The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt


Summary

Background The population of Egypt has a heavy burden of liver disease, mostly due to chronic infection with hepatitis C virus (HCV). Overall prevalence of antibody to HCV in the general population is around 15–20%. The risk factor for HCV transmission that specifically sets Egypt apart from other countries is a personal history of parenteral antischistosomal therapy (PAT). A review of the Egyptian PAT mass-treatment campaigns, discontinued only in the 1980s, show a very high potential for transmission of blood-borne pathogens. We examine the relative importance of PAT in the spread of HCV in Egypt.

Methods The degree of exposure to PAT by cohort was estimated from 1961–86 Ministry of Health data. A cohort-specific exposure index for PAT was calculated and compared with cohort-specific HCV prevalence rates in four regions.

Findings HCV prevalence was calculated for 8499 Egyptians aged 10–50 years. A significant association between seroprevalence of antibodies to HCV and the exposure index (1:31 [95% CI 1:08–1:59]; p=0.007) was identified across four different regions. In all regions cohort-specific HCV prevalence was lowest in children and young adults than in older cohorts. These lower prevalence rates coincided with the gradual and final replacement of PAT with oral antischistosomal drugs at different points in time in the four regions.

Interpretation The data suggest that PAT had a major role in the spread of HCV throughout Egypt. This intensive transmission established a large reservoir of chronic HCV infection, responsible for the high prevalence of HCV infection and current high rates of transmission. Egypt’s mass campaigns of PAT may represent the world’s largest iatrogenic transmission of blood-borne pathogens.

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Introduction

Egypt has a very high prevalence of antibody against hepatitis C virus (HCV) resulting in a high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma. Around 20% of blood donors are seropositive by ELISA for antibodies to HCV. Children have lower rates of disease, but prevalence rises steeply with age. Desert areas of Egypt have the lowest rates of infection and cities have lower rates than rural areas. Rates in the Nile Delta (Lower Egypt) are higher than in the Nile Valley (Middle Egypt and Upper Egypt). Egypt has a much higher prevalence of antibodies to HCV than other countries in the region and elsewhere with comparable socioeconomic conditions and hygiene for invasive medical, dental, or paramedical procedures. The strong homogeneity of HCV isolate subtypes in Egypt (90%) suggests an epidemic spread of HCV throughout the population.

A very potent mode of transmission for blood-borne pathogens, that sets Egypt apart from other countries, is the extensive use of parenteral antischistosomal therapy (PAT) in a mass-treatment setting. A history of this type of therapy, discontinued only in the 1980s, has been previously implicated as a risk factor for HCV and hepatitis B virus (HBV) antibody positivity.

Schistosomiasis in Egypt dates back to dynastic times. Treatment of schistosomiasis became possible in Egypt in 1918 when J B Christopherson in the Sudan discovered that a series of injections with the antimony salt “tartar emetic” (potassium antimony tartrate) could kill the blood flukes and cure the patient. In Egypt, the country with the world’s greatest schistosomiasis problem, PAT has been extensively practised since the 1920s. Rural health centres and travelling clinics dispensed PAT in the form of mass treatment.

Among the antimony-based PAT drugs, a few could be administered intramuscularly such as stibophen and stibocaprate, however, tartar emetic was the most widely used in Egypt. The recommended treatment regimen was 12–16 intravenous injections. Although these doses were originally administered over 2–3 weeks, after 1960 spacing was changed to one injection per week to lessen patients discomfort. Where sterilisation procedures were carried out, the observed period of boiling for the reusable injection equipment was often less than 2 min. However, it is likely that sterilisation between patients was commonly omitted because of equipment and time constraints. Patients in all stages of treatment and of all age-groups, except for children less than 6 years of age, were treated in a mixed setting. Egyptians in rural occupations often received multiple courses of tartar emetic in their lifetime.

