The Relationship between Therapeutic Injections and High Prevalence of Hepatitis C Infection in Hafizabad, Pakistan

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Summary

To determine the prevalence and routes of transmission of hepatitis C virus (HCV) infection in Hafizabad. Pakistan, we collected sera in 1993 from a geographicaEly based random sample of residents, and in 1994 identified 15 HCV.infected individuals (cases) and 67 age and sex matched uninfected individuals (controls).
Initiatly we approached 504 households, and collected serum from a randomly selected household member in 309 (64%). Twenty persons (6.5%) had anti-HCV anlibody; 31% had hepatitis B core antibodies, and 4 3% had hepatitis B surface antigen. In the case-control study, persons who received more lherapeulic injections (categorized as averaging 1. 2-4. 5-9 or >10 injections per year in 1he previous 10 years) were more likely to be infec1ed with HCV (odds ratio 0, 1.5, 2.5 and 6.9 respectively. P = 0.008) compared to persons averaging 0 injections per year. Efforts to limit therapeutic injections to only those that are medically indicated and that use sterite equipment are essential in order to prevent transmission of HCV.

Introduction

Hepatitis C virus (HCV) is a major cause of human morbidity and mortality. In countries with a high prevalence of HCV infection and low prevalence of hepatitis B virus (HBV) infection, HCV is implicated in up to 64% of cases of hepatic cirrhosis[1] and up to 75% of cases of hepatocellular carcinoma.[2] In a case series from a military hospital in Rawalpindi, Pakistan 29% of patients with chronic liver disease and 8% of patients with hepatocellular carcinoma were infected with hepatitis C virus.[3] Characteristically. HCV infection is steadily progressive. Over 90% of individuals infected with hepatitis C following a transfusion develop chronic hepatitis, and of 155 cases of chronic hepatitis C followed for a mean 8.7 years. 30% progressed to cirrhosis and 15% to hcpatocellular carcinoma.[4]
The prevalence of antibodies to hepatitis C among volunteer blood donors in developed countries ranges from 0.06% in Great Britain[5] to 1,9% in Japan.[4] The demonstrated routes of transmission arc parenteral. with injecting drug use and transfusion most commonly implicated.[5-7] Sexual transmission occurs with substantially less efficiency.[8,9] Much of the HCV transmission remains unexplained. In a United Stales study. 40% of persons with HCV infection had no identified parenteral exposure.[6]
Markedly higher prevalence of antibody to HCV is reported from populations in sevcral developing countries[10-11] including 6.5% in a community based study in Gabon[12] and 14.5% among school children from Cameroon.[13] The predominant route of HCV transmission in developing countries and the reasons for the higher prevalence than in developed countries is unknown. Some investigators have noted a high rate of HCV infection in communities where syringes and needles were insufficiently sterilized and speculated that therapeutic injections might be responsible.[13-15]. but a direct relationship between therapeutic injections, and the risk of HCV infection has not been demonstrated.

In Pakistan the Aga Khan Health Services maintain disease surveillance among persons served by its primary health care programs. Between 1 July 1990 and 30 June 1992. 41 persons with jaundice were reported from among a population of 1300 Ismaili Muslims living in Hafizahad, an agricultural town in the Punjab province of Pakistan. Physicians in the town also noted that jaundice, at least some of which was due to end stage liver disease, was also common outside the Ismaili community. The Aga Khan Health Services requested the Aga Khan University to investigate the cause of the large number of cases of liver disease in Hafizabad. Because of the lack of serological data on the population, we initially surveyed the prevalence of antibody to hepatitis viruses in the general community. When we discovered an unexpectedly high prevalence of HCV. were turned to Hafizabad and conducted a case-control study to identify risk factors for HCV infection. This report details the HCV prevalence and associated risk factors in Hafizabad; it also includes selected hepatitis B serologic results as a contrast to assist in under-standing the dynamics of HCV transmission.

Methods

Setting

Flafizabad is a market town with an estimated population of 125.000 in a fertile agricultural region of thev Punjab Province in central Pakistan. Although the town is affluent compared to the rest of Pakistan. sewage flows out of homes through open drains, many homes do not have electricity or piped water and most do not have natural gas lines. The city has a 30 bed hospital with limited facilities. and numerous private clinics run either by physicians or by pharmaceutical dispensers without formal medical training.

