

Prevalence of hepatitis and HIV in Pakistan

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Abstract

Background: Based on the first hepatitis serosurvey conducted in 2008, Pakistan was identified as the country with the second highest hepatitis C disease burden in the world.

Aim: To compare the current hepatitis seroprevalence with the 2008 figures and offer recommendations for elimination in the country.

Methods: Using a stratified two-stage sample design, we collected blood samples from individuals living in the 29 districts of Sindh Province, Pakistan. The samples were tested at the hepatitis control programme laboratory using the national testing guidelines and the data were analysed using Epi Info and SPSS version 19.0.

Results: Of the 6672 persons tested, 70 (1.0%) (42 male, 28 female) were hepatitis positive. Hepatitis prevalence increased with age. Family history of chronic liver disease (odds ratio 2.5) and shaving at the barber's shop (odds ratio 2.2) were the major risk factors. Only 2 people (a husband and wife) were reactive to all the 3 HIV rapid diagnostic tests, giving an overall HIV prevalence of 0.02%.

Conclusion: There is a need for mass testing and treatment in Pakistan through a multisectoral, collaborative approach, to halt the spread of hepatitis and prevent disease progression to cirrhosis and hepatocellular carcinoma.

Keywords: hepatitis, HBV, HCV, HIV, Sindh, cirrhosis, hepatocellular carcinoma, Pakistan

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Introduction

Hepatitis B is a vaccine-preventable disease, and WHO recommends a dose of the monovalent hepatitis B vaccine within 24 hours of birth in countries that have HBsAg prevalence > 2%. Pakistan has not yet introduced hepatitis B birth dose in the Expanded Program on Immunization (EPI), children mostly receive hepatitis B as pentavalent vaccine at 6, 10 and 14 weeks, leaving a 6-week window during which the newborn could get infected. Most hepatitis B virus (HBV) infections occur at birth or during the first few years of life, and once exposed 90% of infected people will carry the virus for life and may develop chronic liver disease, cirrhosis and liver cancer during adulthood. Many HBV infected persons also get infected with delta virus and the dual infection leads to more complications and premature death.

In Pakistan, delta virus is most prevalent in Baluchistan and Sindh provinces, followed by Punjab. Monovalent hepatitis B vaccine costs 5 cents per dose and it can prevent hepatitis B and D infection as well as mother-to-child transmission of HBV and liver cancer. It is therefore cost-effective to prevent hepatitis B and administer the vaccine to all newborn babies within the first 24 hours of life.

There is currently no vaccine for hepatitis C prevention, therefore, prevention of the risk factors is the only prevention strategy. The virus is called a silent killer

because following exposure, it continues to circulate in the body without any signs or symptoms and finally presents as chronic liver disease and cirrhosis, leading to death. WHO recommends that all patients having active hepatitis C virus (HCV) infection should be treated using direct acting antivirals (DAAs). Pakistan currently produces the world's most cost-effective pan-genotypic DAAs and has developed its national hepatitis B and C treatment guidelines with an intention to treat all cases.

HIV usually spreads through sexual contact or intravenous drug use among people with risky behaviours. Transmission of the disease in the general population can occur through interspousal route, transfusion of unscreened blood, use of unsafe injections, and poor infection control. The outbreak of HIV in Ratto Dero District of Sindh was attributed to reuse of syringes for therapeutic injections against common ailments.

The first national serosurvey on hepatitis B and C prevalence in Pakistan was conducted in 2005 and since then many people have been treated with interferon and now with DAAs. Some preventive actions were also taken. Therefore, this serosurvey was conducted to document the prevalence of hepatitis B and C after almost a decade, as well as the prevalence of hepatitis delta and HIV.

Methods

Sample selection

The study population comprised the entire urban and rural populations of Sindh Province as defined by the 2017 census. All household members present at the time of the survey were included except non-residents who were visiting. The Sindh Bureau of Statistics conducted the sampling using the same methodology that was used in the 2008 survey (1). A stratified two-stage sample design was used. The total sample size was 5771 (199 individuals per district). Based on the expected average household size of 5 members, they selected 40 households in each district. They selected 8 clusters of 5 households each using probability proportional sampling in each district to reach the sample size, giving a total of 1160 households.

