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Research Article

# Epidemic of Hepatitis C in a remote village of Kashmir, India

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## Abstract

**Introduction:** Most developed countries have accumulated evidence that the predominant source of new HCV infection over the past few decades is injection drug use. In the developing world, unsafe therapeutic injections and transfusions are likely to be the major modes of transmission. In India, the prevalence appears to be highly variable, according to the geographical site or the population group analysed (0.09–7.89%). There was a cluster of seven cases of hepatitis C in the village Takiya Magam in January 2013. In response, the Rapid Response Team surveyed the entire population for prevalence of antibody against hepatitis C.

**Materials & Methods:** An investigation of the outbreak was conducted by a survey of the household contacts of the 7 hepatitis C cases in the first phase of investigation followed by screening of the entire 2600 population of the village in the second phase. Of the 2600 persons living in the village 2051 (78.88%) agreed to get tested for anti-HCV. The entire village was screened using the Rapid Card Diagnostic Test (SD Bioline rapid immunochromatographic test for antibody Ig G). Blood samples were collected and serum separated within hours of collection and transported to the laboratory for use. All rapid test positive samples were further tested by a third-generation anti-HCV enzyme immunoassay (EIA). Anti-HCV antibodies were detected by ready-to-use third generation SD HCV ELISA third generation kit (containing core, NS-3, NS-4, & NS-5 antigens) from Biostandard Diagnostics Private Limited India. A randomly selected subset of rapid test and EIA anti-HCV (n = 50) positive samples were sent to a national level central laboratory, the National Centre for Disease Control, Delhi. HCV RNA was tested by PCR using and HCV genotype was determined by using genotype specific primers. Allanti-HCV positive cases were further evaluated clinically by a team of gastroenterologists. To investigate the possible source of infection and mode of spread in the community, a questionnaire guided interview was conducted by house to house survey for the entire village. In order to understand spread of infection across the entire district and considering that the alleged exposure practices may be rampant across the district, geographical control villages were selected.

**Results:** Out of the population of 2600, 2051 consented to getting tested. This included 1199 males (49.04%) and 1269 females. Of the 2051 subjects, 787 (38.37%) were anti-HCV positive by both rapid and third generation ELISA. The rates of anti-HCV positivity among males and females were 33.44% (401/1199) and 30.41% ( 386/1269) respectively. HCV genotype 3a was detected in 16 HCV RNA positive samples. The NCDC laboratory confirmed presence of HCV specific 5'UTR gene in 43/50 samples (86%) using RT-PCR technique. Further, DNA finger printing/ DNA signature experiment on 16 RNA positive HCV strains revealed 100% of HCV strains from the outbreak belonged to HCV genotype 3a. The age group ranged from 30 months years to 75 years, with 113 subjects being below the age of 15 years (14.35%). The maximum number of cases is in the age group 15-50 years with a peak at 15-30 years. Some clustering within households was observed. The prevalence of injection use both IV and IM was very high in this village. These injections were provided by local chemists. Injection use was 83.3% among cases and 83.8% among controls which was not statistically significant. However, there was a significantly high prevalence of dental procedures among cases as compared to controls ($p < 0.001$).

**Conclusion:** In our study, we have witnessed the widespread use of injections in all the four villages and the same situation may exist in the rest of the state. Stopping the re-use of unsterilized disposable needles and syringes is important to interrupt the transmission not only of HCV but other viruses that may be transmitted via therapeutic injections. Unregulated use of injections by quacks has to be stopped in conjunction with health education of the population regarding safe injections. Injection equipment needs to be sterile and a regulatory mechanism has to be kept in place throughout the country .In addition, the use of large-volume diluents needs to be stopped because its use is rampant in the state. Moreover, use of safe injections and sterilized equipment during dental procedures is a necessity.

***Keywords:*** *Hepatitis C virus; HCV genotype; Anti-HCV antibodies; Seropositive males*

## Introduction

Since its discovery in 1989, hepatitis C virus has been recognized as a major cause of liver disease worldwide [1]. According to recent estimates by WHO in 2014, more than 185 million people around the world have been infected with the hepatitis C virus (HCV), of whom 350,000 die each year [2]. It is estimated that 3-4 million people are infected with HCV each year [3]. One third of those who become chronically infected are predicted to develop liver cirrhosis or hepatocellular carcinoma [2]. Of the more than 500,000 new cases of liver cancer that occur each year, 22% (>100 000) are attributable to HCV infection. The modes of spread of HCV are blood transfusions from unscreened donors, injection drug use, unsafe therapeutic injections and other health care related procedures [1].

