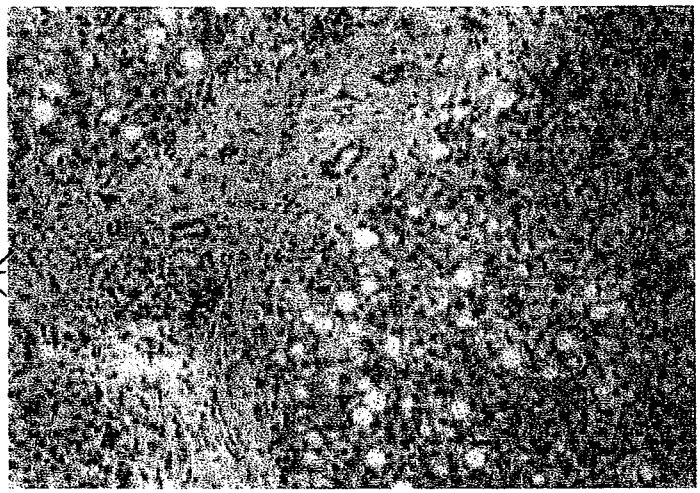
The Silent Epidemic: Hepatitis C

The identification of the hepatitis C virus in 1989 solved a growing mystery. Over the past ten years, large numbers of hepatitis victims had begun to appear, apparently with a virally caused disease. But when examined, these patients tested negative for both hepatitis A and B. The unknown disease was known as non-A, non-B hepatitis. When a test was developed in 1990 to identify individuals infected with hepatitis C, hepatitis C was found to be responsible for the majority of these cases - and it has quickly proved to present a frightening challenge.

In contrast to most other types of hepatitis, more than 80% of hepatitis C (HCV) infections become chronic and lead to liver disease. Hepatitis C, in combination with hepatitis B, now accounts for 75% of all cases of liver disease around the world. Liver failure due to hepatitis C is the leading cause of liver transplants in the United States.

Since hepatitis C infection is typically mild in its early stages, it is rarely diagnosed and is often not recognized until its chronic stages when it has caused severe liver disease. With a typical cycle of disease from infection to symptomatic liver disease taking as long as 20 years, the true impact of this disease on our growing infected population will not be apparent for many years. For this reason, it is often referred to as the "silent epidemic".



Micrograph of liver cells afflicted with the mysterious non-A non-B Hepatitis. Hepatitis C was found to be responsible for many of these cases.

It is suspected that there are, at present, more than 4.5 million people in the United States that are infected with hepatitis C, and more than 200 million around the world - making it one of the greatest public health threats faced in this century, and perhaps one of the greatest threat to be faced in the next century. A vaccine against hepatitis C may not be available for many years to come, and there are already many times more people infected with HCV as have HIV (the virus that causes AIDS). Without prompt intervention to treat infected populations and prevent the spread of disease, the death rate from hepatitis C will surpass that from AIDS by the year 2000 - and it can only get worse.

Disease Progression

The symptoms of hepatitis C are difficult to recognize, for they are progressive in nature and often very mild, at least in the early stages of infection. For more than six months following initial infection, the disease is virtually undetectable.

The most common symptom, commencing sometimes years after initial infection, is fatigue. Other symptoms include mild fever, muscle and joint aches, nausea, vomiting, loss of appetite, vague abdominal pain, and sometimes diarrhea. Many cases go undiagnosed because the symptoms are suggestive of a flu-like illness which just comes and goes, or these symptoms are so mild that the patient is unaware of anything unusual. A minority of patients notice dark urine and light colored stools, followed by jaundice in which the skin and whites of the eyes appear yellow. Itching of the skin may be present. Some people may lose 5 to 10 pounds.

Individuals infected with HCV are often identified because they are found to have elevated liver enzymes on a routine blood test or because a hepatitis C antibody is found to be positive at the time of blood donation. In general, elevated liver enzymes and a positive antibody test for HCV (anti-HCV) means that an individual has chronic hepatitis C. A very small percentage of patients may recover from acute hepatitis C, but their anti-HCV test will remain positive.

Advanced cirrhosis in a human liver

Low level infection, in which the infected individual is virtually asymptomatic but still highly contagious, may continue for years, even decades, before progressing significantly. However, more than 80% of infected individuals eventually progress to the chronic stage of the disease, which seems to eventually result in cirrhosis (scarring of the liver tissue), and end-stage liver disease. This appears to take, on average, about 20 years to develop.

At this point, the symptoms are commensurate with liver disease or liver failure, including jaundice and abdominal swelling (due to fluid retention called ascites), depending on the severity of the liver disease and whether or not cirrhosis has developed. Some patients with cirrhosis do well over time, while others die in 10 and sometimes 5 years. Disorders of the thyroid, intestine, eyes, joints, blood, spleen, kidneys and skin may occur in about 20% of patients. Primary liver cancer can also develop from hepatitis C, a late risk factor which seems to be present 30 years or so after infection.

* SEE PG 4 (304) *

ORIGINAL ARTICLE

A national survey of genitourinary medicine clinic attenders provides little evidence of sexual transmission of hepatitis C virus infection

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Objective: To determine the prevalence and genetic diversity of hepatitis C virus in genitourinary medicine clinic attenders and to assess the extent of sexual transmission of the virus.

Methods: A cross sectional, unlinked, anonymous survey in 14 genitourinary medicine clinics situated in England, Wales, and Northern Ireland. Serum specimens from genitourinary medicine clinic attenders, retained as part of the Unlinked Anonymous Prevalence Monitoring Programme (UAPMP) serum archive, were tested in small pools, for the presence of antibody to hepatitis C virus (anti-HCV). The main outcome measures were prevalence of antibodies to hepatitis C virus and identification of hepatitis C virus genotypes.

Results: Testing of 17 586 specimens from 1995 showed an adjusted prevalence of anti-HCV in genitourinary medicine clinic attenders of 1.03% (95% CI: 0.89 to 1.16) overall and 0.65% (95% CI: 0.51 to 0.78) among those who did not report injecting drug use. Prevalence in injecting drug users attending genitourinary medicine clinics was 36.9% in both 1995 and 1996. Heterosexual injecting drug users had a higher prevalence of anti-HCV than homosexual/bisexual injectors. The most common hepatitis C genotypes were types 3a and 1a. There was a high degree of concordance between genotype and serotype.

Conclusions: The low prevalence of anti-HCV in genitourinary medicine clinic attenders who deny injecting drugs suggests that the majority of hepatitis C infections have been acquired in adult life, mostly by injecting drug use, and that the hepatitis C virus is rarely transmitted sexually. The use of needle exchanges may explain the relatively low prevalence observed in the injecting drug users.