Prevalence study

For the city-wide serological survey we wished to measure viral hepatitis markers that were present among at least 4% of the citys population. We calculated that 368 persons would suffice to detine a 4c prevalence ±2 with 95% confidence. Assuming a 25% refusal rate we planned to approach 500 individuals. We randomly sought households from each of the town's 27 administrative sectors, with the number of households chosen per sector proportional to the population within that sector. A trained interviewer listed all members of the household, then consulted a random number table to select one family member and asked if he or she would answer several questions and provide a serum sample. Parents answered questions for children < 10 years. If either a household or an individual person could not be contacted or refused either the questionnaire or the serum sample. no replacement was recruited. This field work was conducted in November and December 1993.

Case control study

After completing the laboratory tests and analysis we sought more detailed intbrmation on parenteral and sexual exposure and their relationship to HCV infection. We returned to Hafizabad and conducted a follow-up case control study in December 1994. We identified cases by locating as many of the people who were anti-HCV reactive from the 1993 community survey as possible. We attempted to recruit four times as many controls from among anti HCV unreactive subjects from the 1993 serological survey as cases. Controls were frequency matched to cases for age and sex. Team members revisited each household, told the study subject their hepatitis A. B. C and E serological results, counselled them on how to avoid and prevent transmission of the four viruses, and then immediately administered the detailed questionnaire on parenteral and sexual exposures.

We asked six questions to quantify exposure to parenteral injections: (1) how long ago they had received their last injection. (2) how much time elapsed between their last two injections, (3) how many injections they had received in the last year, and (4) in the 5 years preceding the last I year did they think they had received more, fewer or the same number of injections per year as in the past year. We then asked them to ignore the year immediately prior (1994) and (5) estimate the number of

injections they received per year in the preceding 5 years (1989-93) and (6) the preceding 10 years. Responses available were none.1,2-4,5-9,10 and don't know. For questions on sexual exposures we worked with local personnel to develop appropriate translations, and used trained interviewers of the same sex as the study subject.

After completing the HCV risk factor analysis. we looked at the hepatitis B core antibody status of individuals in the HCV case-control study. We defined cases of hepatitis B virus (HBV) infection as individuals with antibody to HBV core antigen. and controls as individuals who tested negative for antibody to HBV core antigen. We analysed the risk factors we had found associated with HCV infection to see if they were also associated with HBV infection.

Environmental investigation

The study team made unannounced visits to three private clinics and the local hospital laboratory to observe needle and syringe sterilization practices.

Laboratory Methods

We collected 5-10 ml of whole blood into plain glass tubes, and centrifuged and separated serum within 12 h of collection. Serum aliquots were then stored at -20°C, and transported on wet ice to the Aga Khan University Hospital t.aboratory in Karachi. Pakistan. The first aliquots of sera were sent for hepatitis Eantibody testing (results not reported here). If a second aliquot was available it was tested for antibody to hepatitis C. Any remaining sera were tested for hepatitis B core antibody. If the specimen was posiive for antibody to HBV core antigen. it was tested for hepatitis B surface antigen. and if positive for hepatitis B surface antigen was tested for HBV core 1gM antibody. The hepatitis B testing was performed using commercial (Abbott) enzyme immuno assays (EIA).

We analysed sera for the presence of anti-HCV antibodies using a second generation recombinant immunoblot assay (RIBA) (Chiron). Sera were graded as reactive according to the manufacturer's criteria, that is. a visible hand of reactivity to any 2 of 4 recombinant HCV antigens (5-1-1. cl00-3. c33c and c22-3). compared with standardized negative sera. We screened the sera using RIBA immunoblot rather than first performing a more traditional EIA test, because of local availability of the reagents. More over, using PCR as a standard, the sensitivity of second generation RIBA tests is 86% with a 94% specificity which is comparable to a second generation ELA test.16 Any misclassification in HCV status by this approach would be expected to underestimate the total HCV burden in Hatizabad and bias any associations toward a null effect.

Statistical Methods

We compared the proportion of categorical differences between cases and controls by odds ratios, used Cornfields approximation to estimate confidence intervals. and used Yates corrected chi square test or Fisher's exact test where appropriate. We tested the differences in means of continuous variables by Students I test when the distnbutions had homogenous variance (by Bartlett's test for homogeneity) and used the Mann-Whitney lest when the variances were significantly (Pc0.05) different. We evaluated the potential dose-effect of exposures using the estendcd Mantel-Haenszel test. We used Epilnfo" Software for all statistical calculation.

