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The burden of hepatitis C virus infection in Punjab, India: A population-based serosurvey

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Abstract

Introduction

Hepatitis C virus (HCV) infection prevalence is believed to be elevated in Punjab, India; however, state-wide prevalence data are not available. An understanding of HCV prevalence, risk factors and genotype distribution can be used to plan control measures in Punjab.

Methods

A cross-sectional, state-wide, population-based serosurvey using a multi-stage stratified cluster sampling design was conducted October 2013 to April 2014. Children aged ≥5 years and adults were eligible to participate. Demographic and risk behavior data were collected, and serologic specimens were obtained and tested for anti-HCV antibody, HCV Ribonucleic acid (RNA) on anti-HCV positive samples, and HCV genotype. Prevalence estimates and adjusted odds ratios for risk factors were calculated from weighted data and stratified by urban/rural residence.

Results

5,543 individuals participated in the study with an overall weighted anti-HCV prevalence of 3.6% (95% Confidence Interval [CI]: 3.0%–4.2%) and chronic infection (HCV Ribonucleic acid test positive) of 2.6% (95% CI: 2.0%–3.1%). Anti-HCV was associated with being male (adjusted odds ratio 1.52; 95% CI: 1.08–2.14), living in a rural area (adjusted odds ratio 2.53; 95% CI: 1.62–3.95) and was most strongly associated with those aged 40–49 (adjusted odds ratio 40–49 vs. 19–29-year-olds 3.41; 95% CI: 1.90–6.11). Anti-HCV prevalence increased with each blood transfusion received (adjusted odds ratio 1.36; 95% CI: 1.10–1.68) and decreased with increasing education, (adjusted odds ratio 0.37 for graduate-level vs. primary school/no education; 95% CI: 0.16–0.82). Genotype 3 (58%) was most common among infected individuals.

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Competing interests: S Kanchi, F Alvarez-Bognar, and V Surlikar are, or have previously been, employees of Merck. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Discussion

The study findings, including the overall prevalence of chronic HCV infection, associated risk factors and demographic characteristics, and genotype distribution can guide prevention and control efforts, including treatment provision. In addition to high-risk populations, efforts targeting rural areas and adults aged ≥40 would be the most effective for identifying infected individuals.

Introduction

There are an estimated 70 million people living with hepatitis C Virus (HCV) infection around the world.[1] Persons living with HCV infection are at risk of developing liver cirrhosis and progressing to end stage liver disease and liver cancer (hepatocellular carcinoma).[2–7] Globally, an estimated 700,000 people die annually due to complications related to HCV infection.[8]

The World Health Organization (WHO) has set ambitious targets to eliminate HCV infection as a public health problem by 2030.[9] In order to achieve these targets, which include reduction of new infections by 90% and deaths by 65%, there is a need to increase prevention strategies and access to treatment. Treatment for HCV has improved dramatically with the addition of direct acting antivirals (DAAs), which are easy to take oral regimens that are highly effective, have minimal side effects, and achieve cure rates of over 90%.[10, 11] In order to establish effective prevention and treatment programs, there is a need to understand the epidemiology and burden of disease in the country or community. However, such data are lacking in many countries, particularly in lower and middle income countries which shoulder most of the burden.[12] There are significant geographical variations in prevalence patterns and genotype distribution globally,[12, 13] with populations in North America and Western Europe having anti-HCV prevalence rates generally less than 1%, while in some areas of Asia and the Middle East, prevalence rates exceed 5%.[1, 12–15] In India, where genotype 3 is thought to be most common,[16] population based studies on HCV infection prevalence are lacking, and the epidemiology is not well described. Some studies from India suggest the HCV prevalence may be low, however, there are significant variations within regions and sub-populations, with some studies demonstrating very high prevalence rates.[15, 17]

Population HCV seroprevalence data are lacking in Punjab, a state in Northern India with an estimated population of 28 million.[18] A survey conducted in one district of Punjab in 2003 found a 5% anti-HCV positive rate; in this study, infection was associated with reuse of needles and syringes, history of surgery, and history of dental extraction.[19] Elevated rates of HCV infection have also been identified among high risk populations (eg. people who inject drugs [PWID]) in Punjab,[20, 21] which may reflect the growing epidemic of injection drug use, a high-risk behavior for HCV infection.[22]

Epidemiological assessment of the burden of disease and related risk factors in the state are essential for public health planning strategies to combat this disease. This study assessed the prevalence of HCV infection in Punjab and identify risk factors associated with the disease.

Materials and methods

Sample design

A cross-sectional seroprevalence survey was conducted in the state of Punjab, India during October 2013 –April 2014. Punjab is divided into three major geographical areas, Doaba,

Majha, and Malwa which contain a total of 22 districts. The survey sample size was calculated to enable estimation of HCV prevalence among individuals age 5 years and older, using the statistical software PASS (NCSS, LLC. 2011 Kaysville, Utah, USA). For expected HCV prevalence of 5% with a 95% confidence interval (CI) of 4–6%, the effective sample size was estimated to include 1,924 households; and assuming a design effect of 2 and overall response rate of 70%, the target sample size was 5,500 individuals.

The study included testing for past and current HCV infection, past infections with hepatitis A virus and hepatitis E virus, and past or current infection with hepatitis B virus (HBV). Results will only be presented for HCV infection in this report. The sample size of 5,500 individuals was expected to be large enough to produce combined estimates with relative standard errors of 10–20%. For stratified analysis, a minimum sample size of 1,000 per strata was expected to produce estimates with relative standard errors of 25% or less. Estimates based on relative standard errors >25% are considered unreliable.

The survey used a multi-stage stratified cluster sampling design using 2011 Punjab Census data,[18] and 10 of the 22 districts in Punjab were selected with probability proportionate to size. In rural areas, 22 sub districts and 87 villages were selected proportionate to size, and 813 households were systematically selected in groups of five. To ensure the selection of a sufficient number of households in rural areas, villages with fewer than five households were excluded, and villages with 5–49 households were combined with neighboring villages, for a minimum of 50 households per sampling unit. In urban areas, 13 sub districts and 41 wards were selected proportionate to size; 1 census enumeration block of 150–200 households was randomly selected per ward; and 586 households were systematically selected in groups of five. For large sampling units, villages and census enumeration blocks with 500 or more households were divided into three or more segments and two segments were selected proportionate to size.

All household residents and guests 5 years of age and older of selected household residents who stayed at the household the previous night were eligible to participate in the study. Selected adults ≥18 years of age who provided informed consent, and children age 5–17 years who provided assent and informed parental/guardian consent were included. Pregnant women were included, since participation in the study did not pose any risk to the mother or her unborn child. Individuals under 5 years of age and those who did not provide consent or assent were not included. No replacement was made if selected household was not available during data collection.

Data collection

Trained survey teams consisting of a doctor, a phlebotomist, a nurse and a social worker visited selected households and administered the survey questionnaire, after obtaining informed consent and assent from children willing to participate. The study questionnaire was administered as a face-to-face interview and inquired about socio-demographic data, medical history, lifestyle information, obstetric history (if applicable), and potential exposures to HCV, including healthcare and lifestyle associated exposures. Each completed questionnaire was reviewed in the field by the team doctor, and if inconsistencies or gaps were identified, an attempt to correct or fill in the missing information was made by revisiting the surveyed individual before leaving the cluster. Each completed interview was labeled with a bar code with a unique identifier.

After completing the interview, a blood sample of approximately 16ml was drawn in a serum separator tube and labeled with a barcode matching the interview form completed by the study subject. Within one hour of collection, the sample was centrifuged for 15 minutes at 3,000 revolutions per minute. Separated serum was pipetted into 2ml cryovials, which were also labeled with bar codes matching the study subjects. Up to eight aliquots of sample per

subject were prepared and frozen at -80C. Specimens were shipped every 2 weeks to a central laboratory (Oncquest Laboratories Ltd) in Delhi for testing. All samples were tested for anti-HCV (Vitros Immunodiagnostic Anti-HCV, Johnson and Johnson Co., New Brunswick, NJ, USA) and all anti-HCV positive samples were tested for HCV RNA (COBAS® TaqMan® HCV Test, Roche, Indianapolis, IN, USA). All HCV RNA positive samples were genotyped by Linear Array HCV genotyping test (Roche, Indianapolis, IN, USA). Survey participants who tested positive for anti-HCV were considered infected with HCV, regardless of HCV RNA results. Survey participants who tested positive for anti-HCV and HCV RNA were considered to have current infection, and those that tested anti-HCV positive and HCV RNA negative were considered to have past infection. Specimens were also tested for hepatitis A virus, hepatitis B virus and hepatitis E virus markers of infection (methods and results not described in this report). Unused blood was disposed of as per healthcare waste management guidelines and all specimens were destroyed following completion of the study.

Counseling and notification of test results

For consenting participants, pretest counseling and educational brochures on HCV transmission and prevention were administered prior to interview and venipuncture. Study participants were notified of their test results for HCV, HBV, HAV, and HEV infection or immunity by telephone and mail within three weeks of the interview date. Patients found to have current (active) HBV or HCV infection were offered post-test counseling by appointment. All participants were counseled about measures to prevent the risk of transmission of the various forms of viral hepatitis.

Ethical considerations

The protocol for this study underwent approval from the Institutional Review Board (IRB) at Dayanand Medical College, Ludhiana, and the Merck Investigator Initiated Study Protocol-Review Committee (MISP-RC). Participation was voluntary and confidentiality was strictly adhered to during the survey. Written consent was documented by the study subject's dated signature or thumbprint on a consent form along with the dated signature of the person who conducted the consent discussion. A copy of the consent form was given to the subject prior to participating in the survey. Consent forms were available in English, Punjabi and Hindi. If the subject was illiterate, a witness was present during the entire informed consent reading and discussion. Afterward, the subjects signed and dated the consent if literate, or a thumb impression was taken. The witness also signed and dated the consent form along with the study staff who read and discussed the consent. Children $\geq$5 years and $<$18 years of age provided assent in addition to having parental permission.

Statistical methods

Analyses of the survey data were weighted according to the population sizes of the wards and villages estimated from the 2011 population census. This weighting was stratified by urban/rural status. The HCV prevalence was estimated for the state as a whole, by urban/rural residence, and by district. A χ^2 test was used to examine whether the proportion of HCV RNA positive patients with each genotype differed by district. Participant characteristics and prevalence of HCV risk factors were tabulated for those testing positive for anti-HCV and those testing positive for HCV RNA. The variables included in these tabulations were district, age-group (5–18, 19–29, 30–45, 46–60, $>$60), sex, urban/rural status, household income in rupees ($<$20,000, $\geq$20,000), education status (never educated/primary education, middle/secondary, graduate/above), the number of injections received in the last 6 months (0, 1–3, 4–8, $>$8), who

administered the last injection received (Medical Doctor, Registered Nurse/Medical Practitioner, Other/Unknown (including chemists and unlicensed practitioners), the number of lifetime blood donations (0, 1–3, 4–6, >7), the number of blood transfusions received (0, 1–3, >3), if ever received a permanent tattoo, if ever used injectable drugs, or had ever received renal dialysis. Proportions and numbers presented in the tabulations were weighted to represent the population surveyed. Tabulations were stratified by urban/rural status. We estimated the association of patient characteristics and HCV risk factors with HCV status using weighted logistic regression models for the total survey population, stratified by urban/rural status, and clustered by household. Age, the number of injections received in the last 3 months, the number of times the person had donated blood, the number of blood transfusions received were included in models as continuous variables. Results are presented as weighted unadjusted and mutually adjusted odds ratios (OR) of having a positive anti-HCV test, with 95% confidence intervals (CI). We also estimated the association of the year of the first blood transfusion received (grouped as before 2002, 2002 or later year, year unknown, and no blood transfusions received; of note, blood bank testing for HBV and HCV became mandatory in Punjab by law in 2002) with HCV status. We used the same mutually adjusted model as above, but instead of including the number of blood transfusions we included the year of first receiving a blood transfusion. A sensitivity analysis excluded participants under 18 years of age because some risk factors only applied to adults, and another sensitivity analysis (not stratified by urban/rural status) only included participants aged 40–59 years of age as these were the two highest prevalence age groups.

We examined the number of injections (categorized: 0, 1–3, 4–8, >8) received in the last 6 months by anti-HCV prevalence. We examined the relationship of cumulative number of different types of potential exposures found to be associated with anti-HCV prevalence by univariate analysis (including having a permanent tattoo, ever received a blood transfusion and received a medical injection within the last 6 months) and testing positive for anti-HCV. We used logistic regression to estimate the adjusted OR of anti-HCV positivity for number of risk factors (1, 2–3) compared with no risk factors.

Results

There were a total of 5,548 individuals who agreed to participate in the study and completed the questionnaire, however, 5 lacked HCV testing results and were excluded, resulting in 5,543 subjects for inclusion in the analyses. The median age of our sample was 35 years (interquartile range 21, 50) while the largest age group was participants age 5–18 years (Table 1). Among the participants, there were more women (53.8%) than men (46.2%), and 62.4% resided in rural areas (Table 1). The majority of participants, 81.9%, lived in households with an income of less than 20,000 Indian rupees (about 300 US dollars) which is below the national average of 27,857 Indian rupees.[23] and 12.5% attended graduate school (Table 1).

When we examined potential exposures for HCV infection, 34.8% of participants had received one or more medical injections in the previous 6 months in the weighted analysis. When asked who administered their last medical injection, 20.4% identified a medical doctor and 56.9% identified a registered nurse or registered medical practitioner (eg. medical care provider not having the qualifications/training of a medical doctor). For those who had received an injection in the last 6 months, 24% received it from a medical doctor, 71% from a registered nurse or registered medical practitioner and 5% from other sources (eg. chemist or pharmacist, unlicensed practitioner, or did not specify). Of the participants, 6.5% stated they had received at least one blood transfusion. Additionally, 8.6% of patients had received a permanent tattoo, while few (0.1%) participants admitted to using injectable drugs.

Table 1. Weighted and unweighted participant demographic characteristics and prevalence of potential exposures and risk factors associated with Hepatitis C (HCV) infection, with percent testing positive for HCV antibodies (anti-HCV) and HCV-RNA cells.

Variables	Unweighted Population	Weighted Population	% with positive anti-HCV (95% confidence intervals)	% with HCV RNA (95% confidence intervals)
Overall	5543	100%	3.6% (3.0%, 4.2%)	2.6% (2.0%, 3.1%)
Age Group (years)				
5–18	1107	20.2%	0.7% (0.1%, 1.2%)	0.4% (0.0%, 0.8%)
19–29	1024	18.3%	1.7% (0.8%, 2.5%)	1.2% (0.5%, 1.9%)
30–39	998	18.0%	4.3% (2.9%, 5.7%)	3.1% (1.8%, 4.3%)
40–49	870	15.7%	6.2% (4.4%, 8.0%)	4.7% (3.1%, 6.2%)
50–59	721	13.0%	5.8% (3.9%, 7.7%)	4.5% (2.7%, 6.2%)
≥60	823	14.9%	4.3% (2.7%, 5.8%)	2.7% (1.4%, 3.9%)
Sex				
Female	3005	53.8%	3.2% (2.5%, 3.9%)	2.3% (1.7%, 2.9%)
Male	2538	46.2%	4.0% (3.1%, 5.0%)	2.8% (2.1%, 3.6%)
Region				
Urban	2083	37.6%	1.6% (1.1%, 2.2%)	1.0% (0.6%, 1.4%)
Rural	3460	62.4%	4.7% (3.8%, 5.7%)	3.5% (2.7%, 4.3%)
Household income (rupees)				
<20,000	4546	81.9%	3.8% (3.1%, 4.5%)	2.7% (2.1%, 3.3%)
≥20,000	997	18.1%	2.5% (1.2%, 3.7%)	1.9% (0.8%, 2.9%)
Education				
Never/Primary School	2114	37.7%	4.7% (3.6%, 5.8%)	3.8% (2.8%, 4.8%)
Middle/Secondary School	2735	49.8%	3.4% (2.6%, 4.1%)	2.1% (1.5%, 2.7%)
Graduate/Above	694	12.5%	1.1% (0.3%, 1.8%)	0.6% (0.1%, 1.2%)
No. injections in last 6 months				
0	3639	65.2%	3.1% (2.4%, 3.8%)	2.2% (1.7%, 2.8%)
1–3	1155	21.1%	3.8% (2.6%, 5.0%)	2.5% (1.6%, 3.4%)
4–8	461	8.3%	4.7% (2.5%, 6.9%)	3.7% (1.6%, 5.7%)
>8	288	5.4%	7.0% (3.5%, 10.4%)	5.0% (2.1%, 7.9%)
Last injection given by				
Medical Doctor	1149	20.4%	2.1% (1.2%, 2.9%)	1.3% (0.6%, 2.0%)
Registered Nurse/Medical Practitioner	3090	56.9%	4.4% (3.6%, 5.2%)	3.3% (2.5%, 4.0%)
Other/Unknown	1304	22.7%	2.9% (2.9%, 4.0%)	1.9% (1.0%, 2.9%)
Number of times blood donated				
0	4808	86.5%	3.6% (2.9%, 4.2%)	2.5% (1.9%, 3.0%)
1–3	528	9.8%	3.3% (1.5%, 5.1%)	3.2% (1.4%, 5.0%)
4–6	115	2.1%	4.6% (0.5%, 8.6%)	3.6% (0.0%, 7.3%)
≥7	92	1.7%	5.3% (0.2%, 10.3%)	2.4% (0.0%, 5.8%)
Number of transfusions received				
0	5175	93.6%	3.4% (2.8%, 4.0%)	2.4% (1.9%, 2.9%)
1–3	353	6.3%	5.9% (3.2%, 8.6%)	4.6% (2.2% (6.9%)
>3	15	0.2%	25.8% (0.0%, 53.7%)	25.8% (0.0%, 53.7%)
Received a permanent tattoo				
Yes	479	8.6%	5.2% (2.8%, 4.1%)	3.7% (1.9%, 5.4%)
No	5064	91.4%	3.4% (3.1%, 7.3%)	2.5% (1.9%, 3.0%)
Use of Injectable Drugs				

(*Continued*)

Table 1. (Continued)

Variables	Unweighted Population	Weighted Population	% with positive anti-HCV (95% confidence intervals)	% with HCV RNA (95% confidence intervals)
Yes	5	0.1%	25.1% (0.0%, 66.8%)	25.1% (0.0%, 66.8%)
No	5538	99.9%	3.6% (2.9%, 4.2%)	2.5% (2.0%, 3.1%)
Any dialysis				
Yes	26	0.4%	0.0% (0.0%, 0.0%)	NA
No	5517	99.5%	3.6% (3.0%, 4.2%)	2.6% (2.0%, 3.1%)

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Overall, of the 5,543 persons tested for hepatitis C, 3.6% (95% CI: 3.0%, 4.2%) tested positive for anti-HCV (ever infected), and 2.6% (95% CI: 2.0%, 3.1%) tested positive for HCV RNA, indicative of current infection. Among the 138 that tested positive for RNA, 130 were successfully tested for genotype, the majority were classified as genotype 3 (61.2%), followed by genotype 1 (27.5%) and genotype 4 (11.3%). No participants in our study were found to have genotype 2. The proportions of RNA positive patients with each genotype differed by province (p = 0.038).

Anti-HCV prevalence was higher among rural residents (4.7% [3.8%, 5.7%]) than urban residents (1.6% [1.1%, 2.2%]) (Table 1). The proportion of persons testing positive for HCV differed by district, ranging from 1.1% in Gurdaspur to 9.0% in Moga (Fig 1); however, this study was designed to estimate prevalence for Punjab as a whole, not to estimate district level prevalence.

When we examined anti-HCV prevalence by age, we found prevalence increased with age up to 40–49 years where it peaked and then decreased with increasing age (Table 1). Overall, prevalence among men and women was similar, (Table 1), and when stratified by age, there were some small differences in seroprevalence by age groups among men and women (Fig 2). Anti-HCV prevalence also decreased with increasing educational attainment, and was lower among persons with higher income (Table 1).