The survey team comprised an enumerator, a male interviewer who was also supervisor of the team, a female interviewer, and a phlebotomist. After identifying the households, the male interviewers interviewed the males while the females interviewed females. The phlebotomist performed finger prick rapid test for HBV, HCV and HIV and collected venous samples. Four teams were trained and assigned 7 districts to cover, except team D which covered 8 districts. The door of each selected household was marked with a unique identifier after interviewing the household members. Permission was taken from the community leaders before the commencement of the survey.

All participants aged ≥ 18 years signed a consent form, and assent was obtained from parents or caregivers of those aged < 18 years. Each member of the selected households filled the questionnaire, which included questions about education, marital status and exposure to risk factors of the disease. All those who took the diagnostic test received their results. The households were visited 2 times in 2 consecutive days to capture those who were absent during the first visit or whose houses were locked. Anyone who could not be reached after repeated visits was classified as absent or no response.

Laboratory testing

The WHO prequalified rapid test device (SD Bioline) was used for hepatitis B surface antigen (HBsAg) and anti-HCV tests. Appearance of two pink lines (control and test) was taken as a reactive test. Three rapid test devices were used for HIV tests: Alere kit (HIV combo), Unigold, SD Bioline. Any participant whose sample was reactive on Alere was tested with Unigold, and any participant whose sample was reactive to Unigold was tested with SD Bioline. Venous samples were collected for all HBsAg and anti HCV reactive cases. HCVRNA and HBVDNA were run on GeneXpert machine at the district headquarters hospitals and delta virus was run on ELISA. Cases with detected HCVRNA or HBVDNA were linked to the hepatitis programme for treatment. There were errors in GeneXpert reporting in 64 cases because of low temperatures in the laboratories, which caused improper

homogenization of the serum. However, Cepheid experts were invited to help resolve the issue, after which new blood samples were collected from those individuals in June 2020. Fourteen of the cases did not agree to participate in the second test run, therefore, HCVRNA for the remaining consenting 50 participants was used for the RTPCR at the hepatitis control programme laboratory.

Case management and data analysis

All cases with HBsAg either alone or coinfecting with delta virus, or those with HCVRNA, or HIV reactive on all 3 tests, were referred to the provincial hepatitis and HIV/AIDS programmes, respectively, for management. To maintain patient confidentiality, all personal identifiers were masked, and data was anonymised.

The data were analysed using Epi Info and SPSS version 19.0. Clinical characteristics were summarized as frequencies and percentages. A 95% confidence interval was used for qualitative categorical variables, $\text{mean} \pm \text{S.D}$ for quantitative or continuous variables, i.e. age and years of education, etc. Statistical comparison was performed using Student's t-test and ANOVA for quantitative variables and Chi-square or Fisher test (for values < 5) for qualitative variables. $P < 0.05$ was considered significant. Disease prevalence was calculated using the total number of participants that were HBsAg or anti-HCV reactive (numerator) and the total number of those who were tested (denominator).

Results

Demographics

The survey was conducted among 1153 households in 29 districts between November 2019 and mid-June 2020. It screened 6672 (98.6%) for HBV, HCV and HIV out of 6769 (94.9%) household members present at the time of survey. There was an average of 6 persons per household. Of the 6769 household members, 3214 (47.5%) were male, 3547 (52.4%) female and 8 transgender (0.1%). Majority (1818 or 57.2%) of the 3181 individuals whose educational information was available were illiterates, 13% were educated up to 5 years, and 16% had 6–10 years education. Four hundred and one cases (11.2%) had family history of liver disease and 61 (15%) had taken HCV treatment in the past.

HBsAg prevalence by gender and age

Seventy (1.0%) of the 6672 persons screened had HBsAg; 42 male and 28 female. All the 8 transgender children were HBsAg negative. HBsAg prevalence increased with age and was higher among male participants (Table 1). Fourteen (20.0%) of the HBsAg cases had family history of liver disease.

