate seroprevalence observed in our study differs from the high seroprevalence (almost 100%) reflected in the studies done in the past.[4,14] However, the study populations in our study and past studies are not directly comparable. For example, Abdool Karim and Coutsoudis[14] looked at seroprevalence in Durban, limited to the black urban population from newborn to 13 years of age, and the results showed that the seroprevalence in this age group in SA was almost 100% (by age 6 years).

Our results indicating a possibility of intermediate HAV endemicity in WCP could be explained by two factors. Firstly, there has been a marked improvement in water sources and sanitation facilities in SA.[15,16] Secondly, there has been socioeconomic development in resource-poor regions, with improved hygiene. Together these factors may lead to change from a high to an intermediate HAV endemicity pattern, a change known as 'epidemiological transition'.[17] Hepatitis A is enterically transmitted, and as hygiene improves, children can be expected to be exposed less frequently, and acquire infection at a later age. Seroprevalence, which reflects past infection, therefore declines in young children.

We were not privy to the socioeconomic status of the subjects tested or their access to clean water sources. However, our selected population may well be representative of an 'average SA household'. In 1990 only 38% of the rural population in SA had access to sanitation facilities, and this figure improved to 61% by 2015.[16] In contrast, 64% of the urban population had access to sanitation facilities in 1990, increasing to 70% by 2015. Access to clean water has improved: in 1990, 66% of the rural population had access to water sources, increasing to 81% by 2015.[15]

The NHLS data from GSH reflected seroprevalence of <90% by age 10, indicating intermediate endemicity from as early as 2009 as per the WHO epidemiological definitions. There was minimal variation through all the age groups from 2009 to 2014. Our analysis of the NICD data on acute HAV infections revealed an increased number of symptomatic infections in the 7 - 40-year group; however, the peak age of symptomatic infection is seen at 6 years.

A similar trend was noted in a recent systematic review of hepatitis A seropreva-

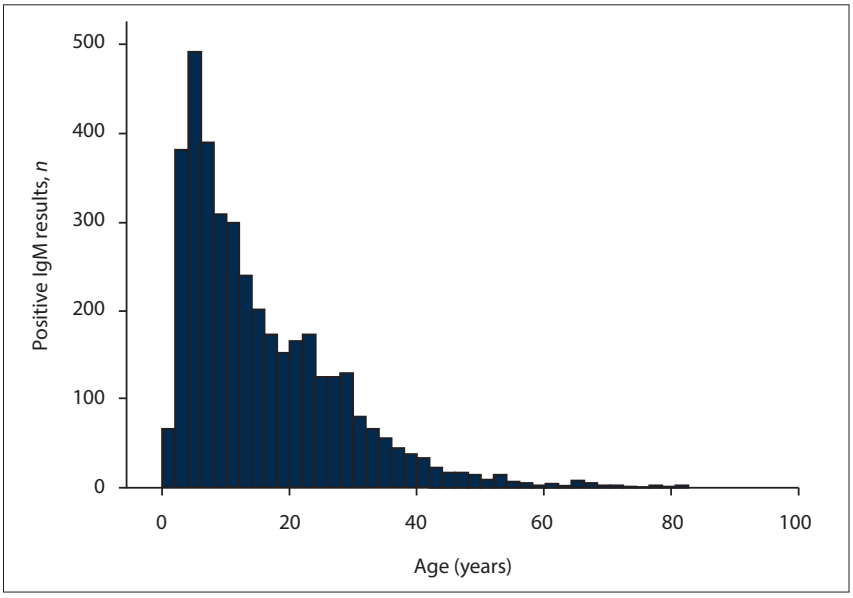

Fig. 3. Age distribution of the NICD WCP hepatitis A surveillance data (absolute numbers). The positive hepatitis A IgM results collected from WCP clinics and hospitals were provided by the NICD, and show a peak of positivity at age 6 years. (NICD = National Institute for Communicable Diseases; WCP = Western Cape Province; IgM = immunoglobulin M.)