When we examined the prevalence of anti-HCV antibody positivity by potential exposures and risk factors, we found that rates were higher as the number of injections received increased (see Fig 3), were highest for those whose last injection was administered by a nurse, registered medical practitioner, or other non–medical doctor, increased with the number of transfusions received, and also were higher among persons who had received a tattoo (Table 1). There were no HCV infections among persons who had a history of receiving dialysis (Table 1); however, the number persons associated with some of the exposures and risk factors, including dialysis (n = 26) and injection drug use (n = 5), was small. When we examined anti-HCV prevalence by the number of unique potential exposures, compared to persons without these potential exposures, the HCV prevalence increased as the cumulative number of unique exposures increased (Fig 4); the same analysis revealed that overall 43.7% of participants had one or more type of potential exposure.

When we examined demographic and potential exposures and risk factors in a multivariable model, calculating adjusted odds ratios, we found similar findings to our bivariate analysis: that testing positive for anti-HCV was associated with increasing age to age 40–49 years with the odds decreasing slightly for older age groups, being male, rural residence, lower educational attainment, and receipt of blood transfusions (Table 2). Results were similar when the analysis was restricted to adults (Table 3), and when the analysis was restricted to the two highest prevalence age groups– 40–49 and 50–59 years (Table 4). When we stratified the analysis by urban and rural residence, all of the associations, except educational attainment, persisted

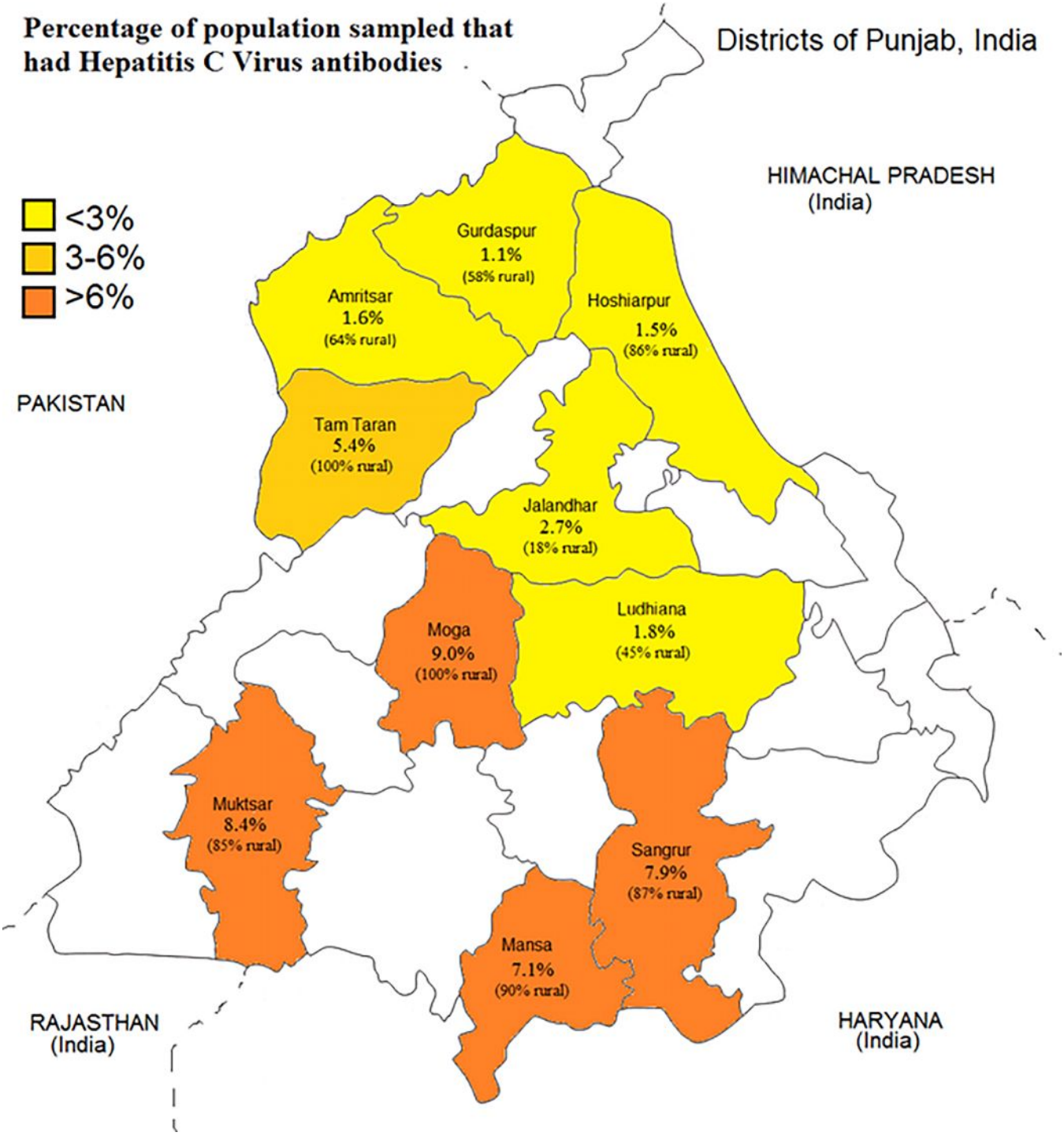

Fig 1. The percentage of participants sampled in each district that had Hepatitis C virus antibodies.

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among rural residents, while among urban residents, only age remained a significant predictor. We did not find a difference in the likelihood of having HCV infection among those who received a blood transfusion before 2002 and those who received one during or after 2002.

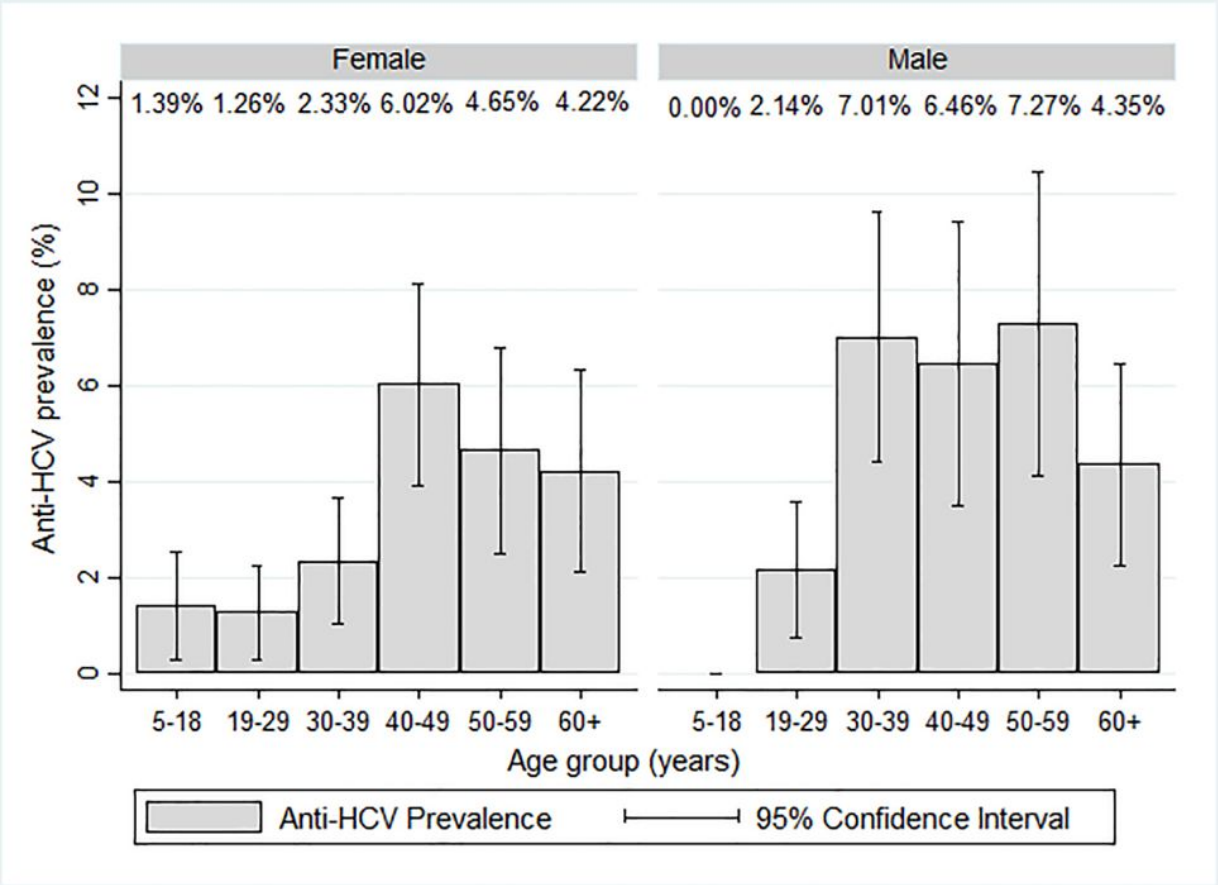

Fig 2. Prevalence of Hepatitis C antibodies (95% confidence interval) by age category and sex.

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Discussion

This study, the first assessing the prevalence and risk factors for HCV infection in Punjab, India, found an overall weighted prevalence of anti-HCV of 3.6% and HCV RNA of 2.6%. We found that males, persons aged 40–59, and persons living in rural areas had the greatest odds of being infected with HCV. Additionally, HCV infection was more common among those who lacked education, received a blood transfusion, and had their last injection given by a nurse or other medical practitioner as compared to a medical doctor. Through multivariable analysis, we found no increased likelihood of being anti-HCV positive with increases in the reported number of participants' medical injections.

The association of HCV with age and rural residence has been observed in previous studies from Punjab.[24] Also consistent with our analysis, studies from other countries have identified a particular age or birth cohort with a high prevalence of HCV compared to others.[25, 26] This cohort effect is demonstrated by persons born between 1945 and 1965, so called "Baby Boomers" in the United States.[27, 28] In the United States, the higher HCV prevalence among Baby Boomers has been attributed largely to injection drug use during their youth, the lack of an HCV screening test for blood and blood products prior to 1990, and to the effect of the HIV epidemic, recognized during the 1980s.[27, 28] In our study, noting the increasing prevalence with age, it would be tempting to consider that transmission risk has decreased over time and younger people are at lower risk, however, the youngest age groups studied,

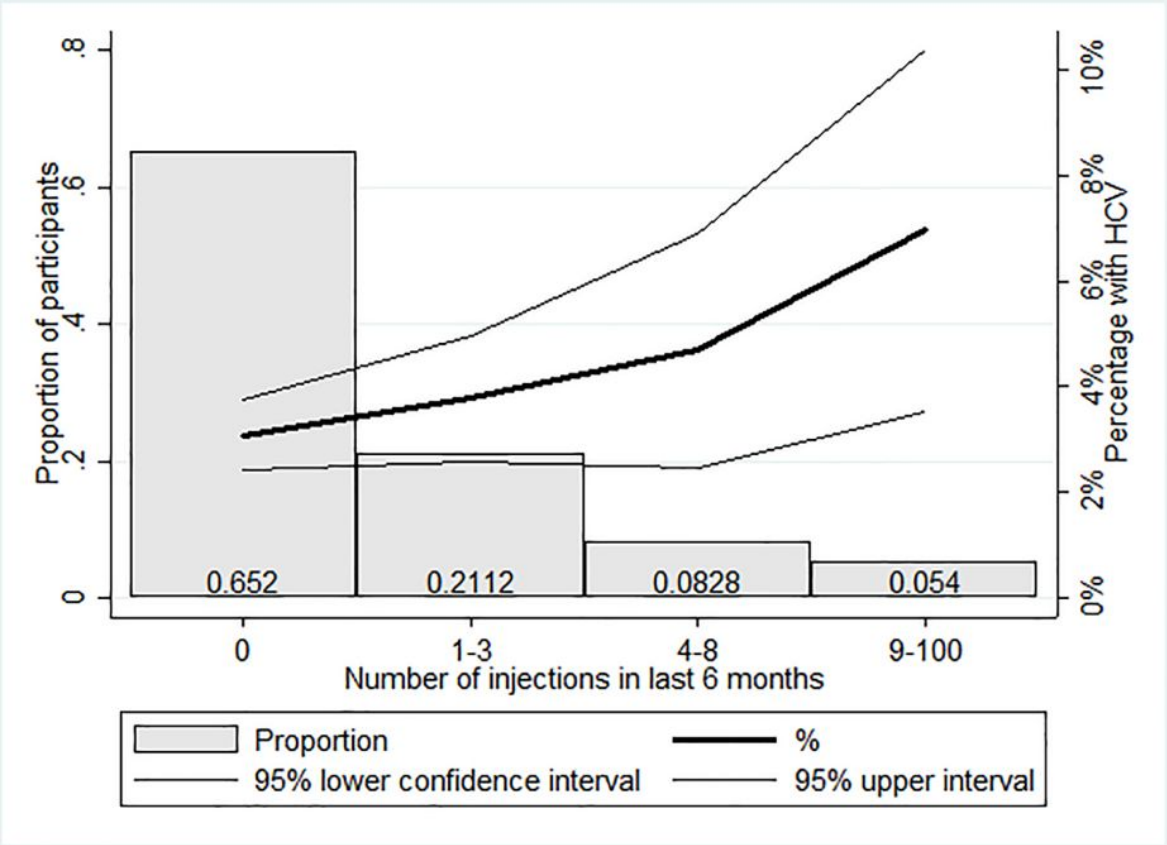

Fig 3. Prevalence of Hepatitis C antibodies by number of medical injections received in the last 6 months.

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5–18 and 19–29 year olds, had HCV seropositive rates of over 1% and 2% respectively, suggesting that transmission risk persists in Punjab. In fact, a rise in prevalence of injection drug use in Punjab has been described among teens and the youth population[29] and may present an emerging risk for HCV infection in similarly aged populations in the years to come. Very few admitted to injection drug use in our survey, which may reflect social desirability bias on the part of participants.

Residence in a rural versus urban area was determined to be an effect modifier in our analysis. Individuals in rural areas of Punjab had 2.5 times the odds of being anti-HCV positive as those in urban settings after adjusting for covariates, a result comparable to other studies in North India[30]. Upon stratification, we found that sex, age and blood transfusions were associated with HCV among participants in rural areas, whereas in urban areas the only significant association was with age. Poverty was not associated with infection. There is a paucity of trained healthcare professionals in rural areas of Punjab, so healthcare in those regions is often delivered by unqualified practitioners who may adopt unsafe injection practices,[31] possibly contributing to the elevated prevalence of HCV among rural residents in Punjab in our study.

The finding that blood transfusions were a risk factor for HCV highlights the need for improved blood safety practices in Punjab. Mandatory testing for HCV was implemented in blood banks in India in 2002.[32] However, participants in our study who received their first transfusion in 2002 or later were no less likely to be anti-HCV positive than those who received transfusions before mandatory testing began. Despite the existence of statewide blood safety guidelines, an association between receipt of a blood transfusion and having HCV infection

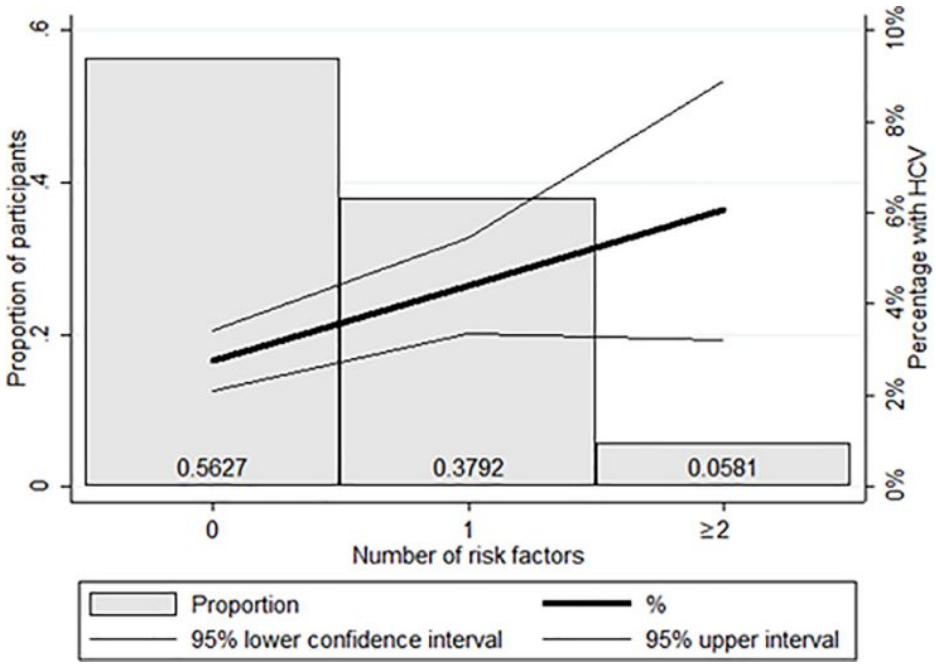

Fig 4. Prevalence of Hepatitis C antibodies by unique potential exposures (whether or not they had a permanent tattoo, whether they had ever received a blood transfusion and whether in the last 6 months they had received a medical injection).

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persisted in our study, regardless of when the blood transfusions were received, and may suggest a persistent mode of HCV transmission in Punjab. These findings underscore the need for greater enforcement and monitoring of blood banks to ensure proper testing procedures are followed to prevent transmission in these settings.

Previous studies have also found inadequate infection control practices among healthcare workers in India,[33, 34] however, the number of medical injections was not associated with HCV after adjusting for covariates in our study. It is important to note that in a cross-sectional study, to identify associations with medical practices is challenging. However, we found an increased likelihood of being anti-HCV positive among those who received their last injection from someone other than a medical doctor, a finding which was not specific to rural areas. A 2002 study in Punjab found that a considerable percentage of physicians with knowledge of parenteral HCV transmission risk nevertheless reused needles and syringes with their patients.[35] Furthermore, throughout India and in Punjab, treatment with injectable medicine is perceived to be the treatment that ensures rapid therapeutic relief.[36] This belief has been inculcated over many years by physicians themselves, and there are financial incentives to deliver treatment through a "procedure", such as an injection.[36] Although increased availability of disposable syringes helps temper these risks, healthcare workers throughout Punjab could benefit from further training on safe injection practices to prevent the spread of HCV and other diseases.

The prevalence of chronic HCV infection found in our study was slightly less than was determined by a 2012 study in the region,[19] but in a population of roughly 28 million, still translates to nearly three quarters of a million people chronically infected in the state of Punjab alone. Future screening efforts need to address this burden of disease to identify infected individuals and link them to care and treatment. The results of this study can be used to target screening and linkage to care efforts in the state, to ensure the highest yield of HCV infected

Table 2. Weighted unadjusted and mutually adjusted odds ratios (OR) for having Hepatitis C antibodies (anti-HCV), by participant characteristics and risk factors, overall and stratified by urban/rural status.