Problems associated with PAT included variable cure rates, high rates of re-infection, and dangerous adverse effects. Most seriously, mass PAT campaigns to control schistosomiasis had great potential to transmit blood-borne pathogens, specifically HCV, because tartar emetic was given in multiple doses by intravenous injection and with insufficiently sterilised injection equipment to people of all age-groups and treatment stages in a mass setting. This
would confer a higher risk of transmission among patients than in vaccination campaigns, where infection equipment was mostly reused among children who would have a low background prevalence of HCV infection. The long duration of the full course of tartar emetic and typical onset of hepatitis C viraemia within 2–4 weeks, would have allowed for those infected with HCV early on in treatment to develop infectious viraemia while still receiving injections. Thus, effective cycles of infection within the treatment units could have been established and sustained. These outbreaks would probably have gone unnoticed because of the absence of acute clinical symptoms in about 80% of recent infections with HCV, the masking side-effects of PAT, and the patients’ underlying schistosomiasis. More noticeable outbreaks of hepatitis caused by HBV were probably a commonplace and commonly considered to be reactions to the tartar emetic. Moreover, immunological effects of chronic schistosomiasis might make individuals less likely to clear HCV after infection.11,12

The first effective oral medications against Schistosoma haematobium—metrifonate and niridazole—became available in the 1970s. Praziquantel, which also has a high cure rate for available in the 1970s. Praziquantel, which also has a high endemic disease treatment between 1961 and 1986, after which use of PAT stopped. To our knowledge, there exists no additional data that accounts for other sources of antischistosomal treatment. Although incomplete, we assumed that the existing data represent a stable proportion of the total treatment that did not vary over time. Population figures for the individual governorates were taken from the census reports 1960, 1966, 1976, and 1986.24 Non-census years were interpolated. Our study focuses on the densely populated governorates along the Nile where 90% of the population live (total population 63·3 million).

A cumulative PAT lifetime exposure index was calculated for every cohort and governorate or region. Most often treated with PAT were children over 5 years of age and adolescents, because they had the highest rates of schistosomiasis infection. This age profile did not change over the duration of the PAT campaigns, and the exposure index is based on the assumption that all residents over 5 years of age in a given year and governorate were at equal risk of infection with schistosomiasis and therefore treated with PAT. This is not completely accurate, but if the differences do not vary over place and time this calculation allows comparisons based on exposures to PAT.

**Procedure**

This specific exposure in a given year and governorate (ery) was defined as the number of antischistosomal injections administered, divided by the population, and multiplied by 100. These governorate specific values of ery were calculated and combined to obtain regional measures of exposure (ery) for four regions situated in the densely populated Nile Delta and Valley: Alexandria; Upper Egypt; Middle Egypt; and Lower Egypt. These regions, the three latter ones consisting of many governorates, differ according to historic prevalence of schistosomiasis and the point in time when PAT was replaced by oral treatment. For each regional age cohort, the annual exposure values of ery were added up to yield the exposure index E ery reflects cumulative exposure to PAT during the years the age cohort was eligible for treatment. For every age cohort (based on age in 1995) and region, these crude PAT exposure risks were then summed for every year that the particular age cohort would have been eligible for treatment (ie, older than 5 years of age). For example, those children aged 15 years in 1995 would have been 6 years old in 1986, and eligible for PAT in 1986 but not in any of the years before. Similarly those aged 40 years in 1995 were 6 years old in 1961 and were theoretically eligible for PAT in every year between 1961 and 1986.

\[ E = \frac{1}{\text{population}} \times \text{PAT} \times 100 \]

Two data sets compiled from large HCV studies done in Egypt in 1995 and 1996 formed the basis for the correlation of HCV antibody prevalence by residence and age cohort. The first, study A, investigated HCV prevalence among Egyptians applying for visas to work abroad.26 The visa applicants were predominantly rural and young to middle-aged adults. The second, study B, is an unpublished community-based study by the Egyptian Ministry of Health and Population,27 which examines the general population by cluster sampling in many different parts of Egypt. The participants were just over 50% female and of all ages, including children and the elderly (figure 1). Both studies used second-generation enzyme immunoassays (version 2.0; Abbott Laboratories, Chicago, IL, USA) to detect antibodies to HCV and the HBV core (HBc). The people who had HCV testing when applying to work overseas gave informed consent for the data to be used for national HCV prevalence calculations. Those people in the community-based study also gave informed consent. All were informed of their test results shortly after the serology was done. Since no one was told that their test results and data would be specifically used for the purpose of this study, all names were removed from the data provided to ensure confidentiality.

To achieve reliable sample sizes in individual age cohorts, prevalence of antibodies to HCV was calculated from the combined samples of studies A and B. The data from study B were adjusted to so that the age of the participants reflected age in 1995, the year the data for study A were collected. Participants who had lived less than 80% of their lifetime in their home governorates were considered to

**Figure 1:** Age distribution and cohort sizes of combined studies A and B

![Figure 1](image-url)
be migrants, and excluded. Based on sampling probabilities it is highly unlikely that any participants took part in both studies.