Risk factors for hepatitis infection

Family history of chronic liver disease (OR 2.5) and shaving at the barber's shop (OR 2.2) were the major and significant risk factors. Of the 70 HBsAg reactive samples, 56 (80%) showed HBVDNA presence on GeneXpert. HBVDNA levels were $> 20\ 000$ in 16 persons,

Table 1. Prevalence of HBsAg by age and gender, Sindh Province, Pakistan

Age (years)	Overall				Male				Female			
	Subject tested	HBs Ag positive			Subject tested	HBs Ag positive			Subject tested	HBs Ag positive		
		No.	%	95% CI		No.	%	95% CI		No.	%	95% CI
< 5	633	2	0.3	0.12–0.75	318	0	0.0	–	311	2	0.6	0.25–1.53
5–11	1492	9	0.6	0.21–1.00	745	6	0.8	0.16–1.45	743	3	0.4	0.05–0.86
12–17	863	7	0.8	0.14–1.25	410	5	1.2	0.02–1.93	453	2	0.4	0.17–1.05
18–24	808	16	2.0	1.02–2.94	356	9	2.5	0.90–4.16	452	7	1.6	0.41–2.69
25–34	954	20	2.1	1.27–3.13	405	14	3.5	1.86–5.54	549	6	1.1	0.22–1.96
35–44	761	8	1.05	0.33–1.78	356	4	1.1	0.03–2.22	405	4	1.0	0.02–1.95
45–54	540	4	0.7	0.02–1.46	259	3	1.2	0.14–2.46	281	1	0.4	0.34–1.05
55–64	361	2	0.6	0.21–2.32	159	0	0.0	–	202	2	1.0	0.38–2.36
65–74	203	2	1.0	0.37–2.34	121	1	0.8	0.79–2.44	82	1	1.2	1.16–3.60
≥ 75	57	0	0.0	–	31	0	0.0	–	26	0	0.0	–
Total	6672	70	1.1	0.80–1.29	3160	42	1.3	0.93–1.73	3504	28	0.8	0.50–1.09

Transgender 8, under 5 years 4, ages 5–11 years 4, all HBsAg -ve

Table 2. HBsAg and HBV DNA positivity by gender and age, Sindh Province, Pakistan

	Tested	HBsAg positive	Detected No (%)	HBV DNA			
				≤ 1999 No (%)	Viral load (IU/ml)		
					2000–9999 No (%)	10 000–19 999 No (%)	≥ 20 000 No (%)
Overall	6672	70	56 (80.0)	29 (51.8)	10 (17.8)	1 (1.8)	16 (28.6)
Gender							
Male	3160	42	33 (78.6)	20 (66.6)	5 (15.2)	1 (3.0)	7 (21.2)
Female	3504	28	23 (82.1)	9 (39.1)	5 (21.7)	–	9 (39.1)
Transgender	8	–	–	–	–	–	–
Age in years							
< 5	633	2	2 (100)	–	–	–	2 (100)
5–11	1492	9	8 (88.9)	2 (25.0)	–	–	6 (75.0)
12–17	863	7	7 (100)	5 (83.3)	–	–	1 (16.7)
18–24	808	16	11 (68.7)	4 (36.4)	2 (18.2)	–	5 (45.4)
25–34	954	20	16 (80.0)	12 (75.0)	3 (18.7)	–	1 (6.3)
35–44	761	8	7 (87.5)	4 (57.1)	2 (28.6)	1 (14.3)	–
45–54	540	4	2 (50.0)	1 (50.0)	–	–	1 (50.0)
55–64	361	2	1 (50.0)	–	1 (100)	–	–
65–74	203	2	2 (100)	1 (50.0)	1 (50.0)	–	–
≥ 75	57	–	–	–	–	–	–
Total	6672	70	56 (80.0)	29 (51.8)	10 (17.8)	1 (1.8)	16 (28.6)

all of whom were < 15 years old and mostly (9) female (Table 2). Twenty-one (32.8%) of the 64 participants screened for anti-delta virus were reactive (mostly in Sanghar, Khairpur and Sukkur) and 413 (6.1%) of the 6672 participants were reactive for anti-HCV. Anti-HCV was reactive in 183 (5.8%) males and 230 (6.6%) females. Sixty-five (18.6%) cases had family history of HCV and 61 (15%) had history of HCV treatment.

Women had higher anti-HCV exposure than men in the 25–44 years age group, but exposure was the same for the older age groups (Table 3). All transgender children were anti-HCV negative.