	Total	Odds Ratio (95% Confidence Interval)		Urban	Odds Ratio (95% Confidence Interval)		Rural	Odds Ratio (95% Confidence Interval)	
Variables	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**
Total	3.6% (3.0%, 4.2%)			1.6% (1.1%, 2.2%)			4.7% (3.8%, 5.7%)		
Age (years)							NA		
5–18	0.7% (0.1%, 1.2%)	0.39 (0.15, 1.01)	0.30 (0.12, 0.80)	0.5% (0.0%, 1.2%)	0.53 (0.10, 2.92)	0.47 (0.08, 2.64)	0.7% (0.0%, 1.5%)	0.34 (0.11, 1.08)	0.27 (0.09, 0.86)
19–29	1.7% (0.8%, 2.5%)	1	1	1.0% (0.0%, 1.9%)	1	1	2.1% (0.9%, 3.3%)	1	1
30–39	4.3% (2.9%, 5.7%)	2.64 (1.43, 4.89)	2.40 (1.30, 4.46)	1.0% (0.0%, 2.0%)	1.02 (0.25, 4.12)	1.00 (0.25, 3.98)	6.4% (4.2%, 8.6%)	3.17 (1.58, 6.37)	2.87 (1.44, 5.72)
40–49	6.2% (4.4%, 8.0%)	3.91 (2.20, 6.96)	3.41 (1.90, 6.11)	4.1% (2.0%, 6.2%)	4.36 (1.41, 13.5)	4.22 (1.39, 12.8)	7.5% (4.9%, 10.1%)	3.78 (1.94, 7.40)	3.21 (1.65, 6.25)
50–59	5.8% (3.9%, 7.7%)	3.66 (2.12, 6.31)	3.01 (1.73, 5.23)	2.4% (0.8%, 4.1%)	2.55 (0.83, 7.89)	2.67 (0.85, 8.36)	8.2% (5.2%, 11.3%)	4.18 (2.23, 7.82)	3.12 (1.68, 5.79)
≥60	4.3% (2.7%, 5.8%)	2.65 (1.43, 4.90)	1.82 (0.98, 3.38)	1.2% (0.0%, 2.5%)	1.20 (0.27, 5.44)	1.11 (0.22, 5.51)	5.8% (3.6%, 8.0%)	2.86 (1.43, 5.70)	1.96 (0.99, 3.86)
Rural (vs urban)		3.01 (2.00, 4.55)	2.53 (1.62, 3.95)		NA	NA		NA	NA
Sex									
Female	3.2% (2.5%, 3.9%)	1	1	1.7% (0.9%, 2.5%)	1	1	4.1% (3.1%, 5.0%)	1	1
Male	4.0% (3.1%, 5.0%)	1.28 (0.95, 1.72)	1.52 (1.08, 2.14)	1.6% (0.8%, 2.3%)	0.94 (0.49, 1.77)	1.08 (0.56, 2.06)	5.5% (4.1%, 7.0%)	1.38 (0.98, 1.93)	1.67 (1.13, 2.48)
Household income									
0–20,000 Rupees	3.8% (3.1%, 4.5%)	1	1	1.8% (1.1%, 2.6%)	1	1	4.8% (3.8%, 5.7%)	1	1
>20,000 Rupees	2.5% (1.2%, 3.7%)	0.64 (0.38, 1.09)	0.95 (0.54, 1.66)	1.2% (0.4%, 2.0%)	0.65 (0.29, 1.44)	0.74 (0.32, 1.73)	4.7% (1.7%, 7.7%)	0.99 (0.50, 1.96)	1.06 (0.54, 2.10)
Education									
None/Primary	4.7% (3.6%, 5.8%)	1	1	1.7% (0.6%, 2.8%)	1	1	5.9% (4.4%, 7.3%)	1	1
Middle/Secondary	3.3% (2.6%, 4.1%)	0.70 (0.52, 0.95)	0.81 (0.58, 1.13)	2.0% (1.1%, 2.8%)	1.16 (0.53, 2.56)	1.19 (0.49, 2.85)	4.2% (3.1%, 5.3%)	0.74 (0.55, 0.99)	0.74 (0.51, 1.07)
Graduate	1.1% (0.3%, 1.8%)	0.21 (0.10, 0.46)	0.37 (0.16, 0.82)	0.8% (0.0%, 1.5%)	0.45 (0.13, 1.50)	0.54 (0.13, 2.19)	1.6% (0.0%, 3.3%)	0.31 (0.09, 1.04)	0.37 (0.13, 1.09)
Last injection given by									
Medical Doctor	2.1% (1.2%, 2.9%)	1	1	1.1% (0.3%, 2.0%)	1	1	3.1% (1.6%, 4.6%)	1	1
Registered Nurse/ Medical Practitioner	4.4% (3.6%, 5.2%)	2.16 (1.37, 3.42)	1.56 (0.97, 2.53)	2.3% (1.3%, 3.4%)	2.08 (0.87, 4.99)	1.71 (0.71, 4.12)	5.3% (4.2%, 6.4%)	2.16 (1.28, 3.66)	1.56 (0.88, 2.75)
Other/Unknown	2.9% (1.7%, 4.0%)	1.38 (0.78, 2.45)	1.25 (0.70, 2.23)	0.9% (0.1%, 1.7%)	0.80 (0.25, 2.52)	0.71 (0.23, 2.21)	4.3% (2.5%, 6.2%)	1.60 (0.71, 3.58)	1.44 (0.73, 2.84)
Number injections received last 6 months	NA	1.02 (1.01, 1.03)	1.01 (0.99, 1.03)	NA	1.03 (0.99, 1.07)	1.02 (0.96, 1.08)	NA	1.01 (1.00, 1.03)	1.01 (0.98, 1.03)
Number of times donating blood	NA	0.99 (0.93, 1.05)	0.96 (0.87, 1.05)	NA	0.99 (0.91, 1.08)	0.97 (0.88, 1.07)	NA	1.01 (0.94, 1.08)	0.96 (0.85, 1.08)
Number of blood transfusions received	NA	1.36 (1.10, 1.69)	1.36 (1.10, 1.68)	NA	1.05 (0.69, 1.60)	0.99 (0.60, 1.64)	NA	1.56 (1.15, 2.10)	1.47 (1.10, 1.96)
Received a permanent tattoo									

(*Continued*)

Table 2. (Continued)

	Total	Odds Ratio (95% Confidence Interval)		Urban	Odds Ratio (95% Confidence Interval)		Rural	Odds Ratio (95% Confidence Interval)	
Variables	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**
No	3.4% (2.8%, 4.1%)	1	1	1.6% (1.0%, 2.2%)	1	1	4.5% (3.6%, 5.5%)	1	1
Yes	5.2% (3.1%, 7.3%)	1.54 (0.97, 2.45)	1.21 (0.74, 1.98)	2.2% (0.1%, 4.3%)	1.42 (0.49, 4.09)	1.36 (0.49, 3.82)	6.9% (3.9%, 10.0%)	1.57 (0.94, 2.63)	1.17 (0.67, 2.05)

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individuals. Screening efforts in Punjab should target rural districts and persons age 30 and older. India's expenditure on health care as a percentage of its gross domestic product (1.3% in 2015–2016) is among the lowest in the world, and the country has no system to monitor patients.[37] Nationwide surveillance of hepatitis is also lacking in the country and focuses primarily on hepatitis A and E.[38] Testing for incident HCV and HBV cases is only supported by the country's national Integrated Disease Surveillance Programme (IDSP) in outbreak situations.[38] Fortunately, treatment costs for HCV infection in India have decreased significantly with the introduction of direct acting antiviral drugs in 2015, which have proven to be highly effective.[39] In 2016 Punjab became the first state in India to make the commitment to treat HCV patients free of charge.[40, 41] Through July 2017, over 32,000 patients have been treated through the program,[40] representing an important step in control of the disease. However, access to treatment alone cannot end the epidemic of HCV globally or in Punjab. More initiative is needed with respect to disease awareness, diagnosis, and prevention. Nevertheless, with treatment options becoming more effective, affordable, and available to patients, there is hope that Punjab could be reaching a turning point to mitigate the burden of HCV.

Our study is subject to several limitations. First, we were not able to independently verify any of the responses on the questionnaire. Also, we could not determine the number of non-responders, though it was reported from the field that interest was very high and 98% of households participated. As with any cross-sectional study that examines a chronic condition, it is challenging to attribute risk due to lack of temporality, as the HCV infection could have occurred at any time during the lifetime of the study subjects. The sampling method of this study, which included multiple participants from a single household, could lead to potential selection bias. Persons living together are more likely to exhibit similar behaviors and could lead to disproportionate risks in the sample that may not be representative of the greater population. Additionally, the sampling method of our study was not designed to produce precise per-region prevalence estimates; there was a preponderance of people surveyed from rural areas in districts that were found to have a high prevalence of HCV. These results should be interpreted with caution, as this could lead to overestimation of the prevalence in these areas. The face-to-face nature of the questionnaire creates the potential for social desirability bias. Injection drug use is a significant risk factor for HCV, but self-report of this behavior was extremely low (0.09%) among participants in our study despite reports of worrisome trends of increased injection drug use in the state.[22] The number of persons associated with some of the exposures and risk factors, notably dialysis (n = 26) and injection drugs (n = 5), was small, making associations of these risk factors with HCV seropositivity difficult to determine. Thus an important risk behavior may be substantially underrepresented in this analysis. Finally, we cannot rule out false positive anti-HCV among those that tested negative for RNA.

Population studies provide critical data for planning control efforts of HCV. The effectiveness and decreasing costs of DAAs are bringing control efforts within reach in many countries.[9] Programs that target screening and linkage to care for the highest risk populations in

Table 3. Weighted unadjusted and mutually adjusted odds ratios (OR) for having Hepatitis C antibodies (anti-HCV), by participant characteristics and risk factors overall and stratified by urban/rural status for adults age 18 or over.

	Total	Odds Ratio (95% Confidence Interval)		Urban	Odds Ratio (95% Confidence Interval)		Rural	Odds Ratio (95% Confidence Interval)	
Variables	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**
Total	4.3% (3.6%, 5.1%)			1.9% (1.2%, 2.6%)			5.8% (4.7%, 6.9%)		
Age									
20–29	1.7% (0.8%, 2.5%)	1	1	1.0% (0.0%, 1.9%)	1	1	2.1% (0.9%, 3.3%)	1	1
30–39	4.3% (2.9%, 5.7%)	2.64 (1.43, 4.89)	2.43 (1.31, 4.51)	1.0% (0.0%, 2.0%)	1.02 (0.25, 4.12)	1.02 (0.26, 4.08)	6.4% (4.2%, 8.6%)	3.17 (1.58, 6.37)	2.89 (1.45, 5.77)
40–49	6.2% (4.4%, 8.0%)	3.91 (2.20, 6.96)	3.41 (1.90, 6.13)	4.1% (2.0%, 6.2%)	4.36 (1.41, 13.5)	4.36 (1.44, 13.2)	7.5% (4.9%, 10.1%)	3.78 (1.94, 7.40)	3.19 (1.64, 6.22)
50–59	5.8% (3.9%, 7.7%)	3.66 (2.12, 6.31)	2.96 (1.70, 5.16)	2.4% (0.8%, 4.1%)	2.55 (0.83, 7.89)	2.85 (0.92, 8.81)	8.2% (5.2%, 11.3%)	4.18 (2.23, 7.82)	3.03 (1.64, 5.63)
≥60	4.3% (2.7%, 5.8%)	2.65 (1.43, 4.90)	1.77 (0.95, 3.28)	1.2% (0.0%, 2.5%)	1.20 (0.27, 5.44)	1.13 (0.23, 5.68)	5.8% (3.6%, 8.0%)	2.86 (1.43, 5.70)	1.88 (0.95, 3.70)
Rural (vs urban)	NA	3.20 (2.09, 4.89)	2.59 (1.63, 4.11)	NA			NA		
Sex									
Female	3.6% (2.8%, 4.3%)	1	1	1.8% (0.9%, 2.7%)	1	1	4.6% (3.5%, 5.8%)	1	1
Male	5.2% (4.0%, 6.5%)	1.50 (1.10, 2.04)	1.73 (1.22, 2.44)	2.0% (1.0%, 3.0%)	1.12 (0.58, 2.15)	1.26 (0.66, 2.41)	7.3% (5.4%, 9.2%)	1.62 (1.15, 2.30)	1.89 (1.27, 2.81)
Household income									
0–20,000 Rupees	4.7% (3.8%, 5.5%)	1	1	2.2% (1.3%, 3.2%)	1	1	5.8% (4.7%, 7.0%)	1	1
>20,000 Rupees	2.8% (1.3%, 4.2%)	0.58 (0.34, 1.00)	0.96 (0.54, 1.70)	1.2% (0.3%, 2.0%)	0.52 (0.22, 1.21)	0.66 (0.27, 1.60)	5.7% (2.1%, 9.3%)	0.97 (0.49, 1.92)	1.11 (0.57, 2.21)
Education									
None/Primary	6.1% (4.6%, 7.5%)	1	1	2.2% (0.7%, 3.8%)	1	1	7.3% (5.5%, 9.1%)	1	1
Middle/Secondary	4.1% (3.1%, 5.0%)	0.66 (0.48, 0.90)	0.76 (0.54, 1.08)	2.3% (1.3%, 3.3%)	1.05 (0.45, 2.42)	1.21 (0.48, 3.06)	5.1% (3.8%, 6.5%)	0.69 (0.49, 0.97)	0.69 (0.47, 1.00)
Graduate	1.1% (0.3%, 1.8%)	0.17 (0.08, 0.36)	0.36 (0.16, 0.81)	0.8% (0.0%, 1.5%)	0.34 (0.10, 1.19)	0.59 (0.14, 2.48)	1.6% (0.0%, 3.4%)	0.21 (0.07, 0.63)	0.36 (0.12, 1.05)
Last injection given by									
Medical Doctor	2.3% (1.2%, 3.3%)	1	1	1.0% (0.1%, 1.9%)	1	1	3.6% (1.7%, 5.5%)	1	1
Registered Nurse/ Medical Practitioner	5.3% (4.3%, 6.3%)	2.43 (1.48, 3.97)	1.75 (1.04, 2.92)	3.0% (1.6%, 4.1%)	2.95 (1.09, 7.98)	2.44 (0.89, 6.67)	6.4% (5.0%, 7.7%)	1.82 (1.02, 3.23)	1.61 (0.89, 2.90)
Other/ Unknown	3.6% (2.2%, 5.1%)	1.64 (0.90, 2.99)	1.45 (0.79, 2.66)	1.1% (0.1%, 2.1%)	1.13 (0.33, 3.95)	0.99 (0.28, 3.47)	5.7% (3.3%, 8.1%)	1.61 (0.81, 3.21)	1.56 (0.78, 3.14)
Number injections received last 6 months	NA	1.02 (1.00, 1.03)	1.01 (0.99, 1.03)	NA	1.02 (0.98, 1.07)	1.02 (0.97, 1.07)	NA	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
Number of times donating blood	NA	0.97 (0.89, 1.04)	0.95 (0.86, 1.04)	NA	0.98 (0.88, 1.08)	0.96 (0.87, 1.07)	NA	0.98 (0.90, 1.08)	0.95 (0.84, 1.07)
Number of blood transfusions	NA	1.32 (1.07, 1.63)	1.37 (1.11, 1.70)	NA	1.03 (0.67, 1.59)	1.01 (0.61, 1.65)	NA	1.48 (1.11, 1.97)	1.49 (1.10, 2.00)
Received a permanent tattoo									
No	4.2% (3.4%, 5.0%)	1	1	1.8% (1.1%, 2.6%)	1	1	5.6% (4.4%, 6.8%)	1	1
Yes	5.5% (3.3%, 7.7%)	1.35 (0.85, 2.14)	1.17 (0.71, 1.92)	2.4% (0.1%, 4.6%)	1.28 (0.44, 3.72)	1.32 (0.47, 3.71)	7.4% (4.2%, 10.7%)	1.35 (0.81, 2.27)	1.13 (0.65, 1.99)

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Table 4. Weighted unadjusted and mutually adjusted odds ratios (OR) for having Hepatitis C antibodies (anti-HCV), by participant characteristics and risk factors overall for adults aged 40–59 years old.

	Total	Odds Ratio (95% Confidence Interval)	
Variables	**Anti-HCV % (95% CI)**	**Unadjusted OR**	**Adjusted OR**
Total	6.0% (4.6%, 7.4%)		
Setting			
Urban	3.3% (1.9%, 4.8%)	1	1
Rural	7.8% (5.7%, 9.9%)	2.48 (1.45, 4.25)	1.82 (1.01, 3.27)
Sex			
Female	5.4% (3.9%, 6.9%)	1	1
Male	6.8% (4.6%, 9.1%)	1.28 (0.84, 1.96)	1.63 (1.02, 2.61)
Household income			
0–20,000 Rupees	6.3% (4.8%, 7.9%)	1	1
>20,000 Rupees	4.8% (2.2%, 7.4%)	0.74 (0.40, 1.36)	1.23 (0.63, 2.39)
Education			
None/Primary	8.6% (6.2%, 11.0%)	1	1
Middle/Secondary	4.7% (3.0%, 6.5%)	0.53 (0.33, 0.83)	0.58 (0.36, 0.95)
Graduate	1.6% (0.0%, 3.3%)	0.17 (0.05, 0.55)	0.24 (0.06, 0.88)
Last injection given by			
Medical Doctor	2.9% (1.1%, 4.8%)	1	1
Registered Nurse/Medical Practitioner	7.9% (5.9%, 9.9%)	2.83 (1.43, 5.61)	2.14 (1.04, 4.40)
Other/Unknown	4.1% (1.8%, 6.3%)	1.40 (0.59, 3.32)	1.30 (0.54, 3.14)
Number injections received last 6 months	NA	1.01 (0.99, 1.03)	1.00 (0.98, 1.02)
Number of times donating blood	NA	0.91 (0.77, 1.08)	0.91 (0.75, 1.11)
Number of blood transfusions received	NA	1.35 (1.02, 1.79)	1.51 (1.18, 1.93)
Received a permanent tattoo			
No	5.9% (4.5%, 7.3%)	1	1
Yes	7.6% (2.4%, 12.8%)	1.30 (0.60, 2.82)	1.03 (0.43, 2.47)

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addition to addressing ongoing transmission risk, are likely to be the most successful and cost effective. Population serosurveys, such as the study in Punjab presented here, can address key information gaps and inform policy makers in efforts to alleviate the public health burden of HCV infection across afflicted regions worldwide.[42]

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References

1. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017; 2(3):161–76. Epub 2017/04/14. https://doi.org/10.1016/S2468-1253(16)30181-9 PMID: 28404132.
2. World Health Organization. Hepatitis C Fact sheet October 2017. 2017.
3. Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. Semin Liver Dis. 2000; 20(1):17–35. PMID: 10895429.
4. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997; 349 (9055):825–32. PMID: 9121257.
5. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med. 2001; 345(1):41–52. https://doi.org/10.1056/NEJM200107053450107 PMID: 11439948.
6. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol. 2014; 61(1 Suppl):S58–68. https://doi.org/10.1016/j.jhep.2014.07.012 PMID: 25443346.
7. Petruzziello A. Epidemiology of Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Related Hepatocellular Carcinoma. Open Virol J. 2018; 12:26–32. Epub 2018/03/16. https://doi.org/10.2174/1874357901812010026 PMID: 29541276; PubMed Central PMCID: PMCPMC5842386.
8. Global Burden of Disease: Mortality Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015; 385(9963):117–71. https://doi.org/10.1016/S0140-6736(14)61682-2 PMID: 25530442; PubMed Central PMCID: PMCPMC4340604.
9. World Health Organization. Combating Hepatitis B and C to reach elimination by 2030. 2016.
10. Ara AK, Paul JP. New Direct-Acting Antiviral Therapies for Treatment of Chronic Hepatitis C Virus Infection. Gastroenterol Hepatol (N Y). 2015; 11(7):458–66. PMID: 27118941; PubMed Central PMCID: PMCPMC4843024.
11. Schietroma I, Scheri GC, Pinacchio C, Statzu M, Petruzziello A, Vullo V. Hepatitis C Virus and Hepatocellular Carcinoma: Pathogenetic Mechanisms and Impact of Direct-Acting Antivirals. Open Virol J. 2018; 12:16–25. Epub 2018/03/16. https://doi.org/10.2174/1874357901812010016 PMID: 29541275; PubMed Central PMCID: PMCPMC5842384.
12. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014; 61(1 Suppl):S45–57. https://doi.org/10.1016/j.jhep.2014.07.027 PMID: 25086286.

13. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006; 144(10):705–14. PMID: 16702586.

14. Balogun MA, Ramsay ME, Hesketh LM, Andrews N, Osborne KP, Gay NJ, et al. The prevalence of hepatitis C in England and Wales. J Infect. 2002; 45(4):219–26. PMID: 12423608.

15. Sievert W, Altraif I, Razavi HA, Abdo A, Ahmed EA, Alomair A, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Liver Int. 2011; 31 Suppl 2:61–80. https://doi.org/10.1111/j.1478-3231.2011.02540.x PMID: 21651703.