Results

Presalence Study

We selected 504 households for the 1993 survey and completed interviews in 484 (96%). We obained consent and collected an adequate serum specimen from the randomly selected member of the household fur 309(64%). Individuals who provided scra were somewhat older and more educated than those who refused, but were similar by gender. number of persons in their household and house size (Table 1).

Table 1. Response rate of community hepatitis survey, Hafizabad, Pakistan 1993.

	Collected sera (n=309)	Refused sera (n=175)	P value
Mean age (years)	24.3	21.4	0.01
Male (%)	131 (42%)	85 (49%)	0.22
No. of persons in household	7.1	7.0	0.48
No. of rooms in household	2.9	2.7	0.60
No. with formal schooling (%)	197 (64%)	91 (52%)	0.01

Twenty (6i%) of the 309 individuals tested had antibodies to HCV by the RIBA immunoblol assay (951k confidence interval[CI] 4.4%,9.9%); 277 (90%) were antibody negative and 12 (4%) were indeterminate.

Eighty-nine (31%) of the 291 individuals who had sufficient remaining sera to test had HBV core antibodies. Twelve (14%) of the 86 core antibody positive specimens for which we had sufficient scra. contained hepatitis B surface antigen. Thes as equivalent to 4.3% HBV surface antigen prevalence in the surveyed population. None of the 10 surface antigen positive specimens for which we had sufficient scra had detectable hepatitis H core 3gM. Fourteen individuals (5%) had antibodies against both HCV and HBV. and two had hepatitis B core surface antigen and antibody to HIV.

The prevalence of HCV infection increased markedly with age (Figure).