There was strong association between hepatitis infection and family history of liver disease (21.62%), use of therapeutic injections (12%), blood transfusion (14.8%), and hospitalization (13.8%) (Table 4). Two hundred and

Table 3. Prevalence of anti-HCV by age and gender (95% CI), Sindh Province, Pakistan

Age (years)	Subject tested	Overall			Subject tested	Male			Subject tested	Female		
		No.	%	95% CI		No.	%	95% CI		No.	%	95% CI
< 5	633	1	0.2	0.00–0.47	318	0	0.0	–	311	1	0.3	0.00–0.95
5–11	1492	4	0.3	0.01–0.53	745	1	0.1	0.00–0.40	743	3	0.4	0.00–0.86
12–17	863	11	1.3	0.53–2.02	410	6	1.5	0.30–2.63	453	5	1.1	0.14–2.07
18–24	808	22	2.7	1.60–3.84	356	12	3.4	1.50–5.25	452	10	2.2	0.86–3.57
25–34	954	82	8.6	6.82–10.37	405	26	6.4	4.03–8.81	549	56	10.2	7.67–12.73
35–44	761	89	11.7	9.41–13.98	356	34	9.6	6.50–12.60	405	55	13.6	10.24–16.92
45–54	540	88	16.3	13.18–19.41	259	46	17.8	13.11–22.42	281	42	15.0	10.78–19.12
55–64	361	68	18.8	14.80–22.87	159	31	19.5	13.34–25.65	202	37	18.3	12.98–23.65
65–74	203	40	19.7	14.23–25.18	121	22	18.2	11.31–25.05	82	18	22.0	12.99–30.91
≥ 75	57	8	14.0	5.02–23.05	31	5	16.1	3.18–29.08	26	3	11.5	0.00–23.82
Total	6672	413	6.2	5.61–6.77	3160	183	5.8	4.98–6.61	3504	230	6.6	5.74–7.38

Transgender 8, under 5 years 4, ages 5–11 years 4, all anti-HCV -ve

Table 4. Risk factors for HCV, Sindh Province, Pakistan

		No. of subjects	HCV prevalence n (%)	OR (95% C.I.)
Live or have ever lived with someone chronic liver disease member	Yes	444	96 (21.6)	** 2.69(2.08–3.47)
	No	322	299 (9.3)	Reference
Received any therapeutic injection in the last 12 months	Yes	2623	315 (12.0)	** 1.63 (1.26–2.09)
	No	1046	81 (7.7)	Reference
Received a blood transfusion	Yes	290	43 (14.8)	* 1.50 (1.05–2.09)
	No	3361	352 (10.5)	Reference
Hospitalized in the last 12 months	Yes	793	110 (13.9)	* 1.47 (1.16–1.86)
	No	2872	284 (9.9)	Reference
Tattooed, pierced or received acupuncture	Yes	488	71 (14.6)	* 1.49 (1.14–1.97)
	No	3184	325 (10.2)	Reference
Received an invasive dental treatment	Yes	455	59 (13.0)	* 1.33 (0.98–1.77)
	No	3217	335 (10.4)	Reference
Shaved by a traditional barber (Males)	Yes	952	105 (11.0)	1.15 (0.83–1.58)
	No	719	70 (9.7)	Reference

ten (60.2%) samples out of 349 tested for HCVRNA were positive (Table 5).

Only 2 participants (a husband and wife) were reactive to all 3 rapid HIV tests, giving an overall HIV prevalence of 0.02%.

Discussion

In our study, the prevalence of anti-HCV was 6.1%, HBsAg 1.1%, anti-delta 32.8%, and HIV 0.03%. The 2008 national hepatitis survey showed 2.5% HBsAg prevalence and 5% anti-HCV prevalence (1), placing Pakistan as the country with the second highest HCV burden (2). Punjab and Sindh provinces conducted serosurveys in 2018 (3) and 2019 (4), which showed a decrease in HBsAg prevalence to 1.1% in both provinces, an increase in HCV prevalence

to 8.9% in Punjab and 6.1% in Sindh, and an overall prevalence of 7.5%. Pakistan currently has the highest HCV burden in the world.