16. Petruzziello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016; 22(34):7824–40. Epub 2016/09/30. https://doi.org/10.3748/wjg.v22.i34.7824 PMID: 27678366; PubMed Central PMCID: PMCPMC5016383.

17. Nandi J, Bhawalkar V, Mody H, Elavia A, Desai PK, Banerjee K. Detection of HIV-1, HBV and HCV antibodies in blood donors from Surat, western India. Vox Sang. 1994; 67(4):406–7. Epub 1994/01/01. PMID: 7535499.

18. Indian State Census 2011. 2011.

19. Sood A, Sarin SK, Midha V, Hissar S, Sood N, Bansal P, et al. Prevalence of hepatitis C virus in a selected geographical area of northern India: a population based survey. Indian J Gastroenterol. 2012; 31(5):232–6. https://doi.org/10.1007/s12664-012-0251-8 PMID: 23073754.

20. Jindal N, Arora U, Singh K. Prevalence of human immunodeficiency virus (HIV), hepatitis B virus, and hepatitis C virus in three groups of populations at high risk of HIV infection in Amritsar (Punjab), Northern India. Jpn J Infect Dis. 2008; 61(1):79–81. PMID: 18219142.

21. Panda S, Roy T, Pahari S, Mehraa J, Sharma N, Singh G, et al. Alarming epidemics of human immunodeficiency virus and hepatitis C virus among injection drug users in the northwestern bordering state of Punjab, India: prevalence and correlates. Int J STD AIDS. 2013; 25(8):596–606. Epub 2013/12/20. https://doi.org/10.1177/0956462413515659 PMID: 24352120.

22. The Economist. Addiction in India: Pushing poppies in Punjab. 2016.

23. Arun P, Sangwan L, Munjal A. Prevalence of markers of hepatitis-B in voluntary blood donors in Fatehabad district of Haryana. Journal of Viral Hepatitis. 2015;Conference: 15th International Symposium on Viral Hepatitis and Liver Diseases, ISVHLD 2015. Berlin Germany. Conference Publication: (var. pagings). 22 (SUPPL. 2):28. PMID: 71956167.

24. Singh P, Kaur R, Kaur A. Frequency distribution of Hepatitis C virus in different geographical regions of Punjab: Retrospective study from a tertiary care centre in North India. J Nat Sci Biol Med. 2014; 5 (1):56–8. https://doi.org/10.4103/0976-9668.127288 PMID: 24678198; PubMed Central PMCID: PMCPMC3961953.

25. Iles JC, Abby Harrison GL, Lyons S, Djoko CF, Tamoufe U, Lebreton M, et al. Hepatitis C virus infections in the Democratic Republic of Congo exhibit a cohort effect. Infect Genet Evol. 2013; 19:386–94. https://doi.org/10.1016/j.meegid.2013.01.021 PMID: 23419346.

26. Strickland GT. Risk factors for HCV infection in Pakistan. J Viral Hepat. 2010; 17(5):305–6. Epub 2010/05/08. https://doi.org/10.1111/j.1365-2893.2010.01285.x PMID: 20447009.

27. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965. MMWR Recomm Rep. 2012; 61(RR-4):1–32. PMID: 22895429.

28. Nave RL. Baby boomers and the hepatitis C boom. Ann Emerg Med. 2013; 62(6):19A–21A. PMID: 24400356.

29. Nadeem A, Rubeena B, Agarwal V, Piyush K. Substance abuse in India. Pravara Med Rev. 2009; 4 (1):4–6.

30. Mahajan R, Midha V, Goyal O, Mehta V, Narang V, Kaur K, et al. Clinical profile of hepatitis C virus infection in a developing country- India. J Gastroenterol Hepatol. 2017. https://doi.org/10.1111/jgh.13995 PMID: 28921677.

31. Singh S. Rural health in Punjab—Needs reforms and investments. Abstracts of Sikh Studies. 2010; (542):37–61.

32. Rehan HS, Manak S, Yadav M, Deepinder Chopra D, Wardhan N. Diversity of genotype and mode of spread of Hepatitis C virus in Northern India. Saudi J Gastroenterol. 2011; 17(4):241–4. https://doi.org/10.4103/1319-3767.82576 PMID: 21727729; PubMed Central PMCID: PMCPMC3133980.

33. Duseja A, Arora L, Masih B, Singh H, Gupta A, Behera D, et al. Hepatitis B and C virus—prevalence and prevention in health care workers. Trop Gastroenterol. 2002; 23(3):125–6. PMID: 12693154.

34. Minhas S, Kotwal A, Singh M. Infection Control in Health Care Facilities. Med J Armed Forces India. 2011; 67(1):7–8. https://doi.org/10.1016/S0377-1237(11)80003-1 PMID: 27365753; PubMed Central PMCID: PMCPMC4920602.

35. Sood A, Midha V, Awasthi G. Hepatitis C—knowledge & practices among the family physicians. Trop Gastroenterol. 2002; 23(4):198–201. PMID: 12833713.

36. Rajasekaran M, Sivagnanam G, Thirumalaikolundusubramainan P, Namasivayam K, Ravindranath C. Injection practices in southern part of India. Public Health. 2003; 117(3):208–13. https://doi.org/10.1016/S0033-3506(03)00065-9 PMID: 12825472.

37. Agoramoorthy G. India Needs Effective Surveillance to Control Hepatitis C. Dig Dis Sci. 2017; 62(2):550–1. https://doi.org/10.1007/s10620-016-4436-3 PMID: 28050785.

38. Kumar T, Shrivastava A, Kumar A, Laserson KF, Narain JP, Venkatesh S, et al. Viral Hepatitis Surveillance—India, 2011–2013. MMWR Morb Mortal Wkly Rep. 2015; 64(28):758–62. PMID: 26203629.

39. Sood A, Midha V, Mahajan R, Narang V, Mehta V, Wander P, et al. Results of sofosbuvir-based combination therapy for chronic hepatitis C cohort of Indian patients in real-life clinical practice. J Gastroenterol Hepatol. 2017; 32(4):894–900. https://doi.org/10.1111/jgh.13628 PMID: 27787910.

40. The Indian Express. World Hepatitis Day: Punjab signs MoU with global firm to treat Hepatitis C patients. 2017.

41. Dhiman RK, Satsangi S, Grover GS, Puri P. Tackling the Hepatitis C Disease Burden in Punjab, India. J Clin Exp Hepatol. 2016; 6(3):224–32. https://doi.org/10.1016/j.jceh.2016.09.005 PMID: 27746619; PubMed Central PMCID: PMCPMC5052426.

42. Wait S, Kell E, Hamid S, Muljono DH, Sollano J, Mohamed R, et al. Hepatitis B and hepatitis C in southeast and southern Asia: challenges for governments. Lancet Gastroenterol Hepatol. 2016; 1(3):248–55. https://doi.org/10.1016/S2468-1253(16)30031-0 PMID: 28404097.

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Original Article

Impact of "Sambhav" Program (Financial Assistance and Counselor Services) on Hepatitis C Pegylated Interferon Alpha Treatment Initiation in India

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Abstract

Background: Financial constraints, social taboos and beliefs in alternative medicine are common reasons for delaying or not considering treatment for hepatitis C in India. The present study was planned to analyze the impact of non-banking interest free loan facility in patients affected with hepatitis C virus (HCV) in North India.

Methods: This one year observational, retrospective study was conducted in Department of Gastroenterology (January 2012-December 2013), Dayanand Medical College and Hospital Ludhiana, to evaluate the impact of program titled "Sambhav" (which provided non-banking financial assistance and counselor services) on treatment initiation and therapeutic compliance in HCV patients. Data of fully evaluated patients with chronic hepatitis, and/or cirrhosis due to HCV infection who were treated with Peginterferon alfa and ribavirin (RBV) combination during this duration (2012-2013) was collected from patient medical records and analyzed. In the year 2012, eligible patients who were offered antiviral treatment paid for treatment themselves, while in 2013, 'Sambhav' program was launched and this provided interest free financing by non-banking financial company (NBFC) for the treatment of HCV in addition to free counselor services for disease management. The treatment initiation and compliance rates were compared between the patients (n = 585) enrolled in 2013 who were offered 'Sambhav' assistance and those enrolled in 2012 (n = 628) when 'Sambhav' was not available.

Results: Introduction of Sambhav program improved the rates of treatment initiation (59% in 2013 vs. 51% in 2012, $P = .004$). Of the 585 eligible patients offered 'Sambhav' assistance in 2013, 233 patients (39.8%) applied but 106/233 (45.4%) received assistance. Antiviral therapy was started in 93/106 (87.7%) of these patients, while only 52 (42.5%) of 127 patients whose applications were rejected underwent treatment. Compliance to antiviral therapy also improved with the introduction of 'Sambhav' program (87.7% vs. 74.1%, $P = .001$).

Conclusion: 'Sambhav' program had significant impact on the initiation of antiviral therapy by overcoming the financial hurdles. The free counselor services helped to mitigate social taboos and imparted adequate awareness about the disease to the patients. Initiatives like 'Sambhav' can be utilized for improving healthcare services in developing countries, especially for chronic diseases.

Keywords: Sambhav Program, Hepatitis C, Pegylated Interferon Gamma, Treatment Access, India

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Key Messages

Implications for policy makers

- Heavy financial burden required for treatment of chronic diseases is a major deterrent for seeking medical aid.
- Lack of disease awareness also contributes towards delayed treatment in developing countries.

Implications for the public

Hepatitis C infection is the most common cause of chronic liver disease. The severity of hepatitis C, its progression, and response to therapy may vary depending on the genotype.

The common modes of transmission of hepatitis C infection are blood transfusion, IV drug use, unsafe therapeutic injection, and health care-related procedures. In India blood transfusion and unsafe injection practices are predominant modes of hepatitis C transmission.

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Introduction

Provision of healthcare security or healthcare insurance in developing countries like India continues to be one of the most important unresolved policy issues. A majority of the patients affected with chronic illnesses spend a large percentage of their income on health-related expenditure, especially when they seek in-patient care for major health issues. Further, the high incidence of sickness cuts into their budget in two different ways: they need to spend large amount of money for treatment and are unable to earn money while they are under treatment. It is estimated that at least 24% of all Indians hospitalized fall below the poverty line because of hospitalization and out of pocket spending on hospital care.[1-4]

Hepatitis C virus (HCV) infection is estimated to affect 0.5%–1.5% of Indian population showing much higher prevalence in some areas of northeast India, in some tribal populations and in certain parts of Punjab. The long-term implications of HCV infection are variable, ranging from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma.[5] The primary goal of HCV therapy is to cure the infection. In India approximately 14 million patients are affected with chronic hepatitis C (CHC), but treatment rate is as low as 1% when compared with diagnosis rate of 6%. The lack of disease awareness, its consequences and financial constraints are the major barriers which prevent successful treatment outcomes.[6]

Until 2011, the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) for 24 or 48 weeks was the standard of care for CHC. With this regimen, sustained virological response (SVR) rates were higher in patients infected with HCV genotypes 2, 3, 5, and 6 (up to about 80%) and intermediate SVR rates (40%–50%) were achieved in those with HCV genotypes 1 and 4. During the study period 2012-2013, the standard of care was peg-interferon with RBV and the average cost of the entire treatment was between 150 000-300 000 INR (US$2345-4695).[5-7] The newer direct acting antivirals (DAAs) which are highly efficacious and cheaper were introduced in India after the study period, ie, after 2014.[8] The prevalence of CHC in Punjab and Haryana has been reported to be as high as 4%. Treatment with Peg-IFN alpha and RBV was costly, and only 0.1% of the patients could afford treatment. In addition to financial constraints, fear of side effects, several myths about HCV among the people and faith in alternative medicines limited the acceptance of therapy with anti-virals.

To address these issues, 'Sambhav' program was launched in 2013, offering interest free loan for the needy patients for the HCV treatment, monitoring compliance and addressing myths through counselor services. We hereby present our analysis of impact of this program on the initiation of treatment and subsequent compliance with Peg-IFN and RBV in patients with CHC.

Methods

Setting

This was an observational, retrospective study conducted between January 2012 and December 2013 in Department of Gastroenterology, Dayanand Medical College and Hospital (DMC & H), Ludhiana, Punjab, India. The aim of the study was to evaluate impact of financial support on treatment access and compliance in CHC. During this period the available treatment for patients with chronic hepatitis or cirrhosis due to HCV included PEG-IFN alpha in combination with RBV. The acceptance and compliance to antiviral treatment in the patients treated for CHC in 2012 (with self-payment) and 2013 (with support from 'Sambhav' program) was retrospectively analyzed.

The "Sambhav" Program

The 'Sambhav' (Hindi word, meaning it is possible) program, launched in 2013, was a novel collaboration between a hospital (Dayanand Medical College and Hospital Ludhiana), Merck pharmaceutical company (MSD) and a financing institution (Fullereton, India) to address the needs of the patients with CHC. This program had two components: first; financing by way of loan and second; provision of free counseling services for proper disease management.

The main objective of Sambhav program was to overcome cash flow issues, remove any excess financial burden on patients choosing this program and remove patient liability if there was no cure. Under the financing program, eligible patients got an interest free, unsecured financing from a non-banking financial company (NBFC), for the treatment of hepatitis C. The loan provided under the financing scheme was payable over period of 2-4 years (depending upon the affordability and preference of the patients) and the payment was to be done in the form of equated monthly installments (EMIs), (calculated using Fullerton software, then rebate given toward end of loan). The loans were provided to traditionally difficult to fund profiles eg, farmers and shop owners etc. Other incentives included zero extra charge and easier loan terms, simplified documentation requirements and waiver of the outstanding EMIs in case of non-cure (defined as drug non-responders at 12 weeks and patients not achieving end of treatment response [ETR] or SVR after completion of therapy).

For disease management the main objectives of HCV counsellors were to optimize the chances of achieving cure of CHC by removing myths, if any, and to help patients understand the importance of treatment and completing the full course. Free counselor services, 'Saarthi' (Sanskrit word for charioteer, signifying the one who helps one to pass through an obstacle) were started to implement this. These included in-person and phone counseling services, free diagnostic tests and assistance in procurement of the loan (Figure).

Patients and Treatment

All patients who had been found to be HCV positive had been assessed for the status of liver disease (liver biochemical tests, ultrasonography and biopsy, if indicated) and viral characteristics (HCV RNA levels and genotype). Those found to be fit for therapy (patients with advanced liver disease, depression, cardiopulmonary disease, renal failure were excluded) had been offered PEG-IFN and RBV. Those who started anti-viral therapy had been monitored for compliance,

efficacy and adverse events. Compliance of treatment was noted as per patients statements. The patients were followed up every 4 weeks in clinic of the gastroenterologist and were weekly monitored for compliance and treatment related queries by the counselor either personally or telephonically. In the year 2012, the patients accepting treatment had to pay for the treatment themselves, while financial assistance and free counseling was provided by the Sambhav program in 2013.

In 2013, the confirmed cases for HCV requiring treatment with PEG-IFN and RBV were introduced to the 'Sambhav' program by the counselor/treating physician. Patients offered 'Sambhav' program included (*a*) All confirmed patients (age <60 years) for HCV requiring treatment (*b*) monthly documented income >INR 10 000 (US$157). The other prerequisites for financial assistance included (*i*) one loan per family; (ii) minimum amount of loan INR 100 000 (US$1565); (*iii*) payment of an interest if loan repayment tenure was more than 2-4 years. The exclusion criteria were (*a*) age >60 years (*b*) single patients (widow/widower, divorcee), and (*c*) monthly documented income <INR 10 000 (US$157).

For analysis the patients were divided into 2 groups:

- Group A: CHC patients presenting to the DMC & H after launch of 'Sambhav' (in year 2013).
  - Group A1: Patients who received the 'Sambhav' assistance.
  - Group A2: Patients who did not receive the 'Sambhav' assistance either because they did not apply or because their application was rejected.
- Group B: Confirmed CHC patients presenting to the clinics prior to SAMBHAV (in year 2012). A designated CRO (Central Record Officer) captured, checked, stored and analyzed the data. CRO followed internal SOPs (Standard operating procedures). The data was transferred to the principal investigator after termination of the study. Quality control audits of all key safety and effectiveness data in the database were made prior to locking the database.

Data Analysis

Data analysis was done using SPSS and was summarized using descriptive summary statistics (mean and standard deviation). Bi-variate analyses were performed to test the relationship between the background characteristics of the patients and the outcome variables such as the HCV treatment initiation and compliance using chi-square tests. P values <.05 were considered to indicate statistical significance. The multivariate logistic regression was used in order to control for the important background factors to verify the bi-variate relationships between the interest free loan through 'Sambhav' and the outcome variables such as the HCV treatment initiation and compliance.

Results

In 2012 a total of 628 patients (self-payment, no 'Sambhav' program) and in 2013, 585 patients (under 'Sambhav' program) were included. The baseline characteristics of the patients are listed in Table 1.

Treatment for CHC was initiated in 318/628 patients (51%) in 2012. All these patients had to make the payment for anti-viral therapy from their own pocket. After the launch of 'Sambhav' program in 2013, the rate of treatment initiation significantly increased to 59% (344/585, P = .004), however there was no significant change in the duration of treatment or rates of compliance to therapy (Table 2).

Of the 233/585 (39.8%) of the patients who applied for the

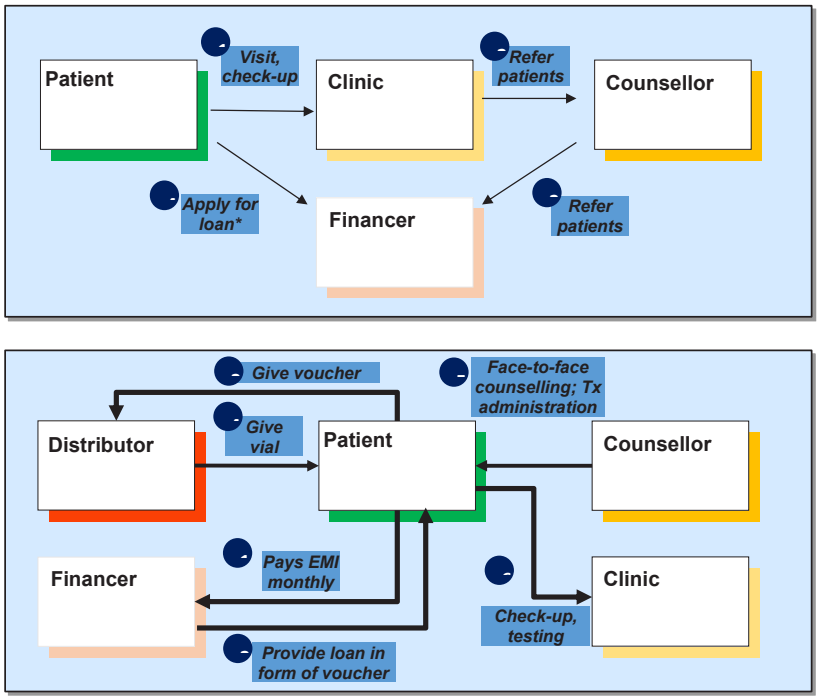

Figure. Depicting the Flow of Patient Enrolment, loan Sanction and Follow up in Sambhav Program.