Cohort-specific prevalence rates for HCV were calculated for each governorate and then combined to reflect cohort-specific prevalence in the previously mentioned four regions. Cohort-specific HCV prevalence curves were smoothed by a 5-year sliding average to account for labelling bias towards ‘even’ ages, and then compared to cohort-specific PAT exposure $E_i$ in the four regions.

**Statistical analysis**

To assess whether there was a statistically significant association between cohort exposure in each governorate and cohort-specific prevalence rates, a logistic-regression model was fit. In addition to including a term for the exposure index, the model included a separate measurement for each 2-year age-group within each region. Thus, the measurement that related to the exposure index in the model quantifies the degree to which the exposure index explained the variation in age-specific prevalence rates between governorates within regions. The model also contained a term to account for the possibility of over-dispersion of the governorate-specific prevalence rates.

Since we expected that HBV would have been transmitted by PAT, at least equally as well as HCV, we compared cohort-specific HBV and HCV antibody prevalence rates in two study B governorates: Cairo (urban) and Sohag (rural).

**Results**

Figure 2 describes the use of PAT in community health centres between 1961 and 1986. The data show the dominance of PAT with tartar emetic in Egypt while intramuscular antimony-based drugs, like stibophen and stibocaptate, had little effect on the overall treatment effort. Between 1964 and 1982 more than 2 million PAT injections per year were given to an average of 250,000 patients. Between 1966 and 1969 more than 3 million injection doses were annually administered, over 96% were tartar emetic given intravenously. In the 1960s the number of injections per patient, averaged over the whole treatment effort, was nine. After 1975 it dropped to six and fewer.

After the exclusion of migrants and combination of the samples from studies A and B, HCV prevalence was calculated for the combined sample of 8499 Egyptians between the ages of 10 and 50 years living in the governorates being assessed (figure 3). Overall age-adjusted prevalence of antibodies to HCV was 21.9% (95% CI 21.0–22.8). Prevalence was lowest in long-term residents of Cairo (8.2%) and Alexandria (5.9%). In the rural regions, prevalence was relatively low in Upper Egypt (19.4%), intermediate in Middle Egypt (26.5%), and highest in Lower Egypt (28.4%). Women had a similar or slightly lower prevalence of antibodies to HCV than men.

The smoothed age prevalence curves of the three regions and two city governorates (figure 4) show a progressive rise in prevalence of HCV to high rates in those people in age-groups over 20 years. In Lower Egypt, prevalence among people were 40–50-years of age reaches 50–55%. The same age-group shows rates of 40–50% in Middle Egypt and 35–40% in Upper Egypt. Among young Egyptians, no clear pattern for prevalence by age is visible. At certain points between the ages of 15 and 24 years, however, prevalence starts to rise steeply in all regions.

Figure 5 compares regional cohort-specific prevalence of antibodies to HCV to regional cohort-specific exposure index values for the age cohorts that include people aged 5 to 40 years, and suggests that the variation in seroprevalence of antibodies to HCV between regions might be explained by PAT exposure. In addition, by means of logistic regression, we assessed the degree to which the exposure index explained variations in prevalence rates between governorates within regions. Fitting a model that controlled for region and age, we found a significant association between seroprevalence of antibodies to HCV and the exposure index with an odds ratio of 1.31 (95% CI 1.08–1.59; p=0.007). According to this model, for any given age-group and region, if the exposure index of one governorate was 100 points higher than that of another, the prevalence of antibody to HCV was 31% greater. In both the governorates selected for assessment, the
Discussion

The rate and geographical pattern of prevalence of antibodies to HCV in Egypt confirm the high prevalence and its distribution reported in previous studies. This pattern corresponds to the distribution of schistosomiasis in this century. Whereas Lower Egypt has always had high rates of schistosomal infection, prevalence in Middle and Upper Egypt increased only as a result of conversion from basin to perennial irrigation. City dwellers have always had lower rates of schistosomiasis.