The HBV prevalence is decreasing because of childhood vaccination administered under EPI (5) and adult vaccination under the hepatitis programme. However, there is a great need to introduce birth dose hepatitis B vaccine at the national level to achieve HBV elimination by 2030.

The risk factors for HCV remain the same as in 2008 (1) but exposure has increased. Establishment of provincial blood transfusion authorities (6), use of auto-disabled syringe in healthcare settings (7), development of HBV and HCV treatment guidelines (8,9), and production of generic DAAs (10) can help remedy the situation.

Table 5. HCV cases by age and gender, Sindh Province, Pakistan

	Tested	Anti-HCV positive No (%)	HCV RNA tested No (%)	Positive No (%)	HCV RNA Negative No (%)	Error No (%)
Overall	6672	413 (6.2)	349 (84.5)	210 (60.2)	125 (35.8)	14 (4.0)
Gender						
Male	3160	183 (5.8)	156 (85.2)	86 (55.1)	65 (41.7)	5 (3.2)
Female	3504	230 (6.6)	193 (83.9)	124 (64.2)	60 (31.1)	9 (4.7)
Transgender	8	0	–	–	–	–
Age in years						
< 5	633	1 (0.2)	1 (100)	–	1 (100)	–
5–11	1492	4 (0.3)	4 (100)	1 (25.0)	2 (50.0)	1 (25.0)
12–17	863	11 (1.3)	11 (100)	5 (45.4)	5 (45.4)	1 (9.1)
18–24	808	22 (2.7)	22 (100)	12 (54.5)	10 (45.5)	–
25–34	954	82 (8.6)	75 (91.5)	52 (69.3)	22 (29.3)	1 (1.3)
35–44	761	89 (11.7)	71 (79.8)	48 (67.6)	20 (28.2)	3 (4.2)
45–54	540	88 (16.3)	78 (88.6)	53 (68.0)	22 (28.2)	3 (3.8)
55–64	361	68 (18.8)	49 (22.1)	21 (42.9)	24 (49.0)	4 (8.2)
65–74	203	40 (19.7)	30 (75.0)	10 (33.3)	19 (63.3)	1 (3.3)
≥ 75	57	8 (14.0)	8 (100)	8 (100)	–	–
Total	6672	413 (6.2)	349 (84.5)	210 (60.2)	125 (35.8)	14 (4.0)

3 (0.04%) cases had coinfection with HBV and HCV

In 2021, the federal government requested the Centre for Disease Analysis, USA, to conduct an HCV modelling for Pakistan (11) and the modelling showed a viraemic prevalence of 4.3%, with 9.8 million cases having HCV and requiring treatment. Yearly data collected from the hepatitis programmes and the private sector (personnel communication) showed that Pakistan has diagnosed only 32% of the infected population and treated 16%. These figures are very low when compared with the WHO's 2030 elimination targets of 90% diagnosed and 80% treated (12).

Considering the high HCV disease burden, Pakistan has developed a national HCV elimination plan, which includes the numbers to be screened, tested and treated and the targets for new infection prevention as well as the costs. The figures indicate that we have to increase the current testing and treatment rates by 5 times and reduce new infections by 8–10 times the current figures to achieve the disease elimination targets. The targets are ambitious but achievable. The modelling experts have shown that any investment in HCV elimination in Pakistan will yield quick dividends within a few years (13). Decentralisation, integration and task-shifting have been found to be effective in HCV elimination in most countries (14). Pakistan also applies the same principle; screening is conducted at the primary care level, reflex testing will be conducted for all anti-HCV reactive cases and the blood samples will be sent to the nearest laboratory for nucleic acid amplification testing. Treatments shall be administered at the nearest health facility to wherever anti-HCV testing was conducted.

Egypt is the first country to achieve HCV elimination with mostly domestic, and some World Bank, funding (15). The Prime Minister of Pakistan has been briefed about the grave situation in the country and he has agreed to mobilise local funding and supply commodities (point-of-care test, PCRs and treatment kits) to the provinces through the national programme.

Limitations of the study

This survey was conducted during the winter months when the temperature was 3–4°C. This caused homogenisation of blood samples, resulting in errors in PCR testing using the GeneXpert machine. Our laboratories are generally airconditioned but do not have heating to maintain 18–20°C.