Table 1. Baseline Patient Characteristics

Variable(s)	Group = 2012 (n = 628)	Group = 2013 (n = 585)
Age (y) (mean ± SD)	43.1 ± 13.2	42.9 ± 11.7
Height (cm) (mean ± SD)	168.6 ± 8.2	168.4 ± 8.4
Weight (kg) (mean ± SD)	70.1 ± 14.2	70.1 ± 13.4
Gender, No. (%)		
Male	422 (67.2)	391 (66.8)
Female	206 (32.8)	194 (33.2)
Education, No. (%)		
Elementary education	241 (38.4)	192 (32.8)
Secondary	304 (48.4)	307 (52.5)
Graduate and above	83 (13.2)	86 (14.72)
Monthly Income, No. (%)		
<10K	255 (40.6)	135 (23.1)
10-25K	255 (40.6)	293 (50.1)
>25K	112 (17.8)	151 (25.8)
Missing data	06 (1.0)	06 (1.0)
Occupation, No. (%)		
Unemployed	230 (36.6)	189 (32.3)
Farmer and shop owner	331 (52.7)	335 (57.3)
White-collar jobs	63 (10.0)	59 (10.1)
Missing data	04 (0.6)	02 (0.3)
Alcohol consumption, No. (%)	180 (28.7)	174 (29.7)
Drug abuse, No. (%)	43 (6.8)	45 (7.7)
Smokers, No. (%)	09 (1.4)	36 (6.2)

Table 2. Treatment Initiation Duration and Compliance

Variable (s)	Group = 2012 (N=628	Group = 2013 (N=585)	*P* Value
Patients initiating treatment, No. (%)	318 (50.6)	344 (58.8)	<.001[a]
Treatment duration (wk), (mean ± SD)	25.9 ± 10.5	26.7 ± 10.6	>.5[b]
Treatment compliance (%)	233/318 (73.3)	271/344 (78.8)	>.05

[a] Based on chi-square test.
[b] Based on independent *t* test.

'Sambhav' program, 106 (45.4%) received the financial assistance. The applications of remaining 127 patients were rejected due to various reasons (age >60 years [05/127, 3.9%], low income [52/127, 40.9%], non-compliance after the initiation of loan process [70/127, 55.1%]).

Among the patients who applied for the 'Sambhav' program, the rate of treatment initiation was higher (93/106, 87.7%) in patients who got financial assistance as compared to the patients who paid for the treatment by themselves due to failure to enroll in the 'Sambhav' program (52/127, 42.5%, *P* <.001).

In 2013, a total of 344 patients were treated with Peg-INF aipha and RBV. Of the 344 patients only 145/344 (42.5%) had applied for Sambhav program while 57.5% (199/344) did not apply for this novel initiative. However more patients (145/233, 62.2% vs. 199/353, 56.5%) initiated treatment when exposed to Sambhav initiative (Table 3). Thus, the introduction of 'Sambhav' program increased the likelihood

Table 3. Treatment Initiation as Compliance in Patients Applying for Financial Assistance (Group = 2013)

	Financial Assistance Granted (n = 106)	Financial Assistance Not-granted (n = 127)	*P* Value
Started treatment, (n = 233) No. (%)	93 (87.7)	54 (42.5)	<.001
Treatment compliance, (n = 147) No. (%)	81 (87.1)	40 (74.1)	<.05

of treatment initiated by an odds ratio of 10 (Tables 4 and 5). The loan was waived of in 12/93 (12.9%) patients loan as they did not respond to drugs at 12 weeks (failed rapid virological response, RVR). The treatment compliance rate also improved with the financial help and counseling from the 'Sambhav' program (87.1% with 'Sambhav' vs. 74.1% without 'Sambhav'). On bivariate analysis between 2012 and 2013 the odds ratio for the SAMBHAV interest free loan after controlling for the patients' socio-economic status indicates likelihood of increase in the compliance by nearly 4 times (Tables 6 and 7).

Discussion

In 2013, 585 patients were enrolled and offered 'Sambhav' assistance and the treatment initiation and compliance rates were compared with 2012 group (n = 628) when 'Sambhav' was not available. Of the 233 patients (39.8%) who applied for 'Sambhav' program, 45.4% (106/233) received the assistance while 127 applications were rejected due to various reasons. There was a significant difference between the two groups in HCV treatment initiation (51% in 2012 and 59% in 2013) (*P* = .004). A majority 87.7% (93/106) of the patients who received 'Sambhav' assistance initiated the treatment compared to only 42.5% (52/127) among those who were offered 'Sambhav' support but did not get it due to various reasons. The compliance rates were also better (87.7% vs. 74.1%) when compared groups with and without 'Sambhav' support.

HCV related liver diseases are major healthcare burden in Punjab. There are many patient, provider, government and payer factors which effectively prevent delivery of HCV care. Patient-related factors are a common source of treatment deferral and include limited awareness, poor compliance to physician recommendations, economic or social pressures, treatment fears, psychiatric disease and injection drug use. Specific factors identified as barriers to medication compliance among patients with low socioeconomic status were high medication costs and poor understanding of medication instructions. Also, the patients lack knowledge about the urgency of the initiating therapy, adverse events and existence of cure for this disease with successful treatment. There is stigma and many myths associated with HCV, leading patients seeking alternative remedies through quacks. Therefore, these patients need counseling about various aspects of disease and therapy.[5-7]

In India, a majority of the financial assistance is provided by the banks but recently NBFC's are becoming popular among

Table 4. Logistic Regression (Patient Initiating Treatment as Dependent Variable)

	B	SE	Wald	*df*	*P* Value	Exp (B)
Age	0.000	0.016	0.000	1	1.000	1.000
Gender	0.227	0.605	0.140	1	.708	1.254
Residential status (0=U/1=R)	-0.806	0.462	3.051	1	.081	0.447
Education score (0 = elementary education)	-	-	1.843	2	.398	-
Education score (1 = secondary)	1.068	0.799	1.788	1	.181	2.910
Education score (2 = ≥ graduate)	0.671	0.681	0.970	1	.325	1.956
Monthly income (0 = <10K)	-	-	13.259	2	.001	-
Monthly income (1 = 10-25K)	-2.337	0.647	13.048	1	.000	0.097
Monthly income (2 = >25K)	-1.674	0.562	8.871	1	.003	0.188
Occupation score (0 = Unemployed)	-	-	1.295	2	.523	-
Occupation score (1 = shopown and farmers)	0.872	0.969	0.811	1	.368	2.392
Occupation score (2 = white-collar jobs)	0.207	0.838	0.061	1	.804	1.231
Family history (0=N/1=Y)	0.434	0.414	1.100	1	.294	1.544
Loan application accepted (0=N/1=Y)	2.350	0.412	32.522	1	.000	10.489
Constant	0.498	1.010	0.243	1	.622	1.646

Abbreviation: SE, standard error.

Table 5. Variables in the Equation With Respect to Table 4

		B	SE	Wald	*df*	*P* Value	Exp(B)	95% CI for EXP(B)	
								Lower	Upper
Step 1	Age	0.000	0.016	0.000	1	1.000	1.000	0.968	1.033
	Gender (1)	-0.227	0.605	0.140	1	.708	0.797	0.243	2.611
	Residential status (1)	0.806	0.462	3.051	1	.081	2.239	0.906	5.534
	Education score	-	-	1.843	2	.398	-	-	-
	Education score (1)	1.068	0.799	1.788	1	.181	2.910	0.608	13.927
	Education score (2)	0.671	0.681	0.970	1	.325	1.956	0.515	7.435
	Monthly income	-	-	13.259	2	.001	-	-	-
	Monthly income (1)	-2.337	0.647	13.048	1	.000	0.097	0.027	0.343
	Monthly income (2)	-1.674	0.562	8.871	1	.003	0.188	0.062	0.564
	Occupation score	-	-	1.295	2	.523	-	-	-
	Occupation score (1)	0.872	0.969	0.811	1	.368	2.392	0.358	15.968
	Occupation score (2)	0.207	0.838	0.061	1	.804	1.231	0.238	6.357
	Family history (1)	-0.434	0.414	1.100	1	.294	0.648	0.288	1.458
	Accepted YN (1)	-2.350	0.412	32.522	1	.000	0.095	0.043	0.214
	Constant	2.703	0.949	8.107	1	.004	14.927	-	-

Abbreviation: SE, standard error; YN, yes/no.

the general public and loan seekers. The banks in India are incorporated by the Banking Companies Act, whereas NBFCs are incorporated by the Companies Act of 1956. NBFCs can just make investment or lend, they do not accept demand deposits. But when it comes to borrowing loan most prefer NBFCs over banks and the reason for this is banks have hard rules and require more time to approve or sanction a loan. On the other hand, NBFCs ensure quicker processing and necessary loan amount is disbursed within days. Though rate of interest is high at NBFCs most of the times as compared to banks, borrowers still prefer to take loans from NBFC considering the ease of getting loan and lesser complications. Moreover, individuals with poor credit rating are considered to be high-risk and generally do not get loans from banks. Unless the credit score is above 600-650, it is very difficult to get a loan sanctioned from banks. NBFCs on the other hand offer loans to individuals with low credit score and have brought down the interest rates to either equal to bank lending rates or at times even lower than that.[3,4,7] Thus, with all the other benefits when rate of interest is also lowered, and borrowers find this easier and affordable. This has also resulted in lower EMI for the borrowers.

In 2012, Merck & Co. launched its pilot Hepatitis Financing Mechanism, or 'Sambhav' Program in the state of Punjab in India. Market research revealed that many patients could not afford the cost of treatment for hepatitis C. So in response, for patients with limited or no insurance coverage, the company developed an innovative financing model for its hepatitis C treatment in high prevalence areas for HCV infection in North India. This novel program had two components: free counselor services for disease management and financing by way of loan. Under the financing program, eligible patients

Table 6. Logistic Regression (Compliance to Treatment as Dependent Variable)

	B	SE	Wald	*df*	*P* Value	Exp (B)
Age	-0.060	0.024	6.223	1	.13	0.941
Gender	1.562	0.895	3.046	1	.081	4.767
Residential status (0=U/1=R)	0.746	0.567	1.733	1	.188	2.108
Education score (0 = elementary education)	-	-	2.941	2	.230	-
Education score (1 = secondary)	0.316	1.112	0.081	1	.776	1.371
Education score (2 = ≥ graduate)	-0.713	0.950	0.565	1	.452	0.490
Monthly income (0 = <10K)	-	-	0.743	2	.690	-
Monthly income (1 = 10-25K)	0.020	0.915	0.001	1	.982	1.021
Monthly income (2 = >25K)	-0.465	0.612	0.578	1	.447	0.628
Occupation score (0 = Unemployed)	-	-	3.965	2	.138	-
Occupation score (1 = shopown and farmers)	1.990	1.202	2.742	1	.098	7.312
Occupation score (2 = white-collar jobs)	0.258	1.000	0.067	1	.796	1.294
Family history (0=N/1=Y)	-0.287	0.591	0.236	1	.627	0.751
Loan application accepted (0=N/1=Y)	1.262	0.542	5.417	1	.020	3.532
Constant	1.980	1.371	2.086	1	.149	7.242

Abbreviations: SE, standard error; YN, yes/no.

Table 7. Variables in the Equation With Respect to Table 6

		B	SE	Wald	*df*	*P* Value	Exp(B)	95% CI for EXP(B)	
								Lower	Upper
Step 1	Age	-0.060	0.024	6.223	1	.013	0.941	0.898	0.987
	Gender (1)	-1.562	0.895	3.046	1	.081	0.210	0.036	1.212
	Residential status (1)	-0.746	0.567	1.733	1	.188	0.474	0.156	1.440
	Education score	-	-	2.941	2	.230	-	-	-
	Education score (1)	0.316	1.112	0.081	1	.776	1.371	0.155	12.127
	Education score (2)	-0.714	0.950	0.565	1	.452	0.490	0.076	3.150
	Monthly income	-	-	0.743	2	.690	-	-	-
	Monthly income (1)	0.020	0.915	0.001	1	.982	1.021	0.170	6.131
	Monthly income (2)	-0.465	0.612	0.578	1	.447	0.628	0.189	2.084
	Occupation score	-	-	3.965	2	.138	-	-	-
	Occupation score (1)	1.990	1.202	2.742	1	.098	7.312	0.694	77.063
	Occupation score (2)	0.258	1.000	0.067	1	.796	1.294	0.182	9.197
	Family history (1)	0.287	0.591	0.236	1	.627	1.332	0.418	4.243
	Accepted YN (1)	-1.262	0.542	5.417	1	.020	0.283	0.098	0.819
	Constant	5.263	1.480	12.641	1	.000	192.966	-	-

Abbreviations: SE, standard error; YN, yes/no.

get interest free, unsecured financing from NBFC, for the treatment of hepatitis C and counselor services were rendered to address various concerns and myths of patients regarding therapy and disease. This was a unique collaboration between a hospital/clinic, pharmaceutical company and financing institution to develop a new business model to address a major unmet patient need – access to medicines by reducing cash flow burden. The benefits of providing financial support were observed as more number of patients initiated treatment. The ultimate aim of any prescribed medical therapy is to achieve certain desired outcomes in the patients concerned. These desired outcomes are part and parcel of the objectives in the management of the diseases or conditions. However, despite all the best intention and efforts on the part of the healthcare professionals, those outcomes might not be achievable if the patients are non-compliant.[9-11] This shortfall may also have serious and detrimental effects from the perspective of disease management. Hepatitis C infection is a chronic liver disease requiring treatment for longer duration and regular follow ups with their treating physicians. Moreover, continuous motivation is required to start treatment considering the social stigma the HCV carries along with it especially in North India. The 'Sambhav' program provided counselor services through its project Saarthi which lead to statistically significant ($P = .001$) difference in the treatment compliance between those who received 'Sambhav' assistance and those who did not (87% among those who received compared to 74% those who did not). It may be recalled that the impact of 'Sambhav' program on the compliance was not significant when we did not differentiate between those actually received the financial assistance and those who did not. This fact highlights the importance of counselor services which allow

patients to understand the disease better, treatment related myths are attended; patients are kept motivated to continue treatment, and are also made aware of any therapy related side effects.

Conclusion

HCV is prevalent in Northern India especially in the state of Punjab. Financial constraints and lack of knowledge are the barriers for not seeking treatment leading to serious liver diseases. As a response to this, an innovative program was initiated in high prevalence states including Punjab not only to provide unsecured interest free loan and also disease management. The treatment initiation rate of the HCV increased and treatment compliance also improved significantly when provided the 'Sambhav' support. In this context, the 'Sambhav' program experience has important implications for policy development.

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Ethical issues

The ethical clearance from the institutional board was sought and the study was conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations; Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology, and with the ethical principles laid down in the Declaration of Helsinki.

Competing interests

Authors declare that they have no competing interests.

Authors' contributions

Concept and design: AS, VanM, and VarM. Aquisition of data: DS, KK, and VS. Analysis and interpretation of data: AS, VanM, SSH, and VN. Drafting of manuscript: AS, VN, and RM. Critical revision of manuscript for intellectual content: AS, VanM. Statistical aanalysis: SSH and VS. Obtaining funding: AS, SSH, and VS. Administrative, material, and technical support: SK and DS.

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References

1. Jhabvala R, Subramanya RKA. *The Unorganised Sector: Work Security and Social Protection*. New Delhi: Sage; 2000.
2. Ahmad E, Dreze J, Hills J, Sen A, eds. Social Security in Developing Countries. Oxford: Clarendon Press; 1991.
3. Gumber A, Shariff A, Duggal R, Alam M. Health care financing and insurance: perspective for the ninth plan, 1997-2002. *Margin*. 1999;31(2):38-68.
4. Gumber A. Burden of disease and cost of ill health in India: setting priorities for health interventions during the Ninth Plan. *Margin*. 1997;29(2):133-172.
5. Gumber A, Kulkarani V. *Health insurance for workers in the informal sector: Detail results from a pilot study*. New Delhi: National Council of Applied Economic Research; 2000.
6. Sood A, Sarin SK, Midha V, et al. Prevalence of hepatitis C virus in a selected geographical area of northern India: a population based survey. *Indian J Gastroenterol*. 2012;31(5):232-236. doi:10.1007/s12664-012-0251-8
7. Puri P, Anand AC, Saraswat VA, et al. Consensus Statement of HCV Task Force of the Indian National Association for Study of the Liver (INASL). Part II: INASL Recommendations for Management of HCV in India. *J Clin Exp Hepatol*. 2014;4(2):117-140. doi:10.1016/j.jceh.2014.06.001
8. Sood A, Midha V, Mahajan R, et al. Results of sofosbuvir-based combination therapy for chronic hepatitis C cohort of Indian patients in real-life clinical practice. *J Gastroenterol Hepatol*. 2017;32(4):894-900. doi:10.1111/jgh.13628
9. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag*. 2008;4(1):269-286.
10. Selvaraj S, Karan AK. Why publicly-financed health insurance schemes are ineffective in providing financial risk protection. *Econ Polit Wkly*. 2012;47(11):60-68.
11. Selvaraj S, Subramanian SV. Financial risk protection & chronic disease care. *Indian J Med Res*. 2012;136(4):544-546.

Clustering of hepatitis C virus antibody positivity within households and communities in Punjab, India

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Clustering of hepatitis C virus antibody positivity within households and communities in Punjab, India

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Summary 200/200 words

To better understand hepatitis C virus (HCV) transmission in Punjab state, India, we estimated the distribution of HCV antibody positivity (anti-HCV+) prevalence using a 2013-2014 HCV household seroprevalence-survey. Household anti-HCV+ clustering was investigated a) by individual-level multivariable logistic regression, and b) comparing the observed frequency of households with multiple anti-HCV+ persons against the expected, simulated frequency assuming anti-HCV+ persons are randomly distributed. Similarly, village/ward level clustering was investigated. We estimated household-level associations between exposures and the number of anti-HCV+ members in a household using multivariable ordered logistic regression. From 1,593 households and 5,543 participants, anti-HCV+ prevalence was 3.6% (95% confidence interval 3.0%-4.2%). Individual-level regression found an odds ratio of 3.19 (2.25-4.50) for someone being anti-HCV+ if another household member was anti-HCV+. Thirty households surveyed had ≥2 anti-HCV+ members, whereas 0/1000 (P<.001) simulations had ≥30 such households. Excess clustering was evident at village-level: 10 villages had ≥6 anti-HCV+ members, occurring in 31/1000 simulations (P=.031). The household-level model indicated the number of household members, living in southern Punjab, lower socio-economic score, and a higher proportion having ever used opium/bhuki were associated with a household's number of anti-HCV+ members. Anti-HCV+ clusters within households and villages in Punjab, India; this should inform screening efforts.

Key results:

- HCV antibody positivity (anti-HCV+) clusters within households and villages in Punjab state, India.
- Living in southern Punjab was associated with a household's number of anti-HCV+ members.
- Lower socio-economic status was also associated with a household's number of anti-HCV+ members.

Introduction

The World Health Organization (WHO) has set global targets for 2030 to reduce new infections of hepatitis C virus (HCV) by 80%, and HCV-related deaths by 65% of the estimated burden in 2015(1). In 2015 an estimated 71 million people were living with HCV infection, and 400,000 people die annually of HCV-related complications, mainly end-stage liver disease and liver cancer(2). Direct-acting antivirals (DAAs) have greatly simplified treatment for HCV infection due to ease of administration (all oral regimens), minimal side-effects, and high effectiveness(3). Better understanding of the risk-factors driving HCV transmission can lead to effective prevention interventions, targeted screening, and linkage to care, which are needed to reach the WHO targets(4).

The global HCV burden is unevenly distributed; half of all HCV infected individuals reside in six countries, one being India(5). Although India's HCV prevalence may be around 1%, because the population is 1.3 billion, approximately 10 million people are living with HCV(6). Despite a recent systematic review(7), the Indian HCV burden is poorly described because of a paucity of community level data(7).

Due to the high cost of DAAs, it has been postulated that for some countries treating all HCV-infected persons would cost more than their total expenditure on pharmaceuticals(8). However, India produces the bulk of the world's generic licensed DAAs, and prices are lower than most countries, removing this barrier to treatment access(9). In 2016, the Indian state of Punjab launched a program to provide treatment free of charge(10).

During 2013-14, a population based serosurvey was conducted in Punjab finding an overall HCV prevalence of 3.6%(11). This serosurvey collected demographic data and information on other exposures possibly associated with HCV(11), identifying associations with the number of blood transfusions received, and the type of practitioner that administered the last medical injection(11). However, the findings did not account for all possible causes of infection, such as risks associated with having been to jail(12).

An understanding of HCV transmission in Punjab can guide prevention efforts and improve the effectiveness of testing and treatment strategies. Understanding if HCV infection concentrates in households or communities can inform screening efforts, resulting in more effective use of resources, contributing to successful HCV elimination in Punjab. We aim to investigate the distribution and clustering of HCV prevalence within Punjab, India.