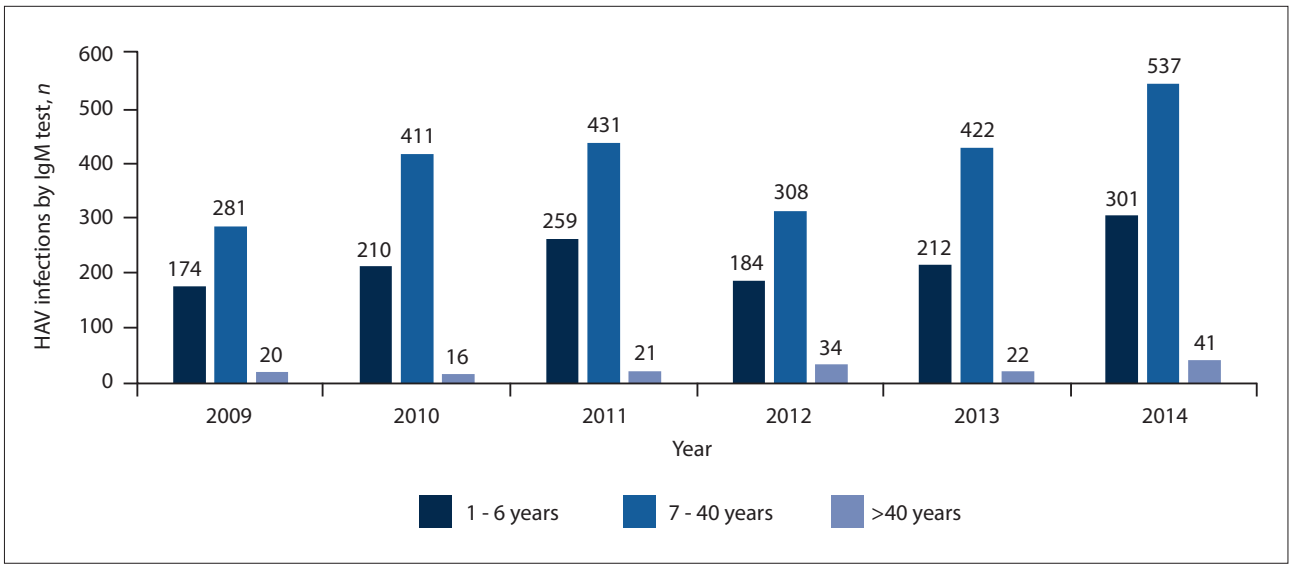

Fig. 4. NICD hepatitis A IgM WCP surveillance data. These are results collected by the NICD from various clinics and hospitals in WCP. The results are displayed as absolute numbers of positive tests and not percentages, as the total number of tested samples per age group (positive and negative) was not available. We grouped the results from the patients into three groups: 1 - 6 years, 7 - 40 years and >40 years. Cases in the >40-year age group across all years were very few. The highest number of clinical hepatitis A cases was in the 7 - 40-year age group from 2009 to 2014. Also, and worryingly, for the period between 2009 and 2014, increasing numbers of cases of hepatitis A acute infection were observed among children aged 1 - 6 years. (NICD = National Institute for Communicable Diseases; WCP = Western Cape Province; IgM = immunoglobulin M; HAV = hepatitis A virus.)

lence in the Middle East and North Africa region (MENA).[18] One of the studies mentioned in this review was conducted in Saudi Arabia and demonstrated a decline in HAV prevalence reported among Saudi children and adolescents over a 20-year period, from 52% in 1989 to 25% in 1997 and 18.6% in 2008.[19] In another study, Memish *et al.*[20] looked at trends in Saudi Arabia from 2000 to 2007, and reported 20 - 30% declining trends. HAV incidence decreased by 42% in <15-year-olds and increased by 61% in >15-year-olds. Another study mentioned in the systematic review looking at seroprevalence in MENA countries was conducted in Tunisia (2000 - 2007), where the prevalence was documented as follows: 91.9% and 80.6% in 2000 and 2007, respectively, among 18 - 20-year-olds, v. 99% and 92% in adults >26 years of age.[21] This study highlighted the susceptibility of adolescents and young adults to HAV. Recent epidemiological studies in India have also shown a decline in hepatitis A seroprevalence among younger children and an increasing susceptibility in older children and young adults,[22] a trend we observed in our study.

A possible explanation for the higher seroprevalence in the NHLS data from GSH as opposed to our cross-sectional study could be selection bias. The NHLS data included results from individuals who were being screened for hepatitis A immunisation status, for example children who were vaccinated and awaiting liver transplants. This could have inflated the seroprevalence in this age group. Nonetheless, the NHLS data also revealed that the seroprevalence was <90% by age 10 and ≥50% by age 15 from 2009 to 2014, which fits the definition of intermediate endemicity as defined by the WHO.[10]

The observed increase in average age of infection is a concern because it is associated with increased morbidity and mortality due to hepatitis A.[17,18,23] For this reason, the WHO recommends integration of the hepatitis A vaccine into the national immunisation schedule for children ≥1 year of age in countries of intermediate or low endemicity. Hepatitis A vaccine is expensive, and its routine use in areas of high endemicity is not cost-effective.[10] Our cross-sectional study showed that >50% of children are already infected with HAV by the age of 4 years. Vaccination against HAV would therefore be beneficial before the age of 2 years in a setting such as WCP. We hypothesise that there will be significant public health benefits in providing routine vaccination against HAV to under-2-year-olds via the Expanded Programme on Immunisation in South Africa.

Study limitations

There were limitations to our study, particularly with regard to the retrospective NHLS data and the NICD surveillance data. The retrospective data only included samples that were sent to the laboratory for testing, and therefore do not represent the population as a whole. Many of the patients whose serostatus was reflected in the retrospective data were also being actively screened for viral hepatitis. The results from the current study also only include samples sent to the laboratory for routine testing from an urban setting in WCP, and therefore do not represent the population as a whole. The samples that were tested for hepatitis A total antibodies only represent the public sector in SA, as we did not obtain samples from the private laboratories. We also did not have data regarding the socioeconomic conditions of the patients whose sera were used. More studies need to be conducted, especially in the rural areas.

Conclusions

The results obtained from the current study reflect a hepatitis A seroprevalence of 44% in the 1 - 7-year-old population. The NHLS data reflect intermediate endemicity from 2009 to 2014. The NICD surveillance data indicate that most of the symptomatic hepatitis A infections occurred in the 7 - 40-year age group in WCP. This pilot study highlights the need for further studies to determine whether a change in the hepatitis A vaccination policy is required. These studies should be extended to the rest of the country, including rural areas.

Declaration. None.

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Author contributions. GDH and BMK conceptualised and designed the study. DRH supervised the laboratory work. AE wrote the study protocol, conducted the sample collection, laboratory assays and data analysis and drafted the manuscript under the supervision of GDH, DRH and BMK. All authors provided comments on the draft manuscript, and approved the final version of the manuscript.

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Conflicts of interest. None.

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