The comparison of age-specific prevalence and exposure index (figure 5) has shown a strong association between the two factors beyond the increase of HCV prevalence with age in any population, supporting the hypothesis that PAT was important in establishing a large reservoir of HCV in Egypt. In Middle and Upper Egypt, PAT was replaced by oral drugs in the mid- to late-1970s. In Alexandria, use of PAT was stopped as soon as praziquantel became available in 1982. In surrounding Lower Egypt, some use of PAT continued into the mid-1980s. Stopping the use of PAT, as reflected by the foot of the exposure index curve and the subsequent rise in exposure with every age cohort, is closely mirrored by a steep increase in prevalence of antibody to HCV in the four regions. In the most extreme case, Lower Egypt, only age cohorts containing children younger than 15 years were not exposed to PAT at all. In PAT-exposed people aged 15 years and older, prevalence of antibodies to HCV rises in unison with the exposure index value. The results of the regression analysis confirm the strong association between exposure index and HCV prevalence by age, even when adjusted for the effects of age and region.

An example of how easily HCV could have infected so many individuals during PAT campaigns is shown by excerpts from a WHO report: “Patients are grouped according to weight and appropriate dose and are lined up in queues for admission in turn for injection . . . . The stranger to mass therapy with Tartar Emetic is certainly to be confounded by the speed and apparent safety of the administration of the drug. . . . The skilful doctor began injecting at 9.20 am and completed 504 injections of men, women and children by 10.10 am. Allowing for a 10-min rest, the time taken for each injection was thus just under 5 s. . . . This remarkable performance is being repeated at various tempos all over Egypt . . . ” and “The used syringe is placed in an ‘out’ tray, from which it is taken by the nurse, washed through and boiled for a minute or two. As soon as the syringe is cold, it is filled with a volume of the drug solution. . . . It is then placed in the ‘in’ tray. . . . There are usually 20 to 30 syringes in rotation.”

The hypothesis that sterilisation procedures for PAT were responsible for HCV transmission is further supported by the HBV test results. If parenteral therapy against schistosomiasis was a major factor spreading HCV and both viruses were present in the population during mass treatment campaigns, one would expect to see even higher rates of prevalence of antibodies to HBc, as HBV is more infectious than HCV. Such a pattern has been found by Darwish and colleagues in a village in Qualioubia. Sherif and colleagues have also previously reported high rates of antibody to HBV in Egypt.

However, one would not predict as strong a correlation between HBV prevalence by age and exposure to PAT as for HCV, since HBV is more easily transmitted sexually and vertically from mother to infant than HCV. As expected, our study shows that prevalence of antibody to HBc by age is consistently higher than that for antibody HCV in the two test governorates in which this was assessed (figure 6).

The data support the hypothesis that nationwide schistosomiasis control campaigns using PAT spread HCV (and probably HBV) throughout Egypt over the course of decades. Whereas other countries have also used injection
therapy against schistosomiasis, Egypt’s efforts are set apart by the enormous size of its schistosomiasis problem, the endemicity of both *S. haematobium* and *S. mansoni*, and—somewhat paradoxical—the commitment and scope of its public-health system. The Egyptian medical and public-health community had recognised schistosomiasis as its major public-health problem early in this century. The country made a major effort to control this problem with the best technology available: widespread mass therapy with intravenous tartar emetic. In other countries with endemic schistosomiasis but where commitment from the public-health community and resources were lacking, schistosomiasis control efforts were less population intensive and geographically extensive. This may explain who other countries with a history of PAT use do not have similarly high rates of HCV seropositivity.

The sheer size of the antischistosomiasis effort in Egypt, combined with the characteristics of PAT, provided an effective mechanism for establishment of HCV in the Egyptian population. This is the world’s largest iatrogenic transmission of blood-borne pathogens known to date, which probably led to a massive increase in the reservoir for HCV and HBV in the general population. Because of the high rate (85%) of chronicity in HCV infections, this reservoir is responsible for the high incidence of HCV transmission in Egypt today.

**Contributors**

Christina Frank designed the study, analysed the data, and wrote the paper. Mostafa K Mohamed helped prepare the protocol, obtained data from the Ministry of Health (MOH), collected data on HCV prevalence, and helped in analysis and writing of the paper. G Thomas Strickland was one of the original researchers who found the characteristics of PAT and HCV prevalence in Egypt. He provided support on the project, took part in designing the study, and participated in writing and revision of the paper. Daniel Lavanchy and Ray Farghaly AG, Barakat RM, Prevailing, impact and risk factors of hepatitis C virus infection in Egyptian blood donors. *Am J Trop Med Hyg* 1993; 49: 440–47.