Hepatitis C virus (HCV) infection has a worldwide distribution and the main routes of transmission have been described.[1] Evidence exists that sexual transmission of hepatitis C virus can occur although the extent of ongoing sexual transmission is less clear.[2 3] Studies of the sexual partners of known hepatitis C positive individuals suggests that the rate of sexual transmission is low but such studies have predominantly been performed on long term monogamous heterosexual relationships.[4 5] Other studies have suggested that multiple sexual partners,[6] sexually transmitted disease clinic attendance,[5] and prostitution[7 8] are associated with an increased risk of HCV infection.

Of the known behavioural risks associated with HCV infection, injecting drug users (IDUs) are among those at highest risk from infection. A number of studies of IDUs in Europe and the United States have found prevalences of antibodies against HCV (anti-HCV) of between 60% and 90%.[9 10] In many of the cross sectional studies undertaken, HCV infection correlated more strongly with injecting practices than with sexual behaviour.[11]

Since 1990 a number of genitourinary medicine (GUM) clinics in England, Wales, and Northern Ireland have contributed to the Unlinked Anonymous Prevalence Monitoring Programme (UAPMP).[12] These surveys have been used to monitor the prevalence of human immunodeficiency virus type 1 (HIV-1) in GUM attenders by sexual orientation and injecting drug use. Anonymised unlinked serum specimens were therefore available to be tested for the presence of anti-HCV. Testing these specimens would determine the baseline prevalence in GUM clinic attenders, and thereby provide an indication of the importance of sexual transmission, and contribute to the future surveillance and control of HCV infection. This paper describes the results of testing these specimens for HCV infection.

METHODS

Serum archive

Residues remaining from syphilis serology were unlinked and anonymised using established methods and tested for the presence of anti-HIV-1 as part of the UAPMP.[13] Archived sera selected by age group and centre from non-injecting drug users at GUM clinics in 1995 were tested for anti-HCV antibodies (table 1). All specimens from GUM attenders in 1995 and 1996 who had reported injecting drug use were also tested. Seven of the 14 participating centres were from the London area. Ethical clearance for the study had been obtained from the ethics committee in each locality where the UAPMP operated.

Pooling

A pooling strategy for testing the serum specimens for anti-HCV, similar to one previously described for anti-HIV, was utilised.[14] This methodology had been used successfully to test for anti-HCV in over 40 000 antenatal specimens from the UAPMP 1996 archive.[15] The initial protocol was shown to have a sensitivity of approximately 99% when using pools of 12 specimens when compared with testing individual specimens for anti-HCV antibodies. Specimens from non-injecting GUM clinic attenders were therefore tested in pools of 12. As the prevalence of hepatitis C infection in IDUs has been shown to be high it was most efficient to test these specimens individually.

* SEE PG 4 (304) *

Table 1 Total number of specimens tested from GUM serum archive (1995)

	Age group (years)					
	<20	20–24	25–34	35–44	45+	Total
London						
Number tested from archive	1229	2211	3342	2252	1148	10182
Serum archive	2163	7923	16125	5236	2231	33678
Outside London						
Number tested from archive	1040	1678	1942	1526	1218	7404
Serum archive	3111	7283	10246	3755	1755	26150
Total number tested from archive	2269	3889	5284	3778	2366	17586
Total serum archive	5274	15206	26371	8991	3986	59828

Serological testing

The pools of 12 serum specimens were tested using the Ortho HCV 3.0 enzyme linked immunosorbent assay (ELISA) test system (enhanced SAVe). Each specimen that had been incorporated in a reactive pool was subsequently tested individually by the standard (short) protocol for the Ortho HCV 3.0 ELISA test system (enhanced SAVe). Each individual serum specimen that was reactive by the Ortho assay was tested also by the Monolisa anti-HCV Plus (Sanofi Diagnostics Pasteur). Specimens with discordant results or those that were weakly reactive in either or both assays were further tested with a recombinant immunoblot assay (Ortho HCV RIBA 3). Individually tested IDUs were tested according to the Ortho standard protocol and reactive specimens were investigated as described above for the non-injecting drug users.

PCR and genotyping

Specimens from non-injectors and IDUs that were RIBA indeterminate were examined by reverse transcription-polymerase chain reaction (RT-PCR) for the presence of HCV RNA. Specimens that had discordant ELISA results but were RIBA negative were also examined by RT-PCR. Simple systematic randomisation was used to select a 12% and 50% sample by age of anti-HCV positive IDUs and non-injectors respectively for PCR analysis. RNA was extracted from PCR positive specimens using the Amplicor HCV Specimen Preparation Kit (Roche Diagnostic Systems, Welwyn Garden City, Herts, UK). The HCV 5′ non-coding region (5′-NCR) was amplified by nested PCR.[16] The products of positive RT-PCRs were digested with restriction enzymes, the digests of which were analysed using the restriction fragment length polymorphism (RFLP) system to determine HCV genotype.[15]

Serotyping

Specimens that were investigated by PCR (both non-injectors and injectors) were also examined by serotyping. The Murex HCV Serotyping 1–6 Assay, which utilises synthetic peptides representing the variable antigenic regions derived from the NS4 gene (non-structural) of HCV, was used for the detection of antibodies to serotypes 1, 2, 3, 4, 5, and 6.

Statistical analysis

Data from all patients who attended in 1995 (regardless of their injecting history) were analysed to provide a complete profile of the clinic attenders from that year. Data from IDUs who attended in 1995 and 1996 were also analysed as a single group. For analytical purposes, all specimens that were either anti-HCV or PCR positive only were included in the overall estimates of prevalence of HCV. Initially the proportions of positive specimens were compared using a χ^2 test. Multivariable logistic regression was used to compare the prevalence of HCV by region, age, sex, country of birth, sexual orientation, injecting drug use, and HIV status. Interactions between all of the factors were also examined. Statistical significance was taken at the 5% level. To adjust for the differential sampling by age, sex, sexual orientation, and injecting drug use, the observed prevalence was applied to the original number of specimens available, enabling an estimate of the overall prevalence in the clinic population (table 1).