In the developing world, unsafe therapeutic injections and transfusions are likely to be the major modes of transmission for hepatitis C [1]. Unsafe injections may be the major source of hepatitis C in the developing world since blood transfusions are not widely available in these countries [4] as evidenced by studies in China [5], Pakistan [4] and Egypt [6]. Countries with high rates of chronic infection are Egypt (22%), Pakistan (4.8%) and China (3.2%). Limited information is available about the prevalence of hepatitis C in the general population of India. In India, the prevalence appears to be highly variable, according to the geographical site or the population group analysed (0.09–7.89%) [7]. One large population–based study which was carried out in West Bengal reported a prevalence of 0.87% with an increase in prevalence with age from 0.31% in subjects <10 years of age to 1.85% in those ≥ 60 years [8]. In a similar sero-epidemiological survey in Punjab the prevalence of anti-HCV positive rate was 5.2% [9].

WHO estimates that at least 12 billion syringes are sold each year for injection purposes [1]. Injection therapy is widespread and popular in the developing world. Of all the injections given, 5% or less has been found to be for immunizations; 95% were given for curative purposes, and most of these were judged to be unnecessary. Whereas, the introduction of disposable syringes largely eliminated the problem of unsafe injections in developed countries, it did not lead to safe injection practices in developing countries [9]. In the absence of a vaccine and high costs of treatment, prevention of infection remains a foremost strategy for public health professionals.

### Study Rationale

In Jammu and Kashmir, India, the State Health system maintains disease surveillance activities throughout the state. It came to the notice of Directorate of Health Services Kashmir on 10th January 2013, that there was a cluster of seven cases of hepatitis C in the village TakiyaMagam. These cases had come to the local Community Health Centre for various surgical procedures and HCV was discovered as part of routine pre-operative examination since the testing for hepatitis B, C and HIV is mandatory before surgical procedures.

In response, the Directorate of Health Services Kashmir through its Rapid Response Team surveyed the household contacts of the 7 cases initially followed by the entire village population for prevalence of antibody against hepatitis C. When an unexpectedly high prevalence of anti-HCV positivity was found further investigation was conducted to determine the epidemiology of HCV infection in the affected area. In addition, three other villages in the district were investigated for HCV from January to February 2013. There is no large scale survey in the state to know the baseline data regarding hepatitis C or other blood borne pathogens.

## Methods

**Characteristics of the affected village:** TakiyaMagam is a remote village nestled in the Himalayas approximately 9 km from Community Health Centre, Kokernag in District Anantnag of South Kashmir. The village is surrounded by high mountains and thick forests. The village has a population 2600 with 538 households. The population in the village are low-paid labourers, poorly educated and subsist on the cultivation of maize. A large number of males migrate to other places in Northern India during winter months for work and return in summer to work and live in the same village. The climate of Anantnag is temperate with a harsh winter from December to February. Most of the families in the village live in extended joint family system with average number of family members being ten. The nearest government health facility is a sub-centre in an adjacent village staffed by a female multi-purpose worker and one male multi-purpose worker which remains open from ten in the morning and closes at four in the evening. There are no qualified medical practitioners in the village and the nearest hospital is at Community Health Centre Kokernag nearly 9 km away. The villagers frequently seek health care from local unqualified pharmacists, locally known as "chemists" for minor ailments such as fever, pain, weakness, toothache, and there is a general preference for injections both intravenous and intramuscular over pills. These chemist shops provide services not only for injections but also for minor surgical procedures such as drainage of abscess, circumcision, suturing of wounds, dental extraction etc.

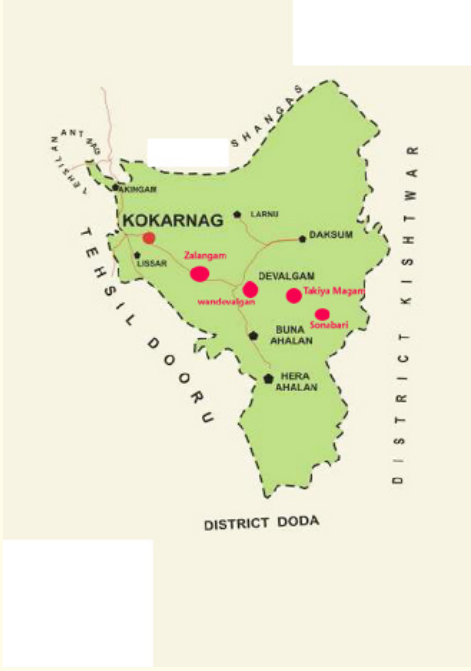
The HCV outbreak investigation in TakiyaMagam was carried out in two phases. In the first phase, blood samples were collected from the 58 household contacts of the initial 7 hepatitis C patients. In the second phase of the investigation, the entire village of 2600 population was screened using the Rapid Card Diagnostic Test (SD Bioline rapid immunochromatographic test for antibody IgG). Blood samples were collected and serum separated within hours of collection and transported to the laboratory for testing. All rapid test positive samples were further tested by a third-generation anti-HCV enzyme immunoassay (EIA). Anti-HCV antibodies were detected by ready-to-use third generation SD HCV ELISA third generation kit (containing core, NS-3, NS-4, & NS-5 antigens) from Biostandard Diagnostics Private Limited India and 324 were tested by fourth generation ELISA. All the serology tests were conducted at Provincial Public Health Laboratory at Srinagar, the state capital. A randomly selected subset of rapid test and EIA anti-HCV (n=50) positive samples were sent to a national level central laboratory, the National Centre for Disease Control, Delhi. HCV RNA was tested by using PCR and HCV genotype was determined by using genotype specific primers for confirmation of diagnosis and further exploratory investigation of the genotypes of the virus. Further testing for genetic sequencing could not be done in the country since the facility is not available.

**Clinical Evaluation:** Allanti-HCV positive cases were further evaluated clinically by a team of gastroenterologists at the Community Health Centre Kokernag, located 9 km from the village, at a later date. All the subjects were offered tests and upper GI endoscopy when required.

**Source of Infection:** To investigate the possible source of infection and mode of spread in the community, the team interviewed all those subjects whose samples were taken for testing. A questionnaire guided interview was conducted by house to house survey for the entire village. In case of young children, parents were asked to provide information. The questionnaire was designed by NCDC Delhi to capture modes of transmission of HCV infection with an objective to identify practices that may be responsible for transmission of infection in the community. We studied the injection use in the past ten years in the life of a subject. The study design was a case-control study in which a case was defined as the TakiyaMagam village subject who tested anti-HCV positive in this recent investigation by the team and controls were defined as residents of this village who tested anti-HCV negative.

In order to understand spread of infection across the entire district and considering that the alleged exposure practices may be rampant across the district, geographical controls were selected (see map). The district has a total population of 1,070,144 people living in 388 villages. Of these three additional villages were selected for this survey as geographical controls: a village (Sonebrari population 3715) adjacent to the affected village of TakiyaMagam, a village (Zallangam, population 3143) not far away from the affected village but close to a large government health facility (CHC Kokernag Hospital), and a village (Veeri, population 2753) very distant from affected village. A systematic random sampling strategy was adopted to acquire the representative samples from the aforementioned villages. A total of 100 subjects from village Sonbrari, 100 subjects from village Zallangam and 200 subjects from village Veeri were selected for

interview. Also serum samples were collected from a sub-set of these (25, 25 and 50 subjects respectively) for serological testing for anti-HCV using ELISA at NCDC and National Institute of Virology, Pune.




***Map***

## Results

**Demographic characteristics of TakiyaMagam:** The Rapid Card Diagnostic Test was offered to all village residents; but some residents were away for work in other parts of the country especially Punjab. Out of the population of 2600, 2051 (79%) were available for testing. This included 1199 males (49%) and 1269 (49%) females. Of the 2051 subjects, 787 (38%) were anti-HCV positive by both rapid and third generation ELISA. The rates of anti-HCV positivity among males and females were 33% and 30% respectively. The NCDC laboratory confirmed presence of HCV specific 5'UTR gene in 43/50 samples (86%) using RT-PCR technique. Further, DNA finger printing/ DNA signature experiments was done on 16 RNA positive HCV strains and of these all were found to be HCV genotype 3a.

Table 1 shows the stratification of the 787 subjects by age. Ages ranged from 30 months to 75 years, with 113 subjects being below the age of 15 years (14%). The maximum number of cases is in the age group 15-50 years with a peak at 15-30. The seropositive males showed an age range of 30 months to 75 years and the females had an age range of 4 years to 73 years. Some clustering within households was observed.

Table 2 shows that the prevalence of injection use both IV and IM was very high in this village. These injections were provided by local chemists. Injection use was 83.3 % among cases and 83.8% controls over the past year which was not statistically significant. However, there was a significantly high prevalence of dental procedures among cases as compared to controls ($p < 0.001$). There was no history of blood transfusion among cases or controls and no history of IV drug abuse. Study of exposures in clinically confirmed cases of hepatitis C revealed that they too had a history of utilization of services from local chemists. In some households, there was history of sharing of razors among men-folk.

| | |
|---|---|
| Total population of Village | 2600 |
| Total number of samples tested | 2051 |
| Total anti-HCV positive | 787 (38.37%)<br>95% C.I. 36.3% to 40.5% |
| No. of males infected | 358 (45.48%)<br>95% C.I. 41.5% to 48.5% |
| No. of females infected | 429 (54.51%)<br>95%C.I. 51% to 57.8% |
| No. of children < 5 years | 2 |
| No. of children <15 years | 93 |

***Table 1:*** *Prevalence of anti-HCV positivity in the studied population.*

| Risk factor | Cases n=787(%) (HCV-Positive subjects) | Controls n=1264(%) (HCV-Negative subjects) | P value |
|---|---|---|---|
| Use of injections (IM or IV) | 656 (83.3) | 1060 (83.8) | 0.75 |
| Dental procedures | 374 (47.5) | 387 (30.6) | <0.001 |
| Ear/nose piercing (only women) | 681 (86.5) | 1085(85.8) | 0.40 |
| Sharing of razors (only men) | 420 (53.3) | 692 (54.7) | 0.55 |
| Male sex | 358(45.48) | 46.13% | |
| Blood transfusion | Nil | Nil | |
| Tattoo | Nil | Nil | |

***Table 2:*** *Frequency of risk factors associated with Anti-HCV positive and negative subjects.*

Table 3 depicts that a high prevalence of injection use was found in village Sonebrari (81.8%) which is adjoining TakiyaMagam and the prevalence of anti-HCV positives was 21%. In village Veeri which is far away from TakiyaMagam 78.4% were found to use injectables but we did not find any anti-HCV positive subjects. However, the prevalence of history of injections/IV drips from local chemists was relatively lower in village Zallangam (45.5%) which is in close proximity to CHC Kokernag, a well-equipped government health facility and here also no anti-HCV positive subjects were found among the samples tested and this is reported as numbers and percentages. The p value using Chi square test is significant for higher injection use in Sonebrari.

| Village | Sonebrari (adjacent village) | Zallangam (near CHC ) | Veeri (distant village) |
|---|---|---|---|
| Samples collected | 100 | 100 | 100 |
| Samples found positive | 21 | 0 | 0 |
| Injection use among subjects interviewed | 83 | 45 | 78 |

***Table 3:*** *Exposure difference between three villages in District Anantnag.*

**Visit to local chemist shops:** The village has five chemist shops which provide services to the local population and the team visited two of these pharmacies. The owners of both the pharmacies had no educational qualification in pharmacy discipline. They reported providing 10-15 injections per day usually antibiotics, analgesics, vitamins and glucose infusions. In each chemist shop there is a small room adjacent to the main pharmacy where IV infusions and injections are given. In this way, the chemist loads injections in one room and provides services in other room. One interesting finding was the use of large volume diluents for injection purpose. The chemist's use a single bottle of a diluents e.g. Normal Saline on patients till it is exhausted after putting one needle into the bottle which is also

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| S.No | Sex | Age | Clinical characteristics | Genotype | Viral load |
|---|---|---|---|---|---|
| 1. | Male | 65 years | Chronic HCV infection end stage liver disease hepato-cellular carcinoma | 3a | - |
| 2. | Female | 28 years | Incidentally discovered as Hep c positive during pre-surgical work up. On treatment | 3a | 1364 |
| 3. | Male | 19 years | Incidentally discovered as Hep c positive during presurgical work up at community Health centre. On treatment | 3a | 108,000 IU/ml |
| 4 | Female | 39 years | G3 P2 pregnant at the time of study incidentally discovered as Hep C positive during antenatal workup by attending obstetrician. Both children are anti-HCV negative | 3 | 2,140,000 IU/ml |
| 5. | Male | 30 years | Was investigated when wife found anti-HCV positive. On treatment. | 3 | 4619 IU/ml |
| 6. | Female | 25 years | Prmigravida was incidentally discovered as Hep C positive during antenatal workup. Wife of serial no.5 | 3 | 12,853 IU/ml |
| 7 | Female | 39 years | Incidentally discovered as Hep c positive during presurgical work up at Community Health centre. On treatment since November 2011 | 3 | 609,000 IU/ml |

***Supplementary table:*** *Parameters of seven clinically confirmed cluster of HCV patient.*

## Discussion

This epidemic can be likened to the epidemic of Hepatitis C in Egypt [6] in which the sero-positivity was 33 % among Egyptian military recruits and was related to the parenteral exposure to the virus. A nationwide campaign against schistosomiasis between 1920 and 1980 played a major role in the extensive spread of hepatitis C virus which involved several injections over the course of weeks and the reuse of syringes without sterilization [10]. Another study which studied the relationship between therapeutic injections and hepatitis C in Pakistan [4] found a high incidence of 6.5% in a community living in Hafizabad, Punjab. The study also concluded that males were slightly more likely to be affected than a female (7.6% vs 5.6%) which has been demonstrated in the present study also. Similarly, a sero-epidemiological community based survey across the border in Punjab, India, found an anti-HCV positive prevalence rate of 5.2% with no difference among males and females. Various risk factors for acquiring HCV infection identified were history of surgery, dental treatment, and unprotected sex [11]. However, a community based study on HCV prevalence in West Bengal India has reported an overall prevalence of 0.9% in India [12]. This means that within India also the distribution of HCV prevalence is patchy with areas of high prevalence and the outbreak mentioned in this study is unprecedented. We took only small samples from the three control villages and only extrapolations can be made. The purpose of inclusion of these geographical control villages was to know the extent of spread of infection in the district through an epidemiological approach.

Another important fact that emerged from our study was that nearly 14.35% were below the age of 15 years and 47 (6%) were below 10 years. In Hafizabad Pakistan, no children below 5 years were found to be infected whereas we found infection in 2 children below the age of five years possibly resulting from vertical transmission of the virus. In the study in Indian Punjab, highest prevalence was noted in the 41-60 year age group, similar to our study [11].

Today, HCV-2 and HCV-3 make up roughly 30% of the chronic HCV infections in the Western world13 HCV-3 itself accounts for 35–80% of chronic HCV infections in regions such as the Indian subcontinent, South-East Asia and Australia [9]. In our study genotype 3a was found in all the specimens tested pointing towards an epidemic form of the disease. The males of this village, visit other parts of North India during winter months as labourers, which may put them at a higher risk of infection: once infected they also serve as a source of transmission of infection both in their village and further afield. The impact of the disease on the individuals, on the state and on the country is unimaginable. The economic considerations are huge both in terms of morbidity, loss of work-days and also in terms of expenditure on treatment.

At an individual level, chronic hepatitis C is linked to the development of cirrhosis and hepatocellular carcinoma in many areas of the world. The abuse of injections in the developing world has reached alarming proportions in recent years. Formal and informal health care providers administer far too many injections to clients who perceive this form of treatment as superior to all other forms of medicine administration [13]. Health care providers charge more for injections than for oral medication and thus providing injections is an economic incentive for them. At the same time this persistent demand for injectables has to be reduced by targeted health education not only among the residents but also health care providers. Massive health education campaigns are required to make people aware of the ill-effects of unsafe injections so that the patients are aware of other, safer options and through continuous education and training of formal and informal health care providers in safe injection practices. The outbreak was followed by large-scale education and awareness programmes in the area regarding safe injection practices and use of safe dental procedures. Education campaigns were conducted both for local population as well was health care workers. Targeted counseling was provided to HCV positive patients about limitation of spread of infection.

There is widespread use of injections in all the four villages in this study, a situation which may exist in the rest of the state. Stopping the re-use of unsterilized disposable needles and syringes is important to interrupt the transmission not only of HCV but other viruses that may be transmitted via therapeutic injections [14]. Unregulated use of injections by untrained individuals must be stopped in conjunction with health education of the population and health care providers regarding safe injections. Injection equipment needs to be sterile and a regulatory mechanism has to be kept in place throughout the country. In addition, the use of large-volume diluents, which are used extensively, needs to be stopped. Moreover, use of safe injections and sterilized equipment during dental procedures is a necessity. How much of infection was contributed to by unsafe injections and dental procedures and how much by use of large volume diluents could not be ascertained.

**Study Limitations**

Genetic sequencing of the HCV was not possible which could have led us to construction of a phylogenetic tree and linking this epidemic to other areas of increased HCV prevalence in India and Pakistan. Recall bias among surveyed individuals about the number of injections/dental procedures they had undergone in the past.

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**At District Level**

1. Dr. Fazil Kochak (Chief Medical Officer Anantnag)
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3. Dr. M .Y. Zagoo (Block Medical Officer Larnoo).
4. Dr. M.Iqbal (Medical Superintendent JLNM Hospital Srinagar).
5. Dr. Imtiyaz Ur Rehman (District Epidemiologist IDSP)
6. Mr. Ishfaq ur Rehman (District Data Manager IDSP )

**At Divisional Level**

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2. Dr. Tasaduq Shafi (District Epidemiologist IDSP)
3. Dr. Feroz Ahmad (State Microbiologist)
4. Mr. Imtiyaz Amin (State DM)
5. Ms Irfana Bhat (State DEO)

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