Conclusions

Pakistan currently has the highest HCV prevalence, there is a need for more efforts to improve prevention. The high number of infected cases found in this study shows the need for timely mass testing and treatment through the national HCV elimination programme to halt disease progression to cirrhosis and hepatocellular carcinoma. Joint action by all relevant stakeholders is needed to eliminate HCV in Pakistan, including necessary legislation and regulation to prevent syringe reuse, ensure adherence to standard guidelines on screening before blood donations, and improve infection prevention and control.

Figure 2. HBsAg prevalence by district, Sindh Province, Pakistan

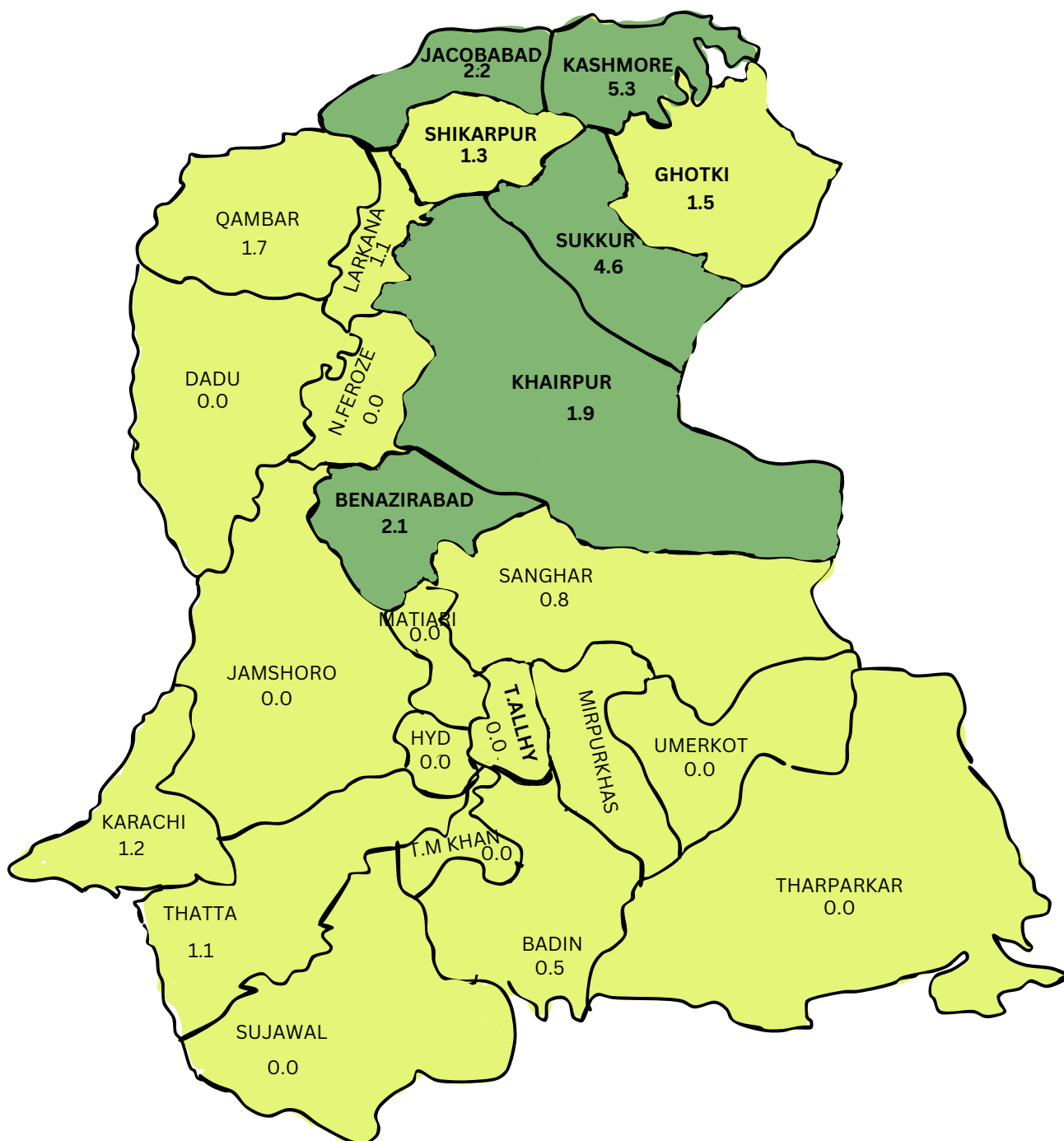
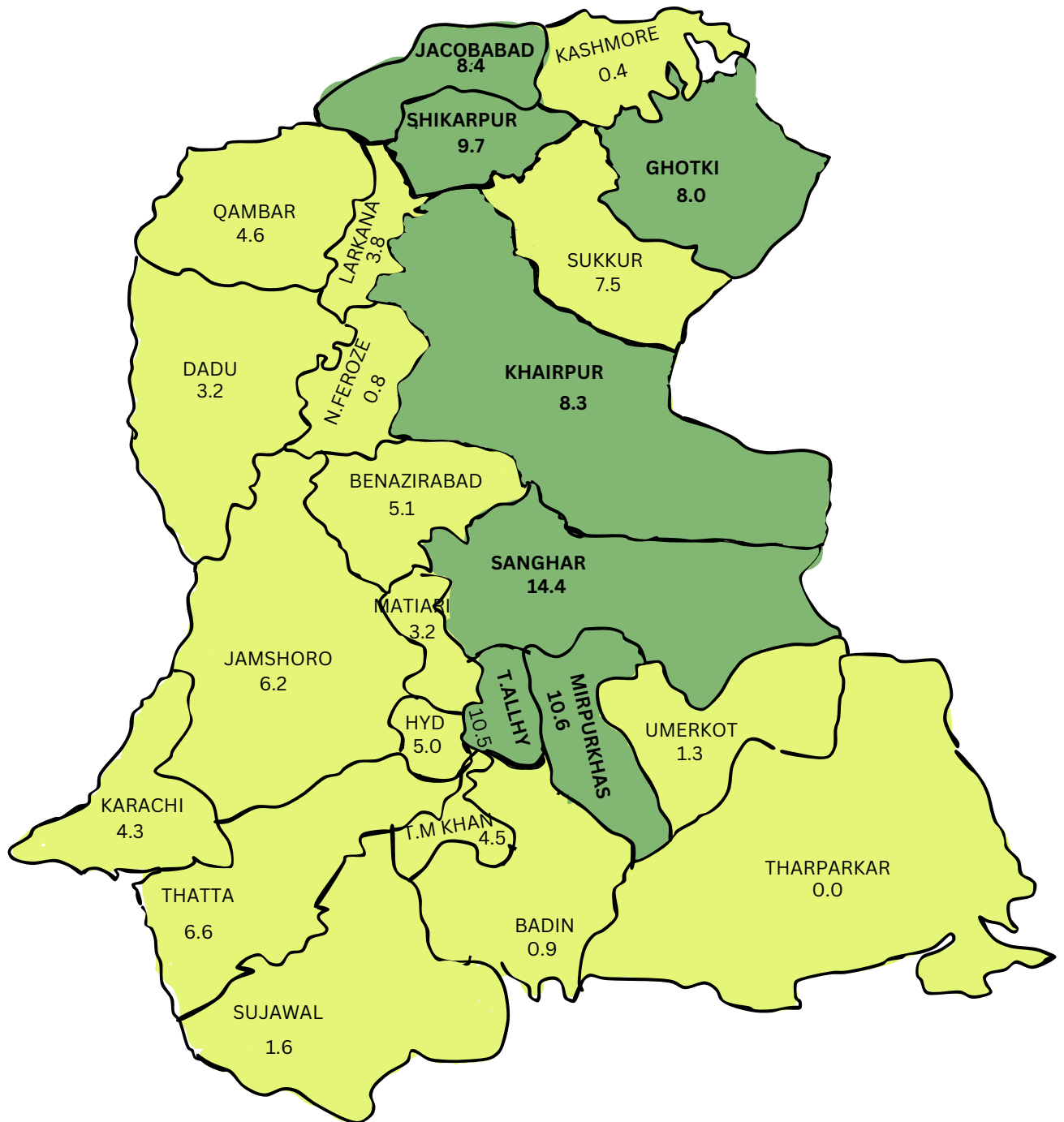


Figure 3. HCV prevalence by district, Sindh Province, Pakistan



Prévalence de l'hépatite et du VIH au Pakistan

Résumé

Contexte : Sur la base de la première enquête sérologique sur l'hépatite menée en 2008, le Pakistan a été identifié comme le deuxième pays au monde ayant la plus forte charge de morbidité due à l'hépatite C.