Methods

Data

This analysis uses data from a cross-sectional seroprevalence survey conducted in Punjab state, India, 2013-2014, described previously(11). Briefly, the study aimed to estimate HCV antibody (anti-HCV) and viremia prevalence among Punjab residents aged ≥5 years. The survey included a questionnaire collecting demographic, economic, medical, risk-factor, and lifestyle information. Participants were tested for anti-HCV and those positive for anti-HCV were tested for HCV ribonucleic acid (RNA) by polymerase-chain reaction. The study employed a multi-stage stratified cluster sampling design, weighted to the 2011 Punjab Census(13). All persons aged ≥5 years in a selected household were eligible to participate.

Questionnaires were administered confidentially by trained survey teams via face-to-face interviews for each individual. After each interview's completion, a blood sample was obtained from consenting participants and tested for anti-HCV (Vitros Immunodiagnostic Anti-HCV, Johnson and Johnson Co., New Brunswick, NJ, USA). History of HCV infection was defined as testing positive for anti-HCV (anti-HCV+).

The study protocol received approval from the Dayanand Medical College, Ludhiana, Institutional Review Board, and an ethical review committee from the Merck Investigator Initiated Study Protocol-Review Committee. Written consent was obtained for each participant. Confidentiality was strictly adhered to. Participation was voluntary; participants age 5-17 years provided assent in addition to informed parental/guardian consent.

Variables considered in regression models

Demographic and Geographic Risk Factors

The following characteristics were investigated for association with anti-HCV positivity: age, sex, rural/urban status, and north/south residence in Punjab. The districts from the south Punjab included in the study were Muktsar, Moga, Ludhiana, Sangrur, and Mansa; the northern districts were Amritsar, Jalandhar, Tam Taran, Gurdaspur, and Hoshiarpur. The north/south analysis was included because previous investigations demonstrated prevalences varied by district (supplementary figure 1(11)); and geographical north/south could be generalized to other provinces not surveyed.

Socio-economic status

Previous studies suggest low socio-economic status (S-ES) is associated with increased HCV infection risk from healthcare exposures, such as re-use of syringes(14). A cumulative S-ES score variable was created to increase power and better capture S-ES than individual variables.

The following socio-economic indicators were included in the S-ES score variable: household income in rupees (≤10,000, 10,001-20,000, 20,001-50,000, >50,000; 10,000 rupees is around 140 US dollars), whether their residence was a kacha (a flimsy construction) or a pucca (more solid), whether their source of water comes from a tube well, their educational level (none/primary, middle/secondary, graduate), and whether their last healthcare provider used was certified (versus an uncertified/alternative healthcare provider).

The S-ES variable was scored on a scale of 0-7 as follows: one point for a household income of 10,001-20,000 rupees, and two points for a household income of >20,000 rupees; one point for a pucca residence; one point for not using a tube well for water; one point for completion of middle/secondary school or two points for completing graduate education; one point for receiving healthcare from a certified healthcare provider.

Medical, social, and other risk-factors

Medically associated risk-factors possibly associated with HCV transmission were: ever had surgery, ever had an invasive medical procedure, ever had a dental procedure, receipt of a medical injection in the previous six months, ever received a streptomycin injection for tuberculosis, ever received a blood transfusion, and ever been hospitalized.

The cumulative risk of medical interventions was estimated on a scale scored from 0-7, allocating one point for each medical risk the participant had ever been exposed to: surgery, an invasive medical procedure, a dental procedure, a medical injection in last six months, a streptomycin injection, a blood transfusion, hospitalization.

Social and other risk-factors

Social risk-factors (ever had a tattoo, shaving by a barber [as opposed to at home], ever had a body piercing); and other risk-factors (ever been jailed, and ever had a motor accident) could also be associated with HCV transmission.

Injection drug use (IDU) is considered a driver of HCV transmission in Punjab(15). People who inject drugs (PWID) have a high HCV prevalence(16). However, only five subjects (0.1%) surveyed admitted to having ever injected drugs, a percentage similar to the estimated prevalence of current IDU in Punjab(17). The prevalence of those currently injecting drugs should be much lower than of ever injecting. Our survey proportion of ever

injectors likely represents an underestimate of the actual prevalence. A recent report linked smoking traditional, plant-based drugs to IDU(18). We examined other exposures/behaviours to investigate using them as proxy measures of IDU. The exposures included: ever used opium or bhuki (an intoxicating wild grass that is ingested(19)), ever drank alcohol, and ever smoked tobacco.

Clustering of anti-HCV+ prevalence by household and ward/village

Individual-level analyses

For individual-level analyses, study subjects were stratified by urban/rural residence, defined by the 2011 Punjab Census(13), and weighted by population sizes of the wards (areas within cities) and villages and clustered by household. Logistic regression was used to estimate associations between S-ES score and anti-HCV status, and medical risk score and anti-HCV status, both overall and stratified by rural/urban setting.

An individual-level logistic regression was also used to estimate odds ratios (ORs) and adjusted odds ratios (aORs) for anti-HCV positivity by various characteristics and risk factors, including a variable of whether another household member was positive for HCV antibodies.

Simulation analyses

To further investigate whether anti-HCV+ persons clustered within households, the observed frequencies of households containing multiple anti-HCV+ members were compared with the expected number from simulated data. This simulation assumed anti-HCV+ persons were randomly distributed with a Binomial distribution with a mean equal to the proportion of anti-HCV+ cases in the unweighted survey data. Using the same household structure as found in the survey, 1,000 simulations were performed, accounting for the varying urban/rural prevalences. We assumed the number of household members surveyed was a proxy for the actual number of individuals living in the household. This simulation method was repeated for analyses investigating clustering of anti-HCV+ persons within the village/ward level.

Household-level analyses

Household characteristics were tabulated by number of anti-HCV+ members (0, 1, and ≥2). Ordered logistic regression models were used to estimate associations between each exposure/characteristic and the number of anti-HCV+ members in a household (0, 1, or ≥2), adjusting for the number of household members, as households with more members have greater probability of containing anti-HCV+ household member(s). The

exposure/characteristics that were associated (P<.05) with anti-HCV+ household members (when only adjusted for the number of household members), were then included in an ordered logistic regression backwards elimination model. The S-ES score variable, rather than its individual components (eg. household income), was included in the backwards elimination model, to increase power. A likelihood-ratio test of proportionality of odds across response categories was performed to test the multivariable ordered logistic regression's assumption of proportional odds.

Results

There were 5,543 eligible participants with available HCV testing results who completed the survey, described previously(11). Briefly, 62% of the surveyed population lived in rural areas, 54% were women, and the median age was 35 years (interquartile range [IQR]: 21-50). The overall anti-HCV prevalence was 3.6% (95% confidence interval [95%CI]: 3.0%-4.2%) and was higher in rural areas, 4.7% (95%CI: 3.8%-5.7%), than urban areas, 1.6% (95%CI: 1.1%-2.2%). Anti-HCV prevalence varied by district (supplementary figure 1) and was higher in the south (4.7% [95%CI: 4.0%-5.5%]) than the north (2.0% [95%CI: 1.4%-2.6%]).

The number of members surveyed in each of the 1,593 households was 1, 2, 3, 4, and ≥5 in 257 (16.1%), 315 (19.8%), 343 (21.5%), 296 (18.6%), and 382 (24.0%), respectively. The largest household had 21 participants surveyed. The median number of household members was 3 (IQR: 2-4). There were 1,433 (90.0%) households that had no members who tested anti-HCV+, 130 (8.2%) had 1 person who tested anti-HCV+, and 30 (1.8%) households had ≥2 test anti-HCV+. The greatest number of persons testing anti-HCV+ in a household was 4.

Individual-level analyses

In individual-level analyses, the proportion of anti-HCV+ people decreased with increasing socio-economic score (OR 0.69 [95%CI: 0.62-0.77]) (figure 1 and table 1). This effect persisted among both rural residents (OR 0.76 [95%CI: 0.66-0.88]) and urban residents (OR 0.76 [95%CI: 0.61-0.95]) (figure 1). Cumulative number of medical exposures was positively associated with anti-HCV prevalence (continuous OR per additional medical exposure 1.31 [95%CI: 1.17-1.46]) (figure 2). The effect was stronger for rural than urban residents: ORs 1.37 [95%CI: 1.21-1.55] and 1.16 [95%CI: 0.92-1.46], respectively.

Table 1 shows the aOR of a household member being anti-HCV+ if another member of that household is anti-HCV+ is 3.19 (95% CI: 2.25-4.50). Living in a rural dwelling was also positively associated with being anti-HCV+ (aOR 1.57 [95%CI: 1.02-2.42]), as was living in the south (aOR 2.60 [95%CI 1.75, 3.87]), age (aOR 1.02 [95%CI 1.01, 1.03]), having ever used opium/bhuki (aOR 2.85 [95%CI 1.71, 4.76]), and being shaved by a barber (aOR 1.78 [95%CI 1.22, 2.60]). Ever having drank alcohol was negatively associated with being anti-HCV positive, aOR 0.56 (95%CI: 0.38, 0.84).

Simulations

Using the same household size distribution found in the survey, 1,000 simulations were conducted, with anti-HCV+ persons randomly distributed among households. The simulations resulted in a median of 14 (IQR: 11-

16) households with ≥2 members testing anti-HCV+. Figures 3 shows none of the 1,000 simulations had 30 households with ≥2 anti-HCV+ members (P<.001).

We compared the distribution of the number of anti-HCV+ persons from each village from the survey with the average number of persons testing positive across 1,000 random simulations. We found a greater proportion of villages surveyed had multiple persons anti-HCV+ than in the simulations. For example, 31 of the 1,000 simulated datasets had 10 villages with ≥6 infections, the number observed in the survey data (P=.03); figure 4.

Household-level analyses

As household size increased, the number of members in the household testing anti-HCV+ increased (Table 2). The number of members testing anti-HCV+ in the household was also associated with living in rural areas and living in Punjab's south. Households with a higher proportion of members that had received a medical injection in the last 6 months were more likely to have more anti-HCV+ members. Select indicators of lower S-ES, including receiving water from a tube well, lower educational level, and receiving healthcare from a certified provider, were associated with a greater number of household members testing anti-HCV+, as was a lower S-ES score. The proportion of members of the household that had ever used opium or bhuki was also associated with having more anti-HCV+ members.

The associations between household level variables and the number of anti-HCV+ household members (0, 1, or ≥2) are shown in table 3. In models only adjusted for the number of household members, the variables associated with a greater number of anti-HCV+ members in the household were: living in a rural area, living in south Punjab, a higher proportion of the household having had a medical injection in the last 6 months, receiving water through a tube well, a higher proportion having ever taken opium/bhuki, and a higher proportion having ever been jailed. Conversely, a higher household income, education level, proportion of the household with certified healthcare, and a higher mean S-ES, were all associated with fewer number of members in the household testing anti-HCV+. A model adjusted for multiple variables found that several factors were independently associated with an increase in the number of household members testing anti-HCV+: more members living in a household, living in south Punjab, a lower mean S-ES, and a higher proportion of household members having ever used opium or bhuki. The proportionality of odds assumption test did not find strong evidence against this assumption (p-value: 0.093).

Screening probabilities

The survey results translate to 13.0% (n=120) of 926 households surveyed in Punjab's south containing someone anti-HCV+ and 2.9% (n=27) of these having ≥2 anti-HCV+ members. These numbers increase to 19.1% and 4.4%, respectively, for the 230 households surveyed in the south that also had a lower S-ES score (≤3). For the north, 6.0% of the 667 households surveyed contained someone anti-HCV+, which increased to 9.2% when limited to the 164 households with a lower S-ES score. Of the 194 households surveyed with ≥1 member that uses either bhuki or opium, 26.3% had 1 anti-HCV+ member and 9.8% had ≥2 anti-HCV+ members.

Discussion

In Punjab, India, anti-HCV+ individuals cluster within households and within villages, with higher prevalence in the south than the north. The number of anti-HCV+ household members was positively associated with the number of household residents, lower S-ES, and greater use of opium or bhuki in these households. In univariable analyses, anti-HCV status was associated with the average number of medical injections received in the last six months, and the proportion of the household that had been jailed. These findings help to elucidate HCV infection in Punjab and could guide prevention and screening strategies for the state-wide care and treatment program(10).

HCV infection is not evenly distributed geographically(7). Reasons for south Punjab's higher HCV prevalence are uncertain but could be due to poorer infection control practices, more syringe re-use, or unreported IDU.

Taking opium or bhuki should not transmit HCV because they are not injected. However, they were strongly related with anti-HCV positivity, possibly indicating they are proxy markers for IDU. Stigma may cause under-reporting of IDU, with the proportion reporting ever injecting drugs lower than recently estimated in Punjab(17). PWID may be under-represented in household surveys because they are more likely to be homeless or imprisoned(12, 20). Although some evidence suggests opium/bhuki use could be gateway drugs leading to heroin use(18), its use as a marker of IDU needs further study to understand the validity of using such proxies.

Household anti-HCV positivity was inversely associated with the household's S-ES. Lower-income households may lack access to higher quality healthcare, leading to greater risk of iatrogenic HCV transmission.

Literature comparison

Anti-HCV positivity clustering within households could be due to intra-familial transmission between household members or by household members being exposed to common risks outside the house, such as sharing a doctor(21). Our study cannot determine if households with multiple persons testing anti-HCV+ acquired their infection from exposures within or outside the household(22). Other studies have looked at HCV clustering at the household/family level, with some in low prevalence countries finding an association(23, 24) or not(25-27), while others in higher prevalence countries(5) found associations. One study found intraspousal HCV transmission more common than other intrafamilial transmission(28). The association found between low S-ES and anti-HCV positivity has been demonstrated previously, including in Thailand(29), the

Netherlands(30), and Pakistan(31, 32). Utilizing advanced molecular diagnostics, such as deep-gene sequencing, could better define transmission patterns within households, elucidating risks and guiding prevention efforts.

Strengths and limitations

This study analysed data from a large serosurvey, covering diverse areas of Punjab. However, the sampling frame used census data, which may underestimate the state's anti-HCV prevalence as it excludes homeless populations, new arrivals, prisons, and new peri-urban slums. A cross-sectional serosurvey asking about recent behaviours cannot accurately capture the effect of lifetime medical exposures and injections with contaminated needles, which are important factors associated with HCV transmission in India, South Asia, and globally(33, 34). This cross-sectional serosurvey is limited to identifying behaviours associated with prevalent, rather than recent infections, and was likely subject to recall and social desirability bias, particularly affecting the reported prevalence of ever having injected drugs. The proxy measures used possibly captured an effect other than IDU such as low socio-economic status, which is itself a proxy measure, possibly of utilizing unsafe healthcare providers(14). The negative association between having ever drank alcohol and being anti-HCV positive is probably a proxy measure for S-ES, maybe caste, or religion(35). This study can only estimate associations, which may be subject to unmeasured confounding. The simulation analyses may be limited by high heterogeneity in anti-HCV prevalence between districts.

Implications

This study found anti-HCV+ persons clustered in households and in villages in Punjab, India. This is an important consideration for the recently launched treatment programme in Punjab aiming to eliminate hepatitis C(1, 33). Officials should consider testing whole families when one family member tests positive for anti-HCV or HCV RNA. This may achieve a higher yield than general testing. Similarly, the reasons for clustering of anti-HCV+ persons in villages could be from sharing a healthcare provider, or barber, or high IDU prevalences in some villages. Further research is required to understand why infection clusters at village and household levels. In households there are a range of possible factors, including sexual transmission, sharing razors, or using the same barber or doctor with poor infection control practices(36).

Understanding these factors will help planners implement interventions that could prevent HCV transmission in this context. For those designing hepatitis C testing and prevention programmes in Punjab, this study provides valuable information, including that households with lower S-ES and households in the south tend to have more anti-HCV+ members. This indicates these groups may benefit from targeted testing and treatment. Furthermore,

in Punjab's south there is approximately a 13% chance that any household screened will yield someone anti-HCV+. This probability increases to roughly 17% for poorer households. Households that have a member reporting opium or bhuki use have over 25% chance of a household member having HCV infection. Information on HCV transmission risks and how to sterilise medical equipment should be targeted to medical practitioners, particularly in high prevalence areas. This could reduce HCV transmission in Punjab, which combined with scaled-up treatment should reduce the high HCV prevalence.

Conflicts of interest

This population survey was sponsored by MSD Pharmaceuticals India Private Limited, a subsidiary of Merck & Co. Inc., Kenilworth, NJ, USA. Sponsoring corporations do not contribute to writing of manuscripts. VS and SK are, or have been, employees of Merck. AS has received funding from Merck.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Table 1: Logistic regression odds ratios (95% confidence intervals) of hepatitis C virus antibody positivity by individual characteristics

	Odds Ratio (95% CI) for having anti-HCV	
	Unadjusted	Adjusted
Another member of household anti-HCV+	4.53 (3.28, 6.27)	3.19 (2.25, 4.50)
Living in rural dwelling	3.01 (2.07, 4.39)	1.57 (1.02, 2.42)
Living in the south	3.25 (2.23, 4.73)	2.60 (1.75, 3.87)
Age (years)	1.03 (1.02, 1.03)	1.02 (1.01, 1.03)
Male	1.28 (0.94, 1.73)	
Medical risks		
Ever had surgery	1.54 (1.14, 2.09)	
Ever had a medical procedure	2.20 (1.23, 3.92)	
Ever had a dental procedure	1.62 (1.20, 2.19)	
Had a medical injection in the last 6 months	1.48 (1.09, 2.01)	
Ever had a streptomycin injection	2.40 (1.01, 5.72)	
Ever received blood	1.96 (1.21, 3.18)	
Ever been hospitalized	1.43 (1.05, 1.95)	
Medical risk score*	1.31 (1.18, 1.46)	1.17 (1.02, 1.33)*
Socio-Economic Indicators		
Receiving water through a tube well	2.25 (1.66, 3.04)	
Certified healthcare	0.53 (0.37, 0.75)	
Kacha (less solid) vs pucca house (more solid)	1.32 (0.83, 2.10)	
Household income (rupees)		
0-10,000	1	
10,001-20,000	0.74 (0.52, 1.05)	
>20,00	0.58 (0.36, 0.92)	
Education level		
None/primary	1	
Middle/secondary	0.70 (0.51, 0.96)	
Graduate	0.21 (0.10, 0.46)	
Socio-economic status score*	0.69 (0.62, 0.77)	0.75 (0.66, 0.86)*
Drugs (ever taken)		
Ever drank alcohol	0.62 (0.44, 0.88)	0.56 (0.38, 0.84)
Ever used opium/bhuki	5.06 (3.25, 7.90)	2.85 (1.71, 4.76)
Ever smoked tobacco	1.21 (0.63, 2.32)	
Social risks		
Have a tattoo	1.54 (0.98, 2.44)	
Use barbers	1.52 (1.08, 2.14)	1.78 (1.22, 2.60)
Have body piercings	0.84 (0.53, 2.85)	
Other variables		
Ever been to jail	2.70 (1.20, 6.08)	1.42 (0.58, 3.46)
Ever had a motor vehicle accident	1.77 (1.25, 2.48)	1.33 (0.92, 1.95)

*For power only socio-economic status score was included out of the socio-economic variables, and only the medical risk score from the medical risk variables

Table 2: Comparing the mean characteristics of households with 0, 1, and ≥2 members testing positive for hepatitis C virus antibody, respectively.