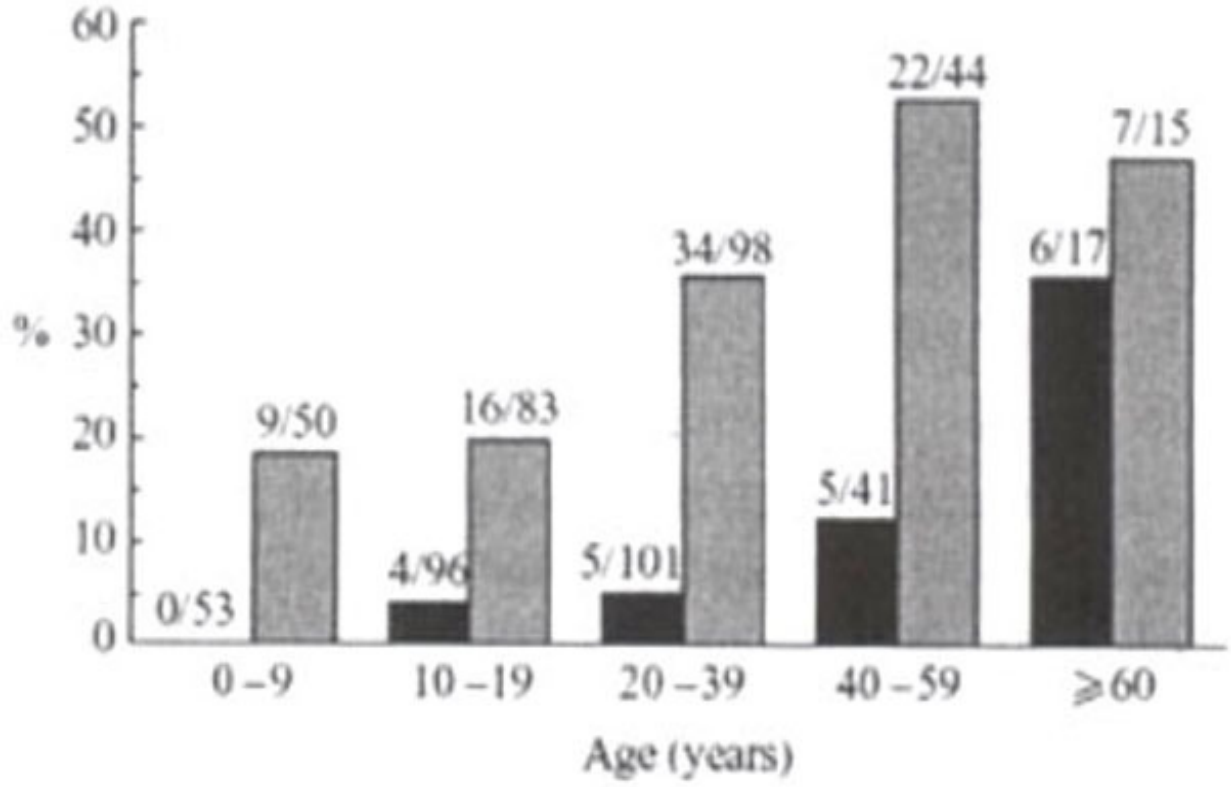

Fig. 1. Community prevalence of hepatitis C antibody (*n*, 308 for HCV; one HCV unreactive subject's age was not obtained) and hepatitis B core antibody (*n*, 291 for HBV; 17 persons had insufficient sera for HBV testing; 1 HBV core antibody reactive subject's age was not obtained) by age group Hafizabad, Pakistan 1993. ■, HCV; ▨, HBV.

In contrast to hepatitis B. none of the 110 children aged <10 years had evidence of infection with HCV. The mean age of HCV infected persons was 43 years. Maics were slightly more likely to be HBV infected than females (76% vs. 5.6%. relative ink 1.4.95% Cl 0.6- 3.!). Eighteen (90%)of HCV antibody positise individuals reported necr having jaundice.

Case Control Study

In December 1994 we re-identified and interviewed IS (75%) of those with HCV-specific antibody from the 1993 community survey. These were the cases. In addition were-identilied 67 individuals who had no HCV specific antibody in the 1993 survey o serve as controls. Those whose 1993 1KW tests were in-determinate were not enrolled as either cases or controls Cases were similar in ageand sex lo controls (mean 44 years vs. 38. Pa 0.26and 47% male vs. 55%. P = 0.65).

Individuals who were HCV infected had received more injections from health care providers in the 5 and 10 years preceding October 1993 than controls of similar age. Individuals who were HCV infected were 8.2 limes more likely to average receiving $ injections per year in the previous 5 years than

controls (36% vs. 6%. Odds Ratio IORI • 8..2, 95% CI 1.9. 41.4. P — 0.002). Similarly. HCV infected persons were 5.4 times more likely to average receiving _ S injections per year in the previous 10 years than controls (34% vs. 9%, 95% CI 1.2. 28, P= 0.03). There was a marked relationship between the average number of injections in the preceding 5 and 10 years and HCV infection (Chi square for linear trend P = 0.006 and 0.008 for injections in the preceding 5 and 10 years respectively (Table 2).

Table 2. Association between presence of antibody to HCV and HBV core antigen with the average number of injections received during 1994 an the 5 and 10 years preceding 1993, Hafizabad, Pakistan.

	HCV positive	HCV negative	HCV odds ratio↑	HBV core antibody positive	HBV core antibody negative	HBV odds ratio§
Average number of injections in the last l year*.±						
0	4	17	1.0 (baseline)	10	9	1.0 (baseline)
1	0	6	0.00	4	0	Undefined
2-4	1	15	0.28	10	3	3.00
5-9	5	10	2.12	6	6	0.90
≥10	5	15	1.42	13	7	1.67
X^2 for trend P value			.294			0.791
Average number of injections per year in the 5 years before serum was testes±.§						
0	2	17	1.0 (baseline)	4	12	1.0 (baseline)
1	0	8	0	1	5	0.60
2-4	1	18	0.47	5	12	1.25
5-9	4	8	4.25	4	6	2.00
≥ 10	8	13	5.23	11	9	3.67
			(baseline)			(baseline)
1	0	8	0	1	5	0.60
2-4	1	18	0.47	5	12	1.25
5-9	4	8	4.25	4	6	2.00
≥ 10	8	13	5.23	11	9	3.67
X^2 for trend P value						
Average number of injections per year in the 10 year before serum was tested^, Ì						
0	1	10	1.0 (baseline)	4	5	1.0 (baseline)
1	0	8	0.00	1	6	0.21
2-4	2	13	1.54	3	10	0.38
5-9	2	8	2.50	1	5	0.25
≥ 10	9	13	6.92	12	10	1.50
X^2 for trend P value			0.008			0.214

* n, 78 for HCV analysis; 4 controls responded 'don't know' on injection history.

± n, 68 for HBV analysis; 10 had insufficient sera to test for HBV; 1 result was borderline; 1 core antibody positive and 2 core antibody negative pers responded 'don't know' on injection history.

↑ n, 79 for HCV analysis; 3 controls responded 'don't know' on injection history.

§ n, 69 for HBV analysis, 10 had insufficient sera to test for HBV; 1 result was borderline; 1core antibody positive and 1 core antibody negative pers responded 'don't know'.