Objectifs : Comparer la séroprévalence actuelle de l'hépatite aux chiffres de 2008 et formuler des recommandations en vue de son élimination dans le pays.

Méthodes : À l'aide d'un plan d'échantillonnage stratifié à deux degrés, nous avons prélevé des échantillons sanguins auprès de personnes vivant dans les 29 districts de la province du Sindh au Pakistan. Ils ont été analysés au laboratoire chargé de la mise en œuvre du programme de lutte contre l'hépatite, conformément aux lignes directrices nationales en matière de dépistage. Les données ont été traitées à l'aide des logiciels Epi Info et SPSS version 19.0.

Résultats : Sur les 6672 personnes testées, 70 (1,0 %), dont 42 hommes et 28 femmes, étaient positives à l'hépatite, et sa prévalence augmentait avec l'âge. Les antécédents familiaux de maladie chronique du foie (odds ratio : 2,5) et le rasage chez le coiffeur (odds ratio : 2,2) étaient les principaux facteurs de risque. Seules deux personnes (mari et femme) ont réagi aux trois tests rapides de dépistage du VIH, donnant une prévalence globale de 0,02 %.

Conclusion : Il est nécessaire de procéder à un dépistage et à un traitement de masse au Pakistan, en appliquant une approche multisectorielle et collaborative qui permettra de freiner la propagation de l'hépatite et d'éviter l'évolution de la maladie vers la cirrhose et le carcinome hépatocellulaire.

معدل انتشار التهاب الكبد وفيروس العوز المناعي البشري في باكستان

هما قريشي، إعجاز عالم، ذو الفقار داريجو، حسن محمود

الخلاصة

الخلفية: استنادًا إلى المسح المصلي الأول لالتهاب الكبد الذي أجري في عام 2008، تبين أن باكستان هي البلد الذي يحتل المرتبة الثانية فيما يخص عبء مرض التهاب الكبد C في العالم.

الهدف: هدفت هذه الدراسة إلى مقارنة معدل الانتشار المصلي الحالي لالتهاب الكبد بأرقام عام 2008، وتقديم توصيات للقضاء عليه في باكستان. طرق البحث: باستخدام تصميم طبقي لجمع العينات على مرحلتين، جمعنا عينات دم من أفراد يعيشون في 29 مقاطعة في إقليم السند بباكستان. واختُبرت العينات في مختبر برنامج مكافحة التهاب الكبد، مع اتباع المبادئ التوجيهية التي وضعتها منظمة الصحة العالمية بشأن الاختبار. وحُللت البيانات باستخدام برنامج Epi Info، وكذلك الإصدار 19.0 من برنامج SPSS.

النتائج: من بين 6672 شخصًا خضعوا للاختبار، تبين أن 70 منهم (1.0%) (42 ذكرًا و28 أنثى) مصابون بالتهاب الكبد، وارتفع معدل انتشار التهاب الكبد مع التقدم في العمر. وأما أهم عوامل خطر الإصابة فهي: التاريخ العائلي للإصابة بأمراض الكبد المزمنة (نسبة الأرجحية: 2.5) والحلاقة في دكان الحلاقة (نسبة الأرجحية: 2.2). كما تبين أن شخصين فقط (زوجًا وزوجة) كانت نتائج تحليلاتهم إيجابية في جميع اختبارات فيروس العوز المناعي البشري السريعة الثلاثة، الأمر الذي يشير إلى معدل انتشار عام للفيروس يبلغ 0.02%.

الاستنتاجات: ثمة حاجة إلى إجراء اختبارات شاملة وعلاج جماعي في باكستان باستخدام نهج تعاوني ومتعدد القطاعات مما سيساعد على وقف انتشار التهاب الكبد ومنع تفاقم المرض إلى الإصابة بتليف الكبد وسرطان الكبد الخلوي.

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