RESULTS

Overall findings

A total of 17 586 specimens collected from GUM clinic attenders in 1995 were tested, and 349 were found to be HCV positive. This includes three RIBA indeterminate (one non-injector) and four RIBA negative specimens (all non-injectors) that were subsequently found to contain HCV RNA. Sixteen specimens were found to be RIBA indeterminate but PCR negative. All of these indeterminate specimens were from the London area: 10/16 (62.5%) were in the 25–34 age group and 11/16 (68.8%) were identified as IDUs. Of all survey clinic attenders, 16 965 did not report illicit injecting drug use, of whom 120 were HCV positive (table 2). Taking into account the specimens selected for testing by age, sex, sexual orientation, and injecting drug use from the original number of specimens available from the archive gives an adjusted prevalence of 1.03% (95% CI: 0.89 to 1.16) for all GUM clinic attenders in 1995, and 0.65% (95% CI 0.51 to 0.78) for the subset of non-injectors. Among the 621 specimens from IDUs, 229 (36.9%) were HCV positive, including the two RIBA indeterminate specimens that contained HCV RNA.

The adjusted prevalence in the London area (1.44%; 95% CI 1.23 to 1.65) was three times higher than in the combined geographical area outside of London (0.49%; 95% CI 0.34 to 0.66). The overall adjusted prevalence was higher in males (1.26%; 95% CI 1.05 to 1.47) than females (0.78%; 95% CI 0.60 to 0.95). Prevalence increased with age, the highest prevalence being in those aged between 25–34 and 35–44 years in both males and females. In males, the adjusted prevalences were 1.45% and 1.90% in those aged between 25–34 and 35–44 years respectively, compared to 0.89% and 1.99% in females of the same age groups. Multivariable logistic regression analysis (table 3) demonstrated a significant variation in prevalence by age ($p<0.0001$). Prevalence also varied by centre and the overall variation between centres was highly significant ($p<0.0001$) after controlling for all other factors. The prevalence of HCV did not differ significantly by sex ($p=0.71$) or by country of birth (UK/abroad) ($p=0.98$) after controlling for all factors.

The overall prevalence of anti-HIV-1 in this study was 2.08% (365/17 586) and the overall prevalence of HCV in the anti-HIV-1 positive specimens was 6.58% (24/365). HCV prevalence did not differ significantly by HIV status (OR = 1.74, $p=0.08$).

HCV prevalence was lower in the homosexual/bisexual group (OR=0.55, $p=0.0013$) compared to heterosexuals. Further analysis of interactions showed that this effect was

Table 2 Prevalence of anti-HCV in GUM clinic attenders (1995) by injecting drug use and geographical area

	Age group (years)				
	<20	20–24	25–34	35–44	45+
IDU	positive/number tested (%)				
London	2/16 (12.5%)	21/78 (26.9%)	101/226 (44.7%)	55/94 (58.5%)	12/20 (60.0%)
Outside London	3/26 (11.5%)	4/59 (6.8%)	15/73 (20.5%)	14/24 (58.3%)	2/5 (40.0%)
Non-IDU	positive/number tested (%)				
London					
Female (heterosexual)	0/822 (0.0%)	2/904 (0.22%)	10/1329 (0.75%)	13/783 (1.66%)	5/341 (1.47%)
Male (heterosexual)	0/345 (0.0%)	6/891 (0.67%)	11/1111 (0.99%)	14/923 (1.52%)	10/566 (1.77%)
Male (homosexual/bisexual)	0/47 (0.0%)	1/337 (0.30%)	11/676 (1.63%)	3/452 (0.66%)	3/221 (1.36%)
Outside London					
Female (heterosexual)	0/406 (0.0%)	0/708 (0.0%)	1/747 (0.13%)	7/685 (1.02%)	4/470 (0.85%)
Male (heterosexual)	0/562 (0.0%)	1/702 (0.14%)	5/816 (0.61%)	5/639 (0.78%)	2/616 (0.32%)
Male (homosexual/bisexual)	0/46 (0.0%)	1/209 (0.48%)	4/306 (1.31%)	1/178 (0.56%)	0/127 (0.0%)

present in the IDUs but not in the non-injectors (p value for interaction = 0.0009). This can be seen in the crude prevalence estimates for the IDUs for whom the HCV prevalence was 39.9% (198/496) in the heterosexual group and 24.8% (31/125) in the homosexual/bisexual group.

Injecting drug users

The prevalence of HCV in IDUs in each of the 2 years sampled was identical at 36.9% (1995, 95% CI: 33.1 to 40.8 (229/621); 1996, 95% CI: 33.3 to 40.5 (261/708)) Four of these specimens (two from 1995 aged 25–34 years and two from 1996 aged 35–44 years) were identified as indeterminate after RIBA testing, but were found to be HCV RNA PCR positive. These four specimens were categorised as HCV positive. Of the remaining 15 RIBA indeterminate specimens (11 from 1995, four from 1996) all were PCR negative. Fourteen (93%) of these indeterminate specimens were from the London area and 11 (73%) were from IDUs aged between 25–34 years.

There was a significantly higher prevalence of HCV in injectors in the London area compared to the geographical area outside of London both in 1995 (44.0% *v* 20.3%; p<0.0001) and 1996 (44.3% *v* 22.0%; p<0.0001). Multivariable logistic regression analysis demonstrated a significant variation in prevalence by centre (p=0.041), the centre variation being largely explained by the significantly higher prevalence seen in London. The majority of infections were in males in both 1995 (65.5%; 150/229) and 1996 (69.7%; 182/261); however, this difference was not significant after controlling for all other factors (p=0.62). In the combined years prevalence increased with age to peak in those aged between 35–44 years in both males and females. In those aged under 20 years prevalence was 10.5% (8/76), compared to 17.4% (48/276) in those aged 20–24 years, 38.2% (247/646) in those aged 25–34 years, 56.6% (155/274) in 35–44 year olds, and 56.1% (32/57) in those aged 45 years and over. There was a highly significant variation in prevalence by age (p<0.0001).

Variation by sexual orientation was highly significant (p=0.0004). In those injectors identifying themselves as heterosexual prevalence was 39.9% (198/496) in 1995 compared to 39.2% (227/579) in 1996. For the homosexual and bisexual injecting drug user group prevalence was 24.8% (31/125) and 26.0% (33/127) for 1995 and 1996, respectively. After controlling for all factors there was no significant difference in prevalence by country of birth (p=0.52). Anti-HIV-1 prevalence in IDUs from both years was 4.8% (64/1329). In 1995 the prevalence of anti-HIV in HCV positive specimens was 7.9% (18/229) compared to 6.5% (17/261) in 1996.