	Number of members anti-HCV* positive in a household			
	0	1	2+	
	Number of households			Test for differences§
Characteristic	1,433	130	30	
Mean number of members in household	3.32	4.72	5.67	P<0.001
Mean proportion in rural dwellings	0.60	0.79	0.87	P<0.001
Mean proportion living in the south	0.56	0.72	0.90	P<0.001
Mean age	38	37	40	P=0.441
Mean proportion male	0.45	0.48	0.51	P=0.320
Medical risks				
Mean proportion that have had surgery	0.44	0.41	0.49	P=0.497
Mean proportion that have a medical procedure	0.04	0.03	0.05	P=0.620
Mean proportion that have had a dental procedure	0.41	0.40	0.47	P=0.571
Mean proportion that have had a medical injection in the last 6 months	0.34	0.41	0.39	P=0.049
Mean proportion that have had a streptomycin injection	0.01	0.02	0.01	P=0.578
Mean proportion that have received blood	0.07	0.09	0.07	P=0.537
Mean proportion that have been hospitalized	0.55	0.54	0.58	P=0.795
Mean medical risk score	1.9	1.9	2.1	P=0.479
Socio-Economic Indicators				
Mean proportion receiving water from a tube well	0.32	0.45	0.68	P<0.001
Mean proportion with certified healthcare‡	0.40	0.27	0.23	P<0.001
Mean proportion in a kacha house (less solid structure)	0.10	0.17	0.04	P=0.022
Household income†	0.62	0.50	0.47	P=0.133
Education level†	1.76	1.64	1.63	P=0.015
Mean socio-economic status score	4.2	3.7	3.5	P<0.001
Drugs (ever taken)				
Mean proportion that have ever drunk alcohol	0.33	0.34	0.30	P=0.827
Mean proportion that have ever used opium/bhuki¶	0.03	0.07	0.16	P<0.001
Mean proportion that have ever smoked tobacco	0.05	0.03	0.05	P=0.257
Social risks				
Mean proportion with tattoo	0.09	0.10	0.08	P=0.588
Mean proportion using barber	0.19	0.21	0.25	P=0.374
Mean proportion with body piercings	0.56	0.54	0.49	P=0.370
Other variables				
Mean proportion that have ever been to jail	0.01	0.02	0.03	P=0.324
Mean proportion that have ever had a motor vehicle accident	0.19	0.20	0.27	P=0.286

*Hepatitis C antibody positive
§ANOVA test
†Education and household income are using an ordinal variables where lower categories indicate lower education or income
‡Receiving healthcare from a certified healthcare provider (as opposed to an uncertified/alternative health care provider)
¶Bhuki is an intoxicating wild grass that is ingested

Table 3: Ordered logistic regression odds ratios (95% confidence intervals) of hepatitis C virus antibody positivity by household characteristics

	Odds Ratio (95% CI) for having 0, 1, or ≥2 members in household with anti-HCV	
	Adjusted†	Fully adjusted, backwards elimination‡
Number of members in household	1.31 (1.22, 1.40)§	1.38 (1.28, 1.48)
Living in rural dwellings	2.88 (1.87, 4.43)§	
Living in the south	3.29 (2.14, 5.04)§	3.15 (1.98, 5.02)
Mean age	1.01 (1.00, 1.02)	
Proportion male	1.83 (0.90, 3.72)	
Medical risks		
Proportion that have had surgery	0.87 (0.47, 1.61)	
Proportion that have had a medical procedure	1.05 (0.30, 3.66)	
Proportion that have had a dental procedure	1.13 (0.67, 1.91)	
Proportion that have had a medical injection in the last 6 months	2.25 (1.30, 3.88)§	
Proportion that have had a streptomycin injection	1.50 (0.20, 11.11)	
Proportion that have received blood	2.21 (0.82, 5.93)	
Proportion that have been hospitalized	1.04 (0.60, 1.80)	
Mean medical risk score	1.16 (0.95, 1.43)	
Socio-Economic Indicators		
Receiving water through a tube well	1.94 (1.33, 2.84)	
Proportion with certified healthcare	0.34 (0.20, 0.58)	
Kacha (less solid) vs pucca house (more solid)	1.77 (1.05, 2.98)	
Household income¶	0.64 (0.49, 0.85)	
Education level¶	0.51 (0.36, 0.74)	
Mean socio-economic status	0.61 (0.51, 0.74)§	0.63 (0.55, 0.74)
Drugs (ever taken)		
Proportion that have ever drank alcohol	0.66 (0.35, 1.24)	
Proportion that have ever used opium/bhuki	26.68 (9.05, 78.62)§	16.69 (5.46, 51.02)
Proportion that have ever smoked tobacco	0.36 (0.06, 2.16)	
Social risks		
Proportion with a tattoo	1.67 (0.63, 4.44)	
Proportion using barbers	1.46 (0.69, 3.07)	
Proportion with body piercings	0.60 (0.31, 1.17)	
Other variables		
Proportion that have ever been to jail	6.01 (1.11, 32.59)§	
Proportion that have ever had a motor vehicle accident	1.74 (0.89, 3.39)	

*Hepatitis C antibodies

†Adjusted for number of members in the household

‡Fully adjusted for all variables selected from a backwards elimination model containing the variables that were associated with HCV in the analyses only adjusting for number of members in the household (only mean socio-economic status was included out of the socio-economic variables)

§Variables entered into the backwards elimination model

¶Education and household income are using ordinal variables where lower categories indicate lower education or income

Figure 1: The proportion hepatitis C virus antibody (anti-HCV) positive individuals by socio-economic score (higher score is more affluent), for all participants (with 95% confidence interval), urban participants, and rural participants.

Figure 2: The proportion hepatitis C virus antibody (anti-HCV) positive individuals by medical risk score, for all participants (with 95% confidence interval), urban participants, and rural participants.

Figure 3: The distribution of the number of households with two or more hepatitis C virus antibody (anti-HCV) positive members in the 1000 simulated datasets assuming HCV randomly distributed, compared to the observed number of households with two or more members with HCV (the dashed line).

Figure 4: Histograms showing the number of hepatitis C virus antibody (anti-HCV) positive members of each village/ward (left panel: observed, right panel: average of 1000 simulations).

References

1. World Health Organization. Combating Hepatitis B and C to reach elimination by 2030. 2016.
2. World Health Organization. Hepatitis C Fact Sheet. 2017.
3. World Health Organization. Guidelines for the Screening Care and Treatment of Persons with Chronic Hepatitis C Infection: Updated Version. WHO Guidelines Approved by the Guidelines Review Committee. Geneva2016.
4. Shahid I, et al. Real-world challenges for hepatitis C virus medications: a critical overview. Crit Rev Microbiol. 2017:1-18.
5. Polaris Observatory HCVC. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017;2(3):161-76.
6. Sievert W, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Liver Int. 2011;31 Suppl 2:61-80.
7. Goel A, Seguy N, Aggarwal R. Burden of hepatitis C virus infection in India: A systematic review and meta-analysis. J Gastroenterol Hepatol. 2018.
8. Iyengar S, et al. Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. PLoS Med. 2016;13(5):e1002032.
9. Love J. The production of generic drugs in India. BMJ. 2011;342:d1694.
10. The Indian Express. Punjab: Government launches special fund for free treatment of Hepatitis C. 2016.
11. Sood A, et al. The Burden of Hepatitis C Virus Infection in Punjab, India: A Population-based Serosurvey PLoS One. 2018.
12. Zampino R, et al. Hepatitis C virus infection and prisoners: Epidemiology, outcome and treatment. World J Hepatol. 2015;7(21):2323-30.
13. Punjab State Census 2011. 2011.
14. Janjua NZ, Mahmood B, Imran Khan M. Does knowledge about bloodborne pathogens influence the reuse of medical injection syringes among women in Pakistan? J Infect Public Health. 2014;7(4):345-55.
15. Basu D. Overview of substance abuse and hepatitis C virus infection and co-infections in India. J Neuroimmune Pharmacol. 2010;5(4):496-506.
16. Panda S, et al. Alarming epidemics of human immunodeficiency virus and hepatitis C virus among injection drug users in the northwestern bordering state of Punjab, India: prevalence and correlates. Int J STD AIDS. 2014;25(8):596-606.
17. National AIDS Control Organisation. District Epidemiological Profiling Using Data Triangulation Fact Sheets Vol-1. 2012.
18. UNAIDS, Ambekar A, Tripathi B. Size Estimation of Injecting Drug Use in Punjab & Haryana. 2008.
19. Drug and Alcohol Rehab in Thailand. Punjab Drug Epidemic.
20. Topp L, et al. Housing Instability among People Who Inject Drugs: Results from the Australian Needle and Syringe Program Survey. J Urban Health. 2013;90(4):699-716.
21. Indolfi G, Nesi A, Resti M. Intrafamilial transmission of hepatitis C virus. J Med Virol. 2013;85(4):608-14.
22. Ackerman Z, Ackerman E, Paltiel O. Intrafamilial transmission of hepatitis C virus: a systematic review. J Viral Hepat. 2000;7(2):93-103.
23. Lankarani KB, et al. Evaluation of hepatitis C virus intrafamilial transmission among families with one index case, a pilot study from Fars province, Iran. Gastroenterol Hepatol Bed Bench. 2016;9(4):250-8.
24. Brusaferro S, et al. A study on the role of the family and other risk factors in HCV transmission. Eur J Epidemiol. 1999;15(2):125-32.
25. Kim YS, et al. Lack of familial clustering of hepatitis C virus infection. Int J Epidemiol. 1998;27(3):525-9.

26. Vegnente A, et al. Lack of intrafamilial transmission of hepatitis C virus in family members of children with chronic hepatitis c infection. Pediatr Infect Dis J. 1994;13(10):886-9.
27. Kim YS, Ahn YO, Kim DW. Familial clustering of hepatitis B and C viruses in Korea. J Korean Med Sci. 1994;9(6):444-9.
28. Demelia L, et al. HCV transmission in family members of subjects with HCV related chronic liver disease. Eur J Epidemiol. 1996;12(1):45-50.
29. Wasitthankasem R, et al. Assessment of hepatitis C virus infection in two adjacent Thai provinces with drastically different seroprevalence. PLoS One. 2017;12(5):e0177022.
30. Vermeiren AP, et al. Identification of hidden key hepatitis C populations: an evaluation of screening practices using mixed epidemiological methods. PLoS One. 2012;7(12):e51194.
31. Umer M, Iqbal M. Hepatitis C virus prevalence and genotype distribution in Pakistan: Comprehensive review of recent data. World J Gastroenterol. 2016;22(4):1684-700.
32. Trickey A, et al. Importance and Contribution of Community, Social, and Healthcare Risk Factors for Hepatitis C Infection in Pakistan. Am J Trop Med Hyg. 2017;97(6):1920-8.
33. Dhiman RK, et al. Tackling the Hepatitis C Disease Burden in Punjab, India. J Clin Exp Hepatol. 2016;6(3):224-32.
34. Pasha O, et al. Household members of hepatitis C virus-infected people in Hafizabad, Pakistan: infection by injections from health care providers. Epidemiol Infect. 1999;123(3):515-8.
35. Prabhu S, et al. Prevalence, Nature, Context and Impact of Alcohol Use in India: Recommendations for Practice and Research. Brown School Faculty Publications. 2010.
36. Omar MZ, et al. Role of intrafamilial transmission in high prevalence of hepatitis C virus in Egypt. Hepat Med. 2017;9:27-33.

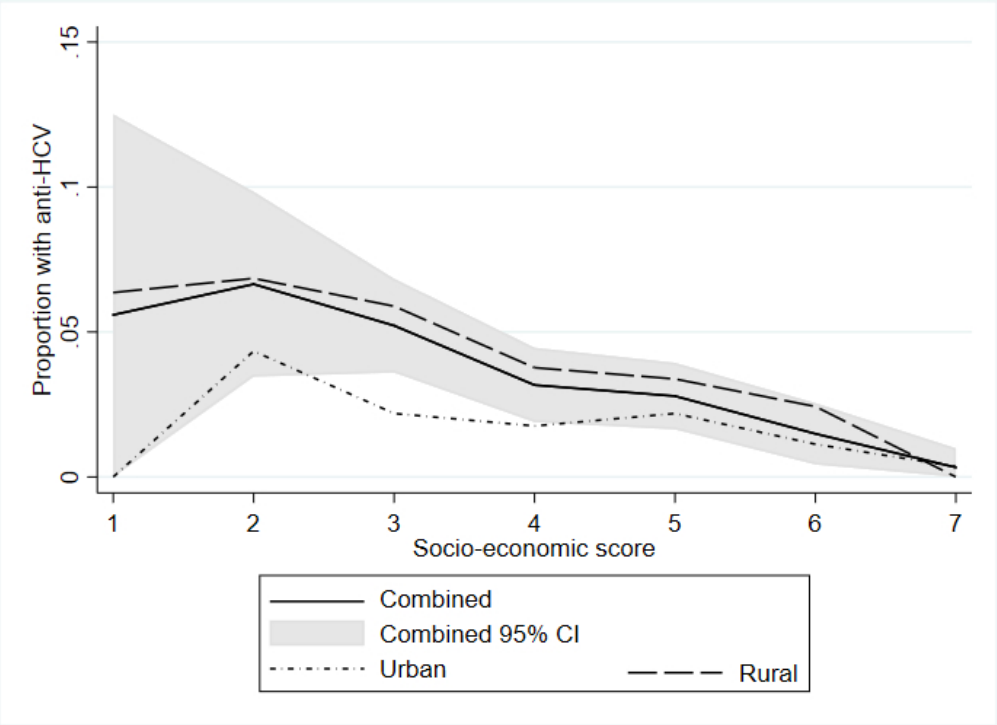

Figure 1: The proportion hepatitis C virus antibody (anti-HCV) positive individuals by socio-economic score (higher score is more affluent), for all participants (with 95% confidence interval), urban participants, and rural participants.

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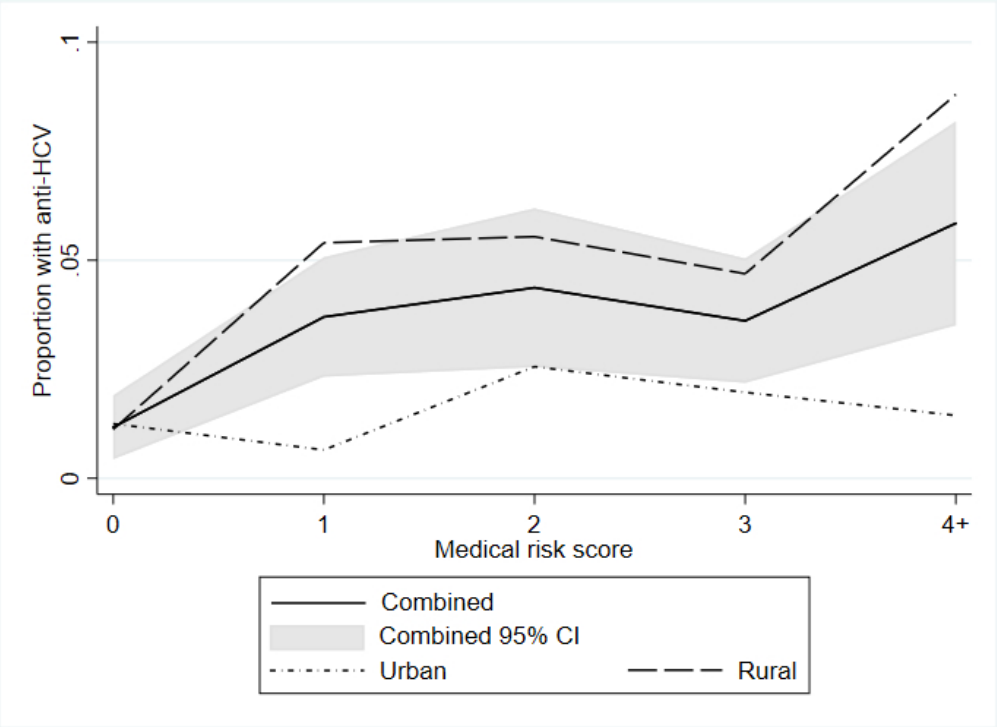
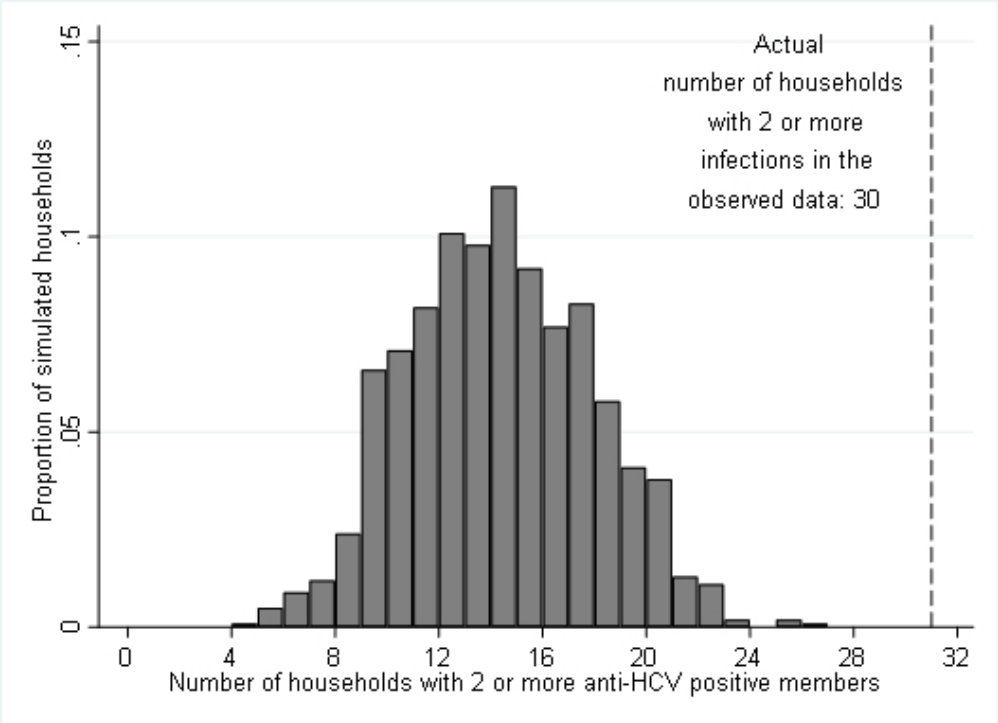


Figure 2: The proportion hepatitis C virus antibody (anti-HCV) positive individuals by medical risk score, for all participants (with 95% confidence interval), urban participants, and rural participants.

241x175mm (72 x 72 DPI)



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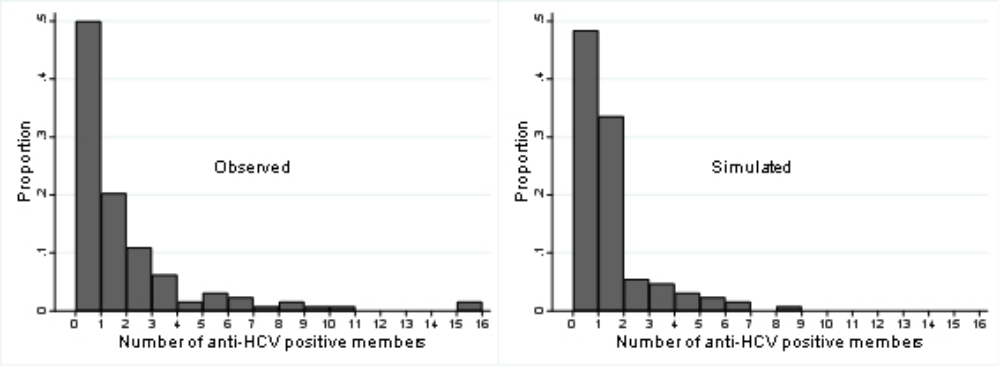
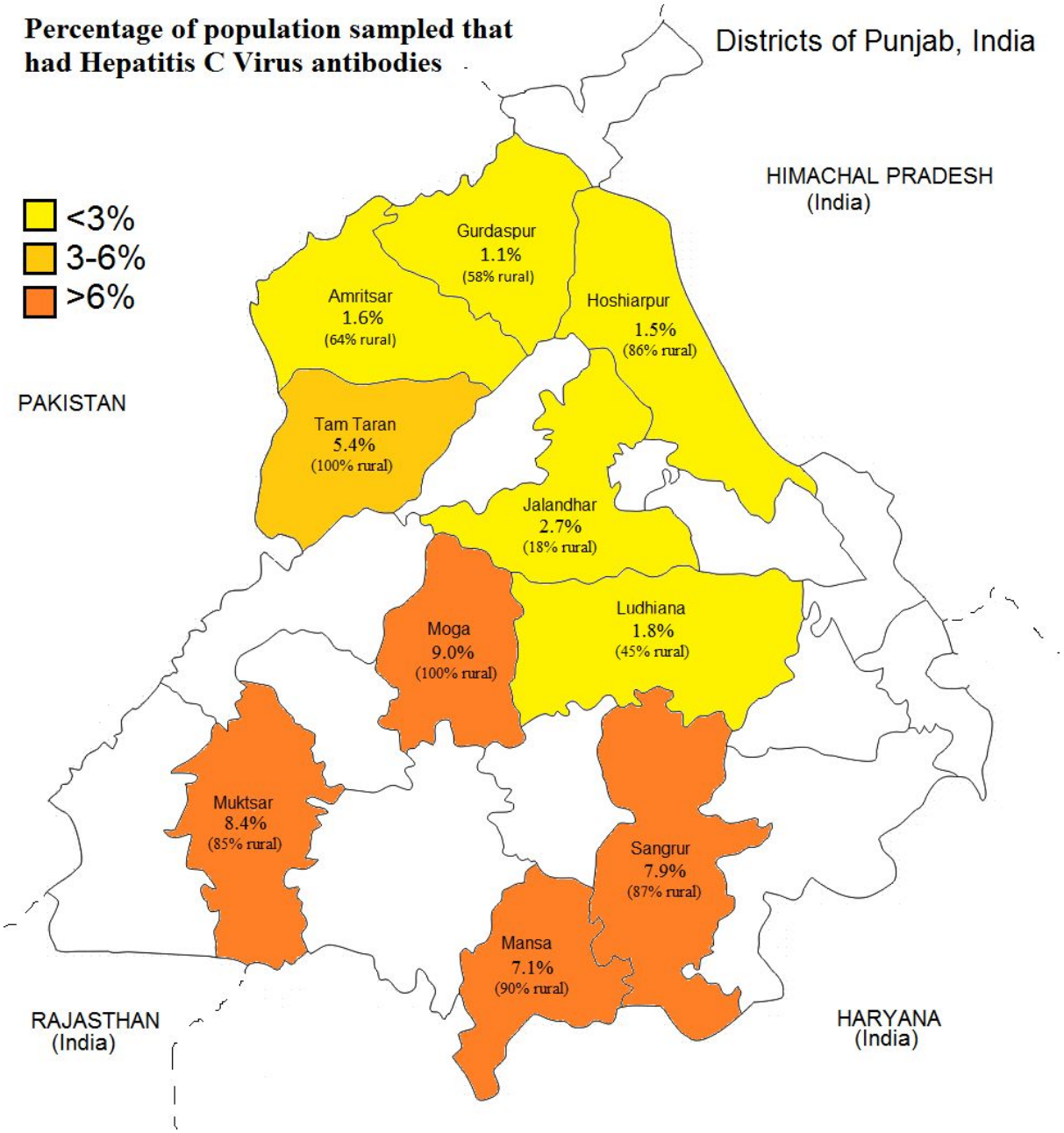


Figure 4: Histograms showing the number of hepatitis C virus antibody (anti-HCV) positive members of each village/ward (left panel: observed, right panel: average of 1000 simulations).

Clustering of hepatitis C virus antibody positivity within households and communities in Punjab, India

Supplementary materials

Supplementary figure 1: The prevalence of hepatitis C (anti-HCV) for each district that participated in the survey, re-printed with permission from Sood et al, 2018*(1)*.



Reference

1. Sood A, Suryaprasad A, Trickey A, Kanchi S, Midha V, Foster M, et al. The Burden of Hepatitis C Virus Infection in Punjab, India: A Population-based Serosurvey PLoS One. 2018.

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Review Paper

Thoughts On A New Draft Bill On Living Will

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ABSTRACT

Introduction: As advancement of life expectancy in years is occurring, people are living long life. Most of them need life support for terminal illness at the end of life. Many of them do not wish to continue sufferings of vegetative life & would like to terminate or discontinue the life support machines or medicines.
Factual Situation: A living will – also known as an advance directive – is a legal document that specifies whether or not you want to be kept on life support if you become terminally ill. 2It permits individual to authenticate their wishes in a written form so that these can be carried out if the relevant situation arises. In addition to the living will, one can select a health-care proxy or health-care power of attorney who is allowed to make decisions for him or her if he or she is incapable of making those choices.
FAQs on Living Will: Who can make a Living Will? An adult with a sound and healthy mind. What it should contain? The circumstances in which medical treatment should be withheld or withdrawn. It should specify that the Will can be revoked any time. How to Create a Living Will? Many people hire a lawyer to prepare their living will. Most people can create this simple document - along with the other typical estate planning documents - without the high legal fees by using a quality software application that accounts for their state's laws.
Make Your Own Will: You can create a legally binding health care directive (living will) without paying an attorney by using reputable estate planning software, like Nolo's award winning Will Maker Plus. It should give the name of the "guardian or close relative" who will give the go-ahead for starting the procedure of passive euthanasia. The Will shall be attested by two independent witnesses and preferably counter-signed by the Judicial Magistrate First Class (JMFC) assigned the jurisdiction by the District Court. The JMFC shall preserve one hard copy, along with one in the digital format, in his office. JMFC shall forward a copy of the Will to the Registry of the District Court JMFC shall inform the immediate family of the executor, if not informed. A copy will be handed over to an official in the local government or municipal corporation or panchayat concerned. This authority shall nominate a custodian for the Living Will.7
Scenario in India: The Supreme Court has given a landmark decision on 7th March, 2018 on Living Will as per Section 11 C. It has confirmed the right to a dignified death as a part of the right to life under article 21 section 11 of the Indian Constitution. The Supreme Court passed a judgment upholding the legality of withholding or withdrawing life-saving medical treatment from terminally ill patients. Families are pushed into poverty tending to the out of pocket expenses of life support.

Key words: living will, euthanasia, assisted suicide

INTRODUCTION

As advancement of life expectancy in years, people are living longer life. Most of them need life support for terminal illness. Many of them do not wish to continue sufferings of vegetative life & would like to terminate or discontinue the life support machines or medicines. In accordance, the Supreme Court has allowed individuals to create a 'living will', which will permit medical professionals to withdraw life-support systems under certain circumstances.

A living will – also known as an advance directive – is a legal document that specifies the type of medical care that an individual does or does not want in the event he or she is unable to communicate his or her wishes. [1]

It is a legal document that specifies whether or not you want to be kept on life support if you become terminally ill and will die shortly without life support, or fall into a persistent vegetative state. [2] It permits individual to authenticate their wishes in a written form so that these can be carried out if the relevant situation arises. In many countries, Advance Directives are legally valid and enforceable; they reduce the use of life-sustaining treatments, which often merely prolong life without improving or even maintaining the same level of health. [3]

In addition to the living will, one can select a health-care proxy or health-care power of attorney who is allowed to make decisions for him or her if he or she is incapable of making those choices. [4]

Types of Euthanasia

Active versus Passive euthanasia

"Active euthanasia" is taking specific steps to cause the patient's death, such as injecting the patient with poison. In practice, this is usually an overdose of pain-killers or sleeping pills.
"Passive euthanasia" is usually defined as withdrawing medical treatment with the deliberate intention of causing the patient's death. For example, if a patient requires kidney dialysis to survive, and the doctors disconnect the dialysis machine, the patient will presumably die fairly soon. Perhaps, the classic example of passive euthanasia is a "do not resuscitate order". Normally if a patient has a heart attack or similar sudden interruption in life functions, staff will attempt to revive them. If they make no such efforts but simply stand and watch as the patient dies, this is passive euthanasia. [5] In other words, the difference between "active" "passive" is that in active euthanasia, something is *done* to end the patient's life; in passive euthanasia, something is *not done* that would have preserved the patient's life. The moral difference between killing and letting die. Many people make a moral distinction between active and passive euthanasia. They think that it is acceptable to withhold treatment and allow a patient to die, but that it is never acceptable to kill a patient by a deliberate act. [6] An important idea behind this distinction is that in "passive euthanasia" the doctors are not actively killing anyone, they are simply not saving him.

Voluntary vs Involuntary

"Voluntary euthanasia" is when the patient requests that action be taken to end his life, or that life-saving treatment be stopped, with full knowledge that this will lead to his death.79 "Involuntary euthanasia" is when a patient's life is ended without the patient's knowledge and consent. It usually means that the patient is unconscious, unable to communicate, or is too sick and weak to be aware of what is happening or to take any action on his own behalf. [7]

The Aruna Shanbaug case which changed euthanasia laws in India

A landmark verdict

The Supreme Court on March 9 ruled that individuals had a right to die with dignity, allowing passive euthanasia with guidelines. The need to change euthanasia laws was triggered by the famous Aruna Shanbaug case. The top court in 2011 had recognised passive euthanasia in Aruna

Shanbaug case by which it had permitted withdrawal of life-sustaining treatment from patients not in a position to make an informed decision.

The attack

Aruna Ramchandra Shanbaug was a nurse in the King Edwards Memorial Hospital in Mumbai. In November 1973, she was assaulted by ward boy, Sohanlal Bhartha Valmiki, of the same hospital while changing her clothes in the hospital basement. Valmiki strangulated Shanbaug with a dog chain around her neck.

Living in a coma

The attack cut off oxygen supply from her brain leaving her blind, deaf, paralysed and in a vegetative state for the next 42 years. From the day of the assault till the day she died on May 18, 2015, Aruna could only survive on mashed food. She could not move her hands or legs, could not talk or perform the basic functions of a human being.

What happened to Valmiki

In 1974, Valmiki was charged with attempted murder and for robbing Aruna's earrings, but not for rape. The police did not take in account that she was sodomized. A trial court sentenced Valmiki seven years imprisonment. This was reduced to six years because he had already served a year in lock up. Valmiki walked out of jail in 1980 and still claims he did not rape Shanbaug.

Facing opposition

The Supreme Court accepted the petition and constituted a medical board to report back on Aruna's health and medical condition. The medical board, comprising three eminent doctors, reported that the patient was not brain dead and responded to some situations in her own way. They felt that there was no need for euthanasia in the case. The staff at KEM Hospital and the Bombay Municipal Corporation filed their counter-petitions in the case, opposing euthanasia for Aruna. The nurses at KEM Hospital were quite happy to look after the patient and they had been doing that for years before petitioner Pinky Virani emerged on the scene.

Finally, at peace

On May 18, 2015, Shanbaug then 66, died of severe pneumonia. She was on ventilator support in KEM's acute care unit. [8]

Countries where active euthanasia is legal

As of March 2018, human euthanasia is legal in the Netherlands, Belgium, Colombia, Luxembourg,Canada and India. Assisted suicide is legal in Switzerland, Germany, South Korea, Japan, and in the US states of Washington, Oregon, Colorado, Hawaii, Vermont, Montana, Washington DC, and California. [9]

Netherlands

In April 2002, the Netherlands became the first country to legalize euthanasia and assisted suicide. It imposed a strict set of conditions: the patient must be suffering unbearable pain, their illness must be incurable, and the demand must be made in "full consciousness" by the patient. In 2010, 3,136 people were given a lethal cocktail under medical supervision. So-called palliative sedation has also become a widespread practice in hospitals, with 15,000 cases a year since 2005, according to the Royal Dutch Medical Association. Patients with a life expectancy of two weeks or less are put in a medically induced coma, and all nutrition and hydration is withdrawn.

France

Euthanasia and assisted suicide are against the law. The president, François Hollande, promised to look at the "right to die with dignity" but has always denied any intention of legalising euthanasia or assisted suicide. In 2005 the Léonetti law introduced the concept of the right to be "left to die". Under strict conditions it allowed doctors to decide to "limit or stop any treatment that is not useful, is disproportionate or has no other object than to artificially prolong life" and to use pain-killing drugs that might "as a side effect, shorten life".

United States

Doctors are allowed to prescribe lethal doses of medicine to terminally ill patients in five US states. Euthanasia, however, is illegal. Oregon was the first US state to legalise assisted suicide. The law took effect in 1997, and allows for terminally ill, mentally competent patients with less than six months to live to request a prescription for life-ending medication. More than a decade later, Washington state approved a measure .And last year, the Vermont legislature passed a similar law. Court decisions rendered the practice legal in Montana and, most recently, in New Mexico. In 2013, roughly 300 terminally ill Americans were prescribed lethal medications, and around 230 people died as a result of taking them. Some patients choose not to take the medication.

Germany and Switzerland

In German-speaking countries, the term "euthanasia" is generally avoided because of its association with the eugenicist policies of the Nazi era. The law therefore tends to distinguish between assisted suicide (*beihilfezumsuizid*) and "active assisted suicide" (*aktivesterbehilfe*). In Germany and Switzerland, active assisted suicide – i.e., a doctor prescribing and handing over a lethal drug – is illegal. But German and Swiss law does allow assisted suicide within certain circumstances. In Germany, assisted suicide is legal as long as the lethal drug is taken without any help, such as someone guiding or supporting the patient's hand. In Switzerland, the law is more relaxed: it allows assisted suicide as long as there are no "self-seeking motives" involved. Switzerland has tolerated the creation of organisations such as Dignitas and Exit, which provide assisted dying services for a fee.

Belgium

Belgium passed a law in 2002 legalising euthanasia, becoming the second country in the world to do so. The law says doctors can help patients to end their lives when they freely express a wish to die because they are suffering intractable and unbearable pain. Patients can also receive euthanasia if they have clearly stated it before entering a coma or similar vegetative state. [10] Advanced Directive (AD) is legally valid and enforceable in the USA [11] Canada, Australia and many countries across Europe. [12] ADs have been endorsed by the United Nations Convention on the Rights of Persons with Disabilities. [13] Whereas half of the Americans have ADs, the concept is unknown by many in India. [14] Australian Scientist Dr. David Gudall,104 years old, was born British but lived in Australia. At the end of his life, he flew to Switzerland for assisted suicide. He fought to die on his terms because of his deteriorating health. Since active euthanasia or assisted suicide is not legalised in Australia, he had to leave his country to die with dignity. [15]

Passive euthanasia, Active euthanasia & the Law in India

Passive Euthanasia Now a Legal Reality in India. Recognising “living wills” made by terminally-ill patients, the Supreme Court has held that the right to die with dignity is a fundamental right. Declaring the right to die with dignity as a fundamental right, the Supreme Court in a landmark judgment on 7 March 2018 passed an order allowing passive euthanasia in the country. [16] The apex court has said that an individual could make an advance “living will” that would authorize passive euthanasia under certain circumstances. Delivering the judgment, Justice Chandrachud

said, "Life and death are inseparable. Every moment our bodies undergo change… life is not disconnected from death. Dying is a part of the process of living." [17]
A Constitution Bench, led by Chief Justice of India Dipak Misra, in three concurring opinions, upheld that the fundamental right to life and dignity includes right to refuse treatment and die with dignity. [18] It can be done by means of the withdrawal of life support to patients in a permanent vegetative state. The decision was made as part of the verdict in a case involving Aruna Shanbaug, who had been in a Persistent Vegetative State (PVS) until her death in 2015.

This judgment was passed in wake of Pinki Virani's plea to the highest court in December 2009 under the Constitutional provision of "Next Friend". It's a landmark law which places the power of choice in the hands of the individual, over government, medical or religious control which sees all suffering as "destiny". The Supreme Court specified two irreversible conditions to permit Passive Euthanasia Law in its 2011 Law: (I) The brain-dead for whom the ventilator can be switched off (II) Those in a Persistent Vegetative State (PVS) for whom the feed can be tapered out and pain-managing palliatives be added, according to laid-down international specifications. The same judgement-law also asked for the scrapping of 309, the code which penalises those who survive suicide-attempts. In December 2014, government of India declared its intention to do so. [19]

Response from different religious leaders were in accordance with their religious scriptures. Christians and the Jains thought passive euthanasia was acceptable under some circumstances [20]. Jains and Hindus have the traditional rituals *Santhara* and *Prayopavesa* respectively, wherein one fasts unto death. The Jain vow of *santhara*, is observed by the Jains only in special circumstances. These are mentioned in the Jain texts. [21] Some members of India's medical establishment were skeptical about euthanasia due to the country's weak rule of law and the large gap between the rich and the poor, which might lead to the exploitation of the elderly by their families. [22] It was observed that the issue was not considered politically contentious in India." [23]

Frequently Asked Questions on Living Will

Who can make a Living Will ?
An adult with a sound and healthy mind can make a living will. It should be voluntarily executed and based on informed consent. It should be expressed in specific terms in a language "absolutely clear and unambiguous".

What it should contain?
It should contain the circumstances in which medical treatment should be withheld or withdrawn. It should specify that, the living will can be revoked any time.

How to Create a Living Will
People can hire a lawyer to prepare their living will. If you need to write or update a will or trust, you can take care of your living will at the same time. You can create a legally binding health care directive (living will) without paying an attorney by using reputable estate planning software, like Nolo's award winning Will Maker Plus. It should give the name of the "guardian or close r elative" who will give the go-ahead for starting the procedure of passive euthanasia. If there are more than one Living Will, the latest one will be valid.

How to preserve it ?
The Will shall be attested by two independent witnesses and preferably counter-signed by the Judicial Magistrate First Class (JMFC) assigned the jurisdiction by the District Court.The JMFC shall preserve one hard copy, along with one in the digital format, in his office. JMFC shall forward a copy of the Will to the Registry of the District Court JMFC shall inform the immediate family of the executor, if not informed. A copy will be handed over to an official in the local government

or municipal corporation or municipality or panchayat concerned. This authority shall nominate a custodian for the Living Will. [24]

Conclusions

It is a great victory for the patients who are terminally ill or on palliative care or vegetative to end their sufferings. It is inhuman to allow someone to die. At the same time, it is inhuman to see someone suffering terribly. We have to take the call as per the basic human rights of living with dignity and patients' autonomy that is living will.

REFERENCES

1. Legalzoom.com. (2018). What Is a Living Will?. [online] Available at: https://www.legalzoom.com/knowledge/living-will/topic/what-is-a-living-will [Accessed 1 Oct. 2018].
2. Ghooi RB, Dhru K, Jaywant S. The urgent need for advance directives in India. Indian journal of medical ethics. 2016;1(4):242-9.
3. Rocketlawyer.com. (2018). Living Will vs. Last Will and Testament | Rocket Lawyer. [online] Available at: https://www.rocketlawyer.com/article/living-will-vs-last-will-and-testament.rl [Accessed 1 Oct. 2018].
4. Bbc.co.uk. (2018). BBC - Ethics - Euthanasia: Active and passive euthanasia. [online] Available at: http://www.bbc.co.uk/ethics/euthanasia/overview/activepassive_1.shtml [Accessed 1 Oct. 2018].
5. Pregnantpause.org. (2018). Euthanasia. [online] Available at: http://www.pregnantpause.org/euth/index.html [Accessed 1 Oct. 2018].
6. India, T., verdict, A., attack, T., coma, L., Valmiki, W., opposition, F. and peace, F. (2018). Euthanasia: The Aruna Shanbaug case which changed euthanasia laws in India. [online] The Economic Times. Available at: https://economictimes.indiatimes.com/news/politics-and-nation/the-aruna-shanbaug-case-which-changed-euthanasia-laws-in-india/a-landmark-verdict/slideshow/63231071.cms
7. The Guardian. (2018). Euthanasia and assisted suicide laws around the world. [online] Available at: https://www.theguardian.com/society/2014/jul/17/euthanasia-assisted-suicide-laws-world [Accessed 1 Oct. 2018].
8. Barta H, Kalchschmid G. Die "Patientenverfügung" in Europa. Wiener Klinische Wochenschrift. 2004 Jul 1;116(13):442-57.
9. Sperrin Á. Independent living for adults with intellectual disabilities in post conflict countries. A comparative analysis of the implementation of Article 19 of the United Nations Convention on the Rights of Persons with Disabilities in Northern Ireland and Bosnia Herzegovina (Doctoral dissertation, NUI Galway).

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