Ì n, 57; for HBV analysis; 10 had insufficient sera to test for HBV; 1 result was borderline; 5 core antibody positive and 9 core antibody negative pers responded 'don't know' on injection history.

Infection with HBV was less strongly associated with injections though there was a significant linear association with injections received in the previous 5 years (Table 2). Neither HCV nor HBV was associated with the number of injections received during 1994. the 1 year period between the initial prevalence study and the follow- up case control study.

Among the 77 respondents who recalled their last injection, 34 (44%) received it from a private general practitioner. 27 (35%) from a non-physician pharmaceutical dispenser, and 7 (9%) from a government hospital. Nineteen (24%) of respondents noted that the syringe used in their most recent injection came from a scaled package and 38 (48%) reported that it came out of a pan of waler. There was no significant association between HCV infection and the most recent injection provider nor where the most recent syringe was taken from.

Older subjects did not report a higher rate of injcctions. The mean age of individuals who reported _1 injection per year over the last 10 years was similar to the mean age of those who reported S injections per year (43.2 vs.37.3 years. P = 0.78). HCV infected individuals reported fewer injections in the recent compared to the more distant past. Thirty-three percent of HCV infected individuals reported _l0 injection in the preceding year compared with 53% averaging >_10 injection per year in the preceding 5 years and 64% in the preceding 10 years. Other investigated exposures were not significantly associated with HCV infection (Table 3).

Table 3. Exposures not significantly associated with anti HCVantibody, Hafizabad, Pakistan, December 1994.

Exposure	Number HCV Reactive (%§) (n=15)	Non-reactive (% §) (n=67	P value*
Male sex	7 (47)	37 (55)	0.65
Blood transfusion ever	1 (7)	4 (6)	1.0
Illicit injecting drug use ever	0 (0)	0 (0)	1.0
Shaved by a barber at least one per month#	4 (80)	24 (77)	0.70
Sharing razors#	0 (0)	1 (4)	1.0
Sharing a tooth brush	1 (9)	2 (4)	0.42
Tatooing in the prior 2 years	1 (7)	0 (0)	0.19
Ear/nose piercing in prior 2 years	1 (7)	0 (0)	0.19
Ever having dental work	5 (33)	25 (39)	0.94
Occupational human blood or needle exposure	1 (7)	7 (10)	1.0
>1 lifetime heterosexual partners	2 (18)	8 (15)	0.82
Ever had sexual intercourse with prostitutes#	0 (0)	2 (7)	1.0
Ever had male to male sexual intercourse#	0 (0)	5 (16)	1.0
Mean age	44	38	0.26
Mean number			
Rooms in house	3.3	2.9	0.91
Persons per hosuehold	5.5	6.7	0.24
Persons per room	2.1	2.8	0.19

* Chi square test for comparison of prevalences and t-test for comparison of means.

§ Persons not answering the question were excluded from the denominator.

Asked only of men.

Only five respondents had received blood transfusions and none reported illicit drug use.

Clinic Inspections

Inspection of three private clinics showed that none drawn. had any new sterile syringes, sterile reusable syringes, or facilities for heat sterilizing medical equipment. All had used disposable syringes and needles soaking in a bowl of tepid water. Practitioners in these clinic reported that their most frequent injections were vitamin 13 complex. chloroquinc. and penicillin. For one of the HCV infected patient's monthly allergy treatment, a practitioner drew blood from the patients vein then injected the blood intramuscularly. The hospital laboratory owned and resterilized two syringes used for taking blood. At the time of our inspection 14 people were in line to get their blood drawn.

Discussion

Applying the rates of HCV infection in the randomly chosen study population to the whole town, we

estimate that 8090 persons in the town were infected with HCV at the time of the 1993 survey. Assuming that transmission is consistent and ongoing. and that seropositive individuals have been infected for a mean of 10 years. we estimate there are 800 new cases of HCV infection in Hafizabad each year (640/100000). Cohort swdies of individuals who were infected with HCV following transfusion report that 30% of HCV infected persons progress to cirrhosis.[4] Of these 2.8% per year die annually of end stage liver disease[19] and 1.7% per year die of hepatocellular carcinoma.[4] From these figures we estimate there are 109 deaths each year (87/100000) from IICV in Hafizabad. Thus. HCV isa major public health problem in Hafizabad.