Table 3 Multivariable analysis for all GUM clinic attenders in 1995

Factor	Level	Odds ratio (95% CI)	Change in deviance (d/f) p value
Centre*	E	1.00 (baseline)	<0.0001
	A	0.71 (0.35 to 1.42)	
	B	1.37 (0.78 to 2.40)	
	C	0.62 (0.32 to 1.18)	
	D	0.79 (0.26 to 2.43)	
	F	1.14 (0.64 to 2.03)	
	G	0.84 (0.41 to 1.66)	
	H	1.15 (0.42 to 3.13)	
	I	0.42 (0.17 to 1.00)	
	J	0.51 (0.24 to 1.08)	
	K	0.26 (0.09 to 0.77)	
	L	0.31 (0.13 to 0.69)	
	M	0.22 (0.08 to 0.58)	
	N	0.45 (0.21 to 0.98)	
Age	<20	0.35 (0.13 to 0.94)	<0.0001
	20–24	1.00 (baseline)	
	25–34	2.71 (1.78 to 4.11)	
	35–44	4.66 (3.00 to 7.24)	
	45+	4.30 (2.52 to 7.32)	
Country	Abroad	1.00 (baseline)	0.98
	UK	0.97 (0.70 to 1.36)	
	Unknown	0.99 (0.52 to 1.87)	
IDU	No	1.00 (baseline)	<0.0001
	Yes	98.0 (72 to 134)	
Gender	Female	1.00 (baseline)	0.71
	Male	0.95 (0.71 to 1.26)	
Sexual orientation	Heterosexual	1.00 (baseline)	0.0013
	Homosexual	0.55 (0.37 to 0.80)	
HIV status	Negative	1.00 (baseline)	0.08
	Positive	1.74 (0.93 to 3.27)	

*Centres A–G based in London.

HCV genotyping and serotyping

Specimens from IDUs from 1995 and 1996 were combined. A total of 78 specimens from both years, 59 from selected anti-HCV positive injecting drug users and 19 RIBA indeterminate injecting drug users were tested for HCV RNA by PCR. Thirty eight (64.4%) of the 59 positive specimens and four (21.1%) of the 19 indeterminate specimens were found to be PCR positive. Genotyping identified type 3a as the most prevalent genotype (42.8%) followed by genotype 1a (28.6%). The number of specimens genotyped was too small to demonstrate significant differences by age, area, or over time.

Of the overall 349 HCV positive specimens collected in 1995 (inclusive of the injectors), 175 (50.1%) were tested by PCR, of which 117 (66.9%) were found to contain HCV RNA. Genotyping of these specimens identified type 3a as the most

Table 4 Comparison of serotyping and genotyping results in all GUM attenders (1995–6)

Serotype	Genotype 1a	1a/1b	1b	2a	2b	3a	3b	4	PCR negative	Total
1	32	2	13	0	0	1	0	0	5	53
1 and 3	0	0	0	0	0	1	0	0	0	1
2	0	0	0	4	2	0	0	0	2	8
3	0	0	0	0	0	29	1	0	3	33
4	0	0	0	0	0	0	0	1	1	2
Untypeable	0	0	3	1	2	10	0	1	7	24
Total	32	2	16	5	4	41	1	2	18	121

common genotype (37.6%), followed by type 1a (27.4%) and then 1b (19.7%). There is no evidence of different genotypes in different age groups (p=0.26). Grouping genotypes into types 1, 2, and 3 showed that there is no significant variation either by geographical area (p=0.19) or by history of injecting drug use (p=0.19).

Of the total of 610 HCV positive specimens from both years in non-injectors and injectors, 121 were serotyped of which 103 (85.1%) were from PCR positive specimens and 18 (14.9%) from PCR negative specimens. Twenty four specimens (17 PCR positive and seven PCR negative) were untypeable (table 4). By serotyping the majority were type 1 (46.6%), followed by type 3 (29.1%), type 2 (5.83%), type 4 (0.97%), and one reactive as both 1 and 3.

There was a high degree of concordance between serotype and genotype (table 4). All but one of the 48 type 1 serotypes had corresponding genotypes of 1a, 1a/1b, or 1b. The remaining type 1 serotype corresponded to a 3a genotype. All of the type 3 serotypes corresponded to either genotype 3a or 3b, serotype 2 to either 2a or 2b, and the single serotype 4 to genotype type 4. The specimen with the mixed 1 and 3 serotype genotyped as 3a only.

DISCUSSION

The overall prevalence of HCV in GUM clinic attenders in 1995 (adjusted for differential sampling by age, sex, sexual orientation, and injecting drug use) was 1.03%. The prevalence of hepatitis C was strongly related to age and to geographical area, with higher hepatitis C positivity in the London area than the rest of England and Wales. The adjusted prevalence of infection in GUM clinic attenders who did not report injecting drug use was low (0.65%) and suggests that the risk of sexual transmission of hepatitis C virus infection in the United Kingdom is low. The pattern of age specific hepatitis C prevalence rates in clinic attenders who did not report injecting resembles that for injectors. Hepatitis C positivity is also higher in the London area. As the prevalence of injecting drug use is higher in the London area,[17] this may reflect limited sexual transmission from drug users or undisclosed drug use. The risk factors for hepatitis C in UK GUM clinics differ from those for HIV, where most infection occurs in homosexual and bisexual males in London. Because of this, the number of co-infections with hepatitis C and HIV is low.

Reports of confirmed hepatitis C infection from laboratories in England and Wales suggest that the virus is not commonly acquired sexually.[18] This is supported by the low prevalence of infection in clinic attenders who did not report injecting drug use in this survey. It has been suggested that among sexually transmitted disease clinic attenders, co-infection with HIV or other sexually transmitted infections may increase the rate of sexual transmission of HCV.[6 17] This is not supported by this survey or by previous studies among females in a London GUM clinic,[20] and of female sex workers in London.[21] A study of GUM clinic attenders in Scotland found overall a low prevalence of antibody to hepatitis C virus in non-injectors,[22] but a high prevalence in clinic attenders that had injected drugs. These authors concluded that the probability of the hepatitis C virus being acquired through sexual intercourse is extremely low. A study of sexually transmitted disease clinic attenders in the United States found an overall antibody prevalence to hepatitis C virus of 7.7%.[23] Hepatitis C infection, was however, mainly associated with injecting drug use and the authors concluded that sexual transmission occurred infrequently. The rate of antibody positivity to hepatitis C virus has been reported not to exceed 1% in the spouses of hepatitis C virus infected haemophiliacs.[24] A study of couples infected with the virus also suggests that overestimation of the risk of sexual transmission masks transmission by other parenteral routes.[25]

Furthermore, most evidence suggests that hepatitis C is not readily spread by sex between men. A cohort analysis of European homosexual men comparing the estimated incidence of hepatitis C, hepatitis B, and HIV suggested that sexual transmission of hepatitis C was a rare event.[26] Our study confirms the low prevalence of hepatitis C in homosexual men attending GUM clinics. The lack of overlap between the HIV and hepatitis C epidemics in the United Kingdom is also emphasised by the lower prevalence of hepatitis C in homosexual/bisexual injecting drug users than in heterosexual injectors. A higher hepatitis C prevalence was also found in heterosexual injectors in Australia compared with homosexual IDUs.[27] In the latter study, hepatitis C prevalence was also higher in opiate users than in stimulant users and the differences in UK prevalence may reflect the different pattern of drug use in homosexual men. The lower prevalence may also be due to homosexual men adopting safer injecting practices than heterosexuals because of heightened awareness of the risk of HIV.

In this study, hepatitis C prevalence was highest among clinic attenders who reported injecting drug use; 37% of attenders in both 1995 and 1996 were hepatitis C positive. The use of needle exchanges in England may explain the relatively low prevalence observed in our study, particularly in younger IDUs. Prevalence of hepatitis C in IDUs was strongly related to age, both inside and outside of the London area, as described in a previous Australian study.[27] It is likely that the increase with age reflects increased duration of drug use. A study from Spain found that duration of drug use was the only drug related variable strongly associated with anti-HCV prevalence.[28] The presence of hepatitis C was also associated with duration of injecting drug use and frequency of needle sharing in an Italian study.[29]

The most common hepatitis C genotypes in GUM clinic attenders are 1a and 3a; genotype 4 was rare. Mixed infections were rarely identified with only two specimens containing a mixture of genotypes 1a and 1b. No significant differences were shown in genotypes by age and the distribution is similar to that described previously in the United Kingdom. A

Key messages

- There is little evidence of sexual transmission of HCV among groups at risk from sexually transmitted infections
- The overall prevalence of antibody to the hepatitis C virus is low in non-drug injecting GUM clinic attenders
- Most of the HCV infections in GUM clinic attenders have been acquired by injecting drug use

study from the north east of England found that most of the patients genotyped were type 1 (69%) followed by genotype 3 (21%).[30] A later UK study from a number of risk groups found that the majority of hepatitis C infections were types 1a (32%), 1b (15%), and 3a (37%),[16] and genotype distribution was similar in all groups except haemophiliacs. The findings of this survey are also similar to those from a number of European countries.[31] It has been suggested that genotypes 1a and 3a were introduced into Europe by needle sharing among IDUs.[31] The consistency of the hepatitis C genotype distribution in all the specimens typed suggests the predominance of a common transmission route, most probably injecting drug use.

This study has demonstrated a high degree of correlation between genotyping and serotyping methods. Serotyping may give inaccurate results because of cross reactivity between types and false negative results because of a lack of sensitivity.[32 33] Serotyping may also be unsuitable for specimens from immunosuppressed patients as they may have insufficient antibody for detection.[32] Concordance between serotyping and genotyping, at least for types 1 to 3, however, was high in our study. It is apparent that for epidemiological purposes hepatitis C types can be established by methods based on serological typing. Advantages of serotyping include its speed, ease of use, and its ability to type anti-HCV positive/RNA negative specimens. Serological assays are at present, however, unable to differentiate between subtypes.

It is apparent that, in the United Kingdom, injecting drug use is the main source of hepatitis C infections and that sexual transmission contributes little to the pool of infected individuals. The potential for increased transmission of hepatitis C through the sharing of injecting equipment still remains. Control of hepatitis C infection in England and Wales will therefore depend upon continuing to aim prevention programmes at IDUs.

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CONTRIBUTORS

MAB, MER, JVP, and CGT designed the study and applied for funding; CM and JAN supervised the archive construction; JVP developed the laboratory methods for hepatitis C antibody testing and, with JAN, supervised the antibody testing and serotyping carried out by LD; KAH carried out the PCR testing and genotyping supervised by CGT; JAN and MAB supervised the data collection; MAB did the epidemiological analysis and NJA did the statistical analysis; MAB and MER wrote the paper with contributions from all authors.

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ECHO

Vaginal leucocytes predict bacterial infection in prepubertal girls

Please visit the Sexually Transmitted Infections website [www.stijournal.com] for link to this full article.

Doctors managing vulvovaginitis before puberty recommend microscopic examination of vaginal fluid for leucocytes at the first visit, with microbiological investigation. Finding leucocytes raises the chances of finding bacterial pathogens, they say.

The authors carried out a retrospective review of girls aged 2–12 years with symptoms of vulvovaginitis. Sexual abuse was not suspected. Vaginal discharge was the commonest symptom, present in 92% of 80 girls. Vaginal secretions were collected aseptically for microscopic examination, Gram staining, and culturing to isolate candida and bacteria.

Bacterial infections occurred in 29 (36%) of all girls, 59% of them with group A β haemolytic streptococci, 24% with *H influenzae*, and 24% with *S aureus*—10% alone and 13% in mixed infections. Candida was not isolated. Twenty five girls with symptoms and bacterial infections received antibiotics and their infection resolved.

Leucocytes were seen in vaginal fluid from 24/29 girls with cultured pathogens and 21/51 without, a sensitivity of 83% and a specificity of 59% for bacterial infection.

Vulvovaginitis is the commonest gynaecological problem in this group. While many girls have no specific cause identified, vulvovaginitis can result from infection with specific bacterial pathogens. The authors point to drawbacks to their study, specifically not screening for sexually transmitted pathogens, on the assumption that the girls had not been abused, and the lack of a control group or repeat screening after antibiotic treatment.

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Lack of evidence for sexual transmission of hepatitis C virus in patients attending STD clinics in Pune, India

The presence of hepatitis C virus (HCV) RNA in semen among two of six (33%) HIV negative and six of 15 (40%) HIV infected males, reported recently suggests that HIV may facilitate genital shedding and subsequent sexual transmission of HCV.[1] We determined HCV prevalence and examined evidence for its sexual transmission in a cohort of STD patients with observed HIV prevalence of 21.2%.

Consecutive serum samples (n = 9141) collected between January 1994 and December 1999 were batched, pooled, and tested for anti-HCV antibody (Ortho HCV 3.0, Ortho-clinical Diagnostic, Germany). As previously described,[2] 25 µl aliquots of five samples were pooled and 20 µl of each pool were screened. Samples from positive pools were then tested individually. Positive sera were tested by HCV RNA polymerase chain reaction (PCR) using standard primers.[3] HIV antibody status of each sample was ascertained using the algorithm described previously.[4] Data were analysed using statistical package SPSS version 10.0. This study was a part of a prospective cohort study that was approved by ethics committee/institutional review boards of the collaborating organisations and blood samples were collected after counselling and informed consent.

Overall prevalence of anti-HCV antibodies was 0.68% (62/9141, 95% CI 0.52 to 0.87). The prevalence among HIV infected individuals (1.5%, 95% CI 1.0 to 2.1) was higher (p = <0.01) than that in those not infected (0.44%, 95% CI 0.3 to 0.6). The annual anti-HCV antibody prevalence rate between 1994 and 1999 was 0.57%, 0.46%, 1.10%, 0.81%, 0.37%, and 0.61%, which did not change significantly over time (table 1). Of the 55 anti-HCV antibody positive sera tested, 27 (49%) were HCV RNA PCR positive.

Univariate analysis revealed that history of past or current STD was not associated with HCV, whereas female sex (OR = 2.07, 95% CI 1.17 to 3.66), prevalent HIV infection (OR = 3.38, 95% CI 2.05 to 5.58), history of tattoo (OR = 2.18, 95% CI 1.31 to 3.63), and being a sex worker (OR = 2.35, 95% CI 1.27 to 4.35) were significantly associated with presence of anti-HCV antibody. However, multivariate analysis revealed that prevalent HIV infection and tattooing increased the likelihood of presence of anti-HCV antibodies by 3.08-fold (AOR 3.08, 95% CI 1.86 to 5.11, p = <0.00) and 1.87-fold (AOR 1.87, 95% CI 1.12 to 3.13, p = 0.017), respectively (table 1).

Table 1 Characteristics of study participants and association with prevalent anti-HCV antibody

Variable	No	Anti-HCV antibody positive (%)	Unadjusted OR (95% CI)	p Value	Adjusted OR (95% CI)*	p Value*
1 Year screened					Not included in multivariate analysis	
1994	1901	11 (0.57)	1 (Referent)			
1995	1933	9 (0.46)	0.80 (0.33 to 1.94)	0.628		
1996	1997	22 (1.10)	1.91 (0.93 to 3.96)	0.08		
1997	1109	9 (0.81)	1.41 (0.58 to 3.40)	0.45		
1998	1064	4 (0.37)	0.65 (0.21 to 2.04)	0.459		
1999	1135	7 (0.61)	1.07 (0.41 to 2.76)	0.895		
TOTAL	9139	62 (0.67)				
2 Males who had contact with sex worker					Not included in multivariate analysis	
YES	6281	40 (0.69)	1.63 (0.69 to 3.86)	0.259		
NO	1535	6 (0.39)	1 (Referent)			
TOTAL	7816	46 (0.58)				
3 Sex						
Women	1323	16 (1.21)	2.07(1.17 to 3.66)	0.013		0.469
Men	7816	46 (0.59)	1 (Referent)			
Total	9139	62 (0.67)				
4 Sex worker						
Yes	933	13 (1.39)	2.35 (1.27 to 4.35)	0.006		0.231
No	8206	49 (0.59)	1 (Referent)			
Total	9139	62 (0.67)				
5 HIV serostatus						
Pos	2102	31 (1.47)	3.38 (2.05 to 5.58)	<0.001	3.08 (1.86 to 5.11)	<0.001
Neg	7037	31 (0.44)	1 (Referent)		1 (Referent)	
Total	9139	62 (0.67)				
6 History of tattoo						
Yes	3703	37 (0.98)	2.18 (1.31 to 3.63)	0.003	1.87 (1.12 to 3.13)	0.017
No	5424	25 (0.46)	1 (Referent)		1 (Referent)	
Total	9127	62 (0.67)				

*Multivariate analysis was done using binary logistic regression by forward LR method.
OR = odds ratio.

A rapid spread and high HCV prevalence of 80% has been reported recently among a cohort of injecting drug users from Kolkata, India.[5] In contrast, we observed a low and stable prevalence of anti-HCV antibody among STD clinic attendees over the past 6 years in an urban setting where HIV transmission was predominantly sexual. Given that a high HIV prevalence was reported among female sex workers (FSWs) in this population[4] and about 70% of males attending STD clinic had visited FSWs in the past 3 months, stable HCV prevalence over 6 years suggests that HCV is not efficiently transmitted sexually. Additionally, no association was found between past or current STD and HCV prevalence, and a high prevalence and incidence of HBV, a known sexually transmitted infection, have been reported in this population.[6] Our analysis failed to identify any evidence that could support sexual transmission of HCV.

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Monosymptomatic hypochondriacal psychosis

Dr O'Mahony illustrates in his literary and graphic way the difficulties associated with dealing with this condition (from which his patient was almost certainly suffering).[1] It is good to know that his hospital is taking seriously the issue of actual or threatened violence to staff. Having had several similar cases over the past couple of years, including one who eventually committed suicide, I have been able to make appropriate arrangements with a psychiatrist who was unequivocal in his advice that he should be in on a subsequent consultation right from the start and be introduced to the patient as a double consultation. The ethics of this include the fact that such delusional patients are, of course, psychotic and unable to bring rational decision making processes to the problem.

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Reinfection is common after rechallenge of previously infected chimpanzees, although manifestations of HCV infection are generally reduced in secondary infections. Reinfections with both homologous and heterologous HCV strains indicate that poor immunity is not only related to antigenic variation among different strains of HCV.[52, 74] Chimpanzees differ though from humans in that they make a weak (if any) humoral immune response to the structural proteins.[39]

Another host response to HCV is the induction of interferon.[39]

However, HCV persists despite the induction of a broad humoral and cell-mediated immune response. One mechanism of HCV persistence occurs via the generation of immune-escape mutants.[39]

Immunosuppressed organ recipients infected with HCV often do not seroconvert to the nonstructural proteins, but they do to envelope glycoproteins and the nucleocapsid proteins.[39]

HCV readily causes a persistent infection, although some individuals spontaneously control infection. 'Successful' immune responses appear to be multi-specific and sustained-including a major role for CD4(+)T cells. Some antiviral CD8(+)T cells show reduced capacity to secrete antiviral cytokines either temporarily ('stunning') or in the long term ('stunting'). The co-ordination of multiple immune effector functions may be required to gain control of HCV.[29, 47]

Prevalence

HCV is parenterally transmitted and has been found in every part of the world where it has been sought.[74, 101]

Prior to donor screening for anti-HCV (1992), HCV was the most common cause of post-transfusion hepatitis worldwide, accounting for about 90% of this disease in the USA.[52]

Studies carried out in the 1970s suggested that about 7% of transfusion recipients developed NANB hepatitis, and that up to 1% of blood units might contain the responsible virus.[52] The introduction of anti-HCV screening has reduced the transmission by up to almost 100%.[52, 84, 95]

Currently in the USA HCV accounts for about 20% of acute viral hepatitis cases, of which less than 5% are associated with blood transfusion. The prevalence of anti-HCV is highest in injecting drug users and haemophilia patients (up to 98%)33, 54, 65, 76, 85, 105, highly variable in haemodialysis patients (<10%-90%)12, 15, 42, 59, 66, 81, 83, low in heterosexuals with multiple sexual partners, homosexual men, healthcare workers and family contacts of HCV infected persons (1%-5%), and lowest in volunteer blood donors (0.3%-0.5%). In the general population it varies (0.2%-18%).[52, 102]

Areas of higher prevalence include countries in the Far East, Mediterranean countries and certain areas in Africa and eastern Europe.[39, 41, 52, 104]

World Health Organization
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whocdscsrlyo2003/en/index3.htr

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Ways You CAN Get Hepatitis C

- Sharing needles (works) to use drugs.
- Blood transfusion before 1992.
- Sharing drug-use paraphernalia like filters or straws.
- Tattooing and body piercing.

Ways You CAN Get Hepatitis C

- Needle-stick accidents.
- Getting someone else's blood inside you.
- Sharing objects that might carry blood, like razors and toothbrushes.

Department of Veterans Affairs   HCRC VA Hepatitis C Resource Center   www.hepatitis.va.gov

June 2005

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Conference Reports for NATAP

AASLD (American Association for the Study of Liver Diseases)

Back

November 9-13, 2001, Dallas

abstract 177. TIMING THE ANCESTRY OF HEPATITIS C VIRUS GENOTYPE 1A STRAINS IN THE UNITED STATES: the number of mutations don't seem to be associated with disease progression

Yasuhito Tanaka, National Inst of Health, Bethesda, MD; Masashi Mizokami, Nagoya City Univ Med Sch, Nagoya Japan; James W Shih, Harvey J Alter, National Inst of Health, Bethesda, MD

Background/aims: Long-term, prospective studies demonstrate that hepatitis C virus (HCV) is generally a slowly progressive disease that causes relatively low mortality and overt morbidity during the first 25 years after infection. This study investigates the molecular evolution of HCV in serial samples from patients with long-term chronic infection.

Materials and Methods: Serial samples were obtained from subjects enrolled in prospective studies of transfusion-associated hepatitis conducted at the NIH since 1972 and from anti-HCV positive blood donors whose exposure history suggested infection of >20 years duration. 37 serial samples (2-7 serial samples each) from 11 subjects with HCV genotype 1a, which is the most prevalent in USA, were studied. The sample intervals for each subject ranged from 7-21.6 (mean, 14.6±5.4) years. Some of the samples were obtained within the first 6 months of infection. Sequences in the core, E1, E2, and NS5B regions of each isolate were determined directly or after cloning and then the numbers of nucleotide substitutions per site were estimated and the genetic distances determined.

Results: A phylogenetic ancestral comparison using these long-term serial sequences showed mutation rates that ranged from 0.491 to 0.949 (mean, 0.777) 10(3) bases per site per year in E1, 1.163-2.624 (mean, 2.010) 10(3) in E2 and 0.183 to 0.983 (mean, 0.531) 10(3) in NS5B region. These rates of HCV molecular evolution appear to be slower than previously reported. The origin of the major current ancestral sequence of HCV genotype 1a is estimated to have occurred around 1930 in the USA as also supported by a maximum-likelihood phylogenetic analysis. The divergent ancestral points calculated for each subject suggests that most HCV 1a expanded in the US population between 1960 and 1980, consistent with increased illegal drug use during that period. Among these subjects, there was no apparent correlation between the individual mutation rate and clinical outcome; for instance one patient with mild, non-progressive chronic hepatitis had the most rapid evolutionary rate and one patient with cirrhosis had a slow evolutionary rate. In addition, some subjects indicated different mutation rates during the course of infection.

Conclusions: Current genotype 1a appears to have emerged in the USA around 1930 and to have further diversified in the 1960s and 70's. The overall mutation rate may be slower than previously reported and may vary at different stages of infection. There is no apparent association between HCV mutation rate and the clinical course of hepatitis C, but more subjects need to be studied over longer intervals to better elucidate the effect of viral mutation on clinical outcome.

* -SEE PG 2 (83) *
-SEE PG 4 (85)

Epidemiology of Hepatitis C Virus (HCV) Infection

Shamweel Ahmad Ph.D[1], Sajad Ahmad Salati MRCS[2], Essam H. Mattar Ph.D[3], Abdul Malik Hussain Al-Sabban M.B.B.S.[4] and Abubaker M. Hamad M.Sc[1]

Summary:
Hepatitis C virus (HCV) infection is a major global public health problem. Approximately 3 percent of the world's population is infected with the Hepatitis C virus (HCV) with the highest prevalence rates noted in Africa and Asia and as many as 4 million new infections occur annually. Incidence rates across the world fluctuate and are difficult to calculate given the asymptomatic, often latent nature of the disease prior to clinical presentation. Of those exposed to HCV, almost 85% of cases can become chronic and experience serious long-term complications, such as hepatic cirrhosis or carcinoma. HCV infection is recognized as the most common blood-borne infection in injection drug users (IDU). HCV infection also increases the number of complications in persons who are co-infected with HIV. This article reviews an overview of the prevalence, genotype data, transmission risk and prevention.

Prevalence:
Since its discovery in 1989, hepatitis C virus (HCV) has been shown to be the causative agent of most cases of parenteral non-A, non-B hepatitis.[1] In patients with chronic HCV HCV infection, especially those who have chronic active hepatitis with cirrhosis, the virus has been directly linked to the development of hepatocellular carcinoma (HCC).[2] An estimated 170 million people worldwide have hepatitis C virus (HCV) infection.[3-4] (Table-I). Although the virus is found throughout the world, the various genotypes of hepatitis C are distributed differently.[5] The prevalence of HCV infection varies throughout the world, with the highest number of infections reported in Egypt. The use of parenteral antischistosomal therapy in Egypt is thought to have contributed to a prevalence of antibodies against HCV in various regions ranging from 6 to 28 percent (mean 22 %).[6] In the United States, 1.8 % of population is positive for HCV antibodies.[7, 8] Between Central and South America, the estimated prevalence of HCV in 2001-2002 was 6.3 %.[8] In Europe, general prevalence of HCV is about 1 % but varies among the different countries.[9] Prevalence rate of HCV antibody is high in Italy (3.2%),[10] and low in Hungary (0.73%).[11] The estimated prevalence in Australia has been reported as 2.3%.[12] Rates of 1.6% in Ethiopia and 0.9% in Kenya.[13-14] have been reported. The prevalence rates of HCV, 0.49% in Japan,[15] 1% in China,[16-17] 1.6% in Malaysia[18] and 0.54% in Singapore[19] have been reported. In Thailand, the prevalence rates are (3.2%-5.6%).[20] Prevalence rate is 4.5% in Pakistan,[21] 1.8% in SaudiArabia[22] and 2.1% in Yemen.[23] In New Delhi, India the prevalence rate is 1.85%.[24] HCV infection is expected to be even a great public health problem in Egypt, where 10% - 20% of the general population is infected.[25-28]

Genotypes of HCV:
On the basis of phylogenetic analysis of nucleotide sequences, multiple genotypes and subtypes of HCV have been identified. The complete HCV genome was determined by Choo *et al* in 1991[29]. After that several HCV isolates from different parts of the world were obtained and sequenced. This led to the identification of several different types that may differ from each other by as much as 33% over the whole viral genome. In 1994, at the 2nd international conference of HCV and related viruses, a consensus nomenclature system was proposed that is to be used in future studies of HCV genotypes, subtypes and quasispecies.[30] (Table-II). According to this system, HCV is classified on the basis of the similarity of nucleotide sequence into major genetic groups designated genotypes. HCV genotypes are numbered (Arabic numerals) in the order of their discovery. The more closely related HCV strains within some types are designated subtypes, which are assigned lower case letters (in alphabetic order) in HCV genotypes are important

epidemiological markers and may alter the sensitivity and specificity of diagnostic assays for detection of HCV. HCV genotyping in combination of other markers, such as quantitative evaluation of HCV RNA may be beneficial in the management of chronic hepatitis C infection and the selection of candidates for interferon treatment. Genotype 1 is less responsive to alpha-interferon therapy compared to genotypes 2 and 3. It is therefore important to track the different genotypes of the HCV virus.[31,32] Epidemiologically and clinically 11 genotypes and more than 70 subtypes have been identified. Substantial regional differences appear to exist in the distribution of HCV genotypes.[33] (Table-III). Genotype 1b is the most common genotype globally and is principally transmitted through contaminated blood products. Although HCV genotypes 1, 2 and 3 appear to have a worldwide distribution, their relative prevalence varies from one geographical area to another. Although the impact of HCV heterogeneity and genotypes on day to day clinical management of chronic HCV infection has not been established, its role as an epidemiological marker has been clearly shown. The exact role of genotypes in the clinical presentation, progression of liver disease, outcome of HCV infection or incidence of HCC are much less well understood than their role as an epidemiological marker. The geographical distribution and diversity of HCV genotypes may provide clues about the historical origin of HCV.[34] The presence of numerous subtypes of each HCV genotype in some regions of the world, such as Africa and Southeast Asia, may suggest that HCV has been endemic for a long time. Conversely, the limited diversity of subtypes observed in the United States and Europe could be related to the recent introduction of these viruses from areas of endemic infection.

Transmission:

Risk factors associated with HCV infection include injection drug use (or intranasal if using a blood contaminated device), receipt of blood products, long term haemodialysis, organ transplantation, receipt of tattoo from an unsanitary facility, vertical transmission during pregnancy and sexual or nosocomial exposure.[35-37] Sexual transmission of the virus appears to be inefficient means, certainly less efficient than HIV-1; [38] whether this is due to the low levels of the virus in genital fluids and tissues or to a lack of appropriate target cells in the genital tract is not known. Maternal fetal transmission occurs but is infrequent and often associated with coinfection with HIV-1 in the mother.[39-40] Co infection with HIV-1 appears to increase the risk of both sexual and maternal fetal transmission of HCV.[39,41] Virus can be recovered from saliva of infected persons[42] and although chimpanzees have been experimentally infected by the injection of saliva from HCV-infected persons,[43] casual household contact and contact with the saliva of infected persons also appear to be very inefficient modes of transmission.[42,44] Nosocomial transmission has been documented, such as from patient to patient by a colonoscope,[45] during dialysis,[46] and during surgery.[47-48] Needle stick injuries in the health care setting continue to result in nosocomial transmission of the virus. The rate of transmission after a needle stick injury, involving known blood, to be ranged from 0% to 10% in various studies.[36,49] A rough estimate of the comparative risks of transmission through a needle stick injury is provided by the rules of three: HBV is transmitted in 30% of exposures, HCV in 3%, and HIV-1 in 0.3%. These numbers are most likely influenced by the size of the inoculums, the size of the needle and depth of inoculation.

Prevention:

There is no vaccine against HCV. Research is in progress but the high mutability of the HCV genome complicates vaccine development. Lack of knowledge of any protective immune response following HCV infection also impedes vaccine research. The value of prophylactic immune globulin (IG) is not clear. [50,51] Post exposure prophylaxes with IG are not effective in preventing infection.

In absence of a vaccine, all precautions to prevent infection of HCV should target reduction of transmission of the virus. The only means of protection are the implementation universal precautions and safe injection practices. Screening and treatment of blood products is the only way to prevent transfusion associated cases.[52,53] Needle exchange programmes for injecting drug users may help to limit the spread of HCV infection.[54] Prevention should target those at risk of acquiring the virus and should involve providing education , risk reduction counseling, HCV screening and substance abuse treatment. To date, screening the general population for HCV infection has been controversial.

HCV carriers should be strongly discouraged from drinking alcohol because there is evidence that acts as a cofactor in developing more severe liver injury. [50, 55, 56] Patients who do not have serologic evidence of immunity to hepatitis A and B should be vaccinated, [57- 59] especially since infection with the hepatitis A virus in patients with chronic HCV may result in a more severe infection than in patients without HCV. Comprehensive strategy to prevent and control hepatitis C virus (HCV) infection and HCV-related disease [60-61]:

- Primary prevention activities include
  - Screening and testing of blood, plasma, organ, tissue, and semen donors
  - Virus inactivation of plasma-derived products
  - Adequate sterilization of reusable material such as surgical or dental instruments
  - Risk-reduction counseling and services
  - Implementation and maintenance of infection control practices
  - Needle and syringe exchange programs
- Secondary prevention activities include
  - Identification, counseling, and testing of persons at risk
  - Medical management of infected persons
- Professional and public education
- Surveillance and research to monitor disease trends and the effectiveness of prevention