The evidence implicating injections as the major route of transmission of HCV is persuasive. There was a strong and dose dependent association between number of injections received by individuals during the preceding 5 and 10 years and their risk of infection with HCV. Other potential routes of transmission including those routes reported from developed countries such as transfusion. illicit injecting drug use, and sexual transmission[5-9], were evaluated but were not associated with HCV infection in our study. The observed unsanitary needle hygiene practices support injections as a route of transmission. Indeed, their use of non-sterilized needles has been implicated in the associations between HCV infection and injecting drug use[5,20] tattooing[5,19] and nosocomial needle stick injuries.[21] Hepatitis B, which may be transmitted through unsanitary needles[22], was less strongly associated with therapeutic injections in Hafizabad. than was HCV. This is likely because a larger proportion of the HBV infections in Hafizabad were not transmitted by therapeutic injections. but rather through vertical and sexual transmission. Vertical transmission of HCV is uncommon.[23] Indeed, in Ilafizabad there were no HCV infections among 53 children <10 years of age compared with 9 HBV infections among 50 children in the same age group. Similarly, sexual transmission of HBV is more efficient than sexual transmission of HCV.[23] In the relatively small sample size of this study substantial non-needle associated routes of HBV transmission would be expected to weaken the observed association with needle transmission.

Health care providers in Hafizabad have a strong financial incentive to give parenteral injections. Many individuals actively seek injections because they believe them to be more powerful than other treatments. Thus, health care providers can charge more for an injection than for either medically sound advice or non-parenteral medication. Our very limited field work among health care providers suggested that most of these injections were not medically indicated. The three medications they most commonly reported injecting were all available as oral preparations, and for the vast majority of clinical syndromes the oral route is preferred. It is possible that HCV circulated within Halizabad or other parts of Pakistan at low prevalence for several decades or longer maintained by relatively inefficient sexual and vertical trans-mission. The relatively recent importation of medical technology may be responsible for markedly increasing the efficiency of HCV transmission and so the number of persons infected.

Hafzabad. Pakistan is one community, but the administration of frequent injections using unsterilized needles and syringes is common throughout Pakistan[3] and among many underdeveloped countries.[23] Indeed, some of the difference in HCV seroprevalence between developing and developed countries may reflect the less safe and less regulated use of medical injections in developing countries. Stopping the re-usc of unsterilized needles and syringes is important to interrupt not only HCV transmission, but also the transmission of other viruses that may be transmitted via therapeutic injections.[22,28]

An important limitation of this study is that needle exposure was estimated based upon self-reported history. It is possible that individuals with hepatitis C might have systematically over-estimated the number of previous injections. However, this is unlikely for four reasons. First, cases had no more time to consider their exposures than controls; both cases and controls were asked their exposure history immediately after learning their serological results. Second, there were several other parenteral risk

factors discussed with study subjects including sexual transmission, sharing razors, and blood transfusions that were not associated with HCV infection. Third. the associations with needle use were consistent with the known long latency of the virus. Frequency of injections in the one previous year (1994) were not strongly associated with HCV infection. In contrast, average annual injections over the 5 and 10 years preceding 1994 which would be expected to more accurately reflect the total cumulative exposure to this agent with a long latent period, were strongly associated with HCV infection. Fourth, analysis of a different population in Hafizabad (families of infected persons) who were administered the same questionnaire before their HCV antibody status was known, also demonstrated a strong relationship bctwccn number of injections and HCV infection (Pasha. unpublished observations).
Another potential explanation for the association
between injections and HCV infection is that HCV infected individuals became Symptomatic from their infection and so sought more health care, and so received more injections. This explanation. however, is not consistent with the data. Hepatitis C typically has a long asymptomatic latent pcriod. Symptoms emerge and worsen as liver disease progresses and nears end stage. If HCV symptoms were causing people to seek more injections, we would expect to find more injections later in the course of their HCV infection, than in the distant past. However the data from Hafizabad showed precisely the opposite. HCV infected persons reported averaging more injections in the previous 5 and 10 years than in the previous year. Indeed, it was injections in the previous 5 and 10 years. and not within the last 1 year. that were strongly associated with HCV.
People need to understand the risks of injections. Governments and organizations committed to promoting health need to encourage both health care providers to dispense and the general population to receive injections only if they are medically indicated. Injection equipment needs to be sterile. Widely available injections in an unregulated setting with a monetary inccntivc for parenteral drug administration and little investment in prevention puts communities throughout the developing world at substantial risk for iatmgenic blood borne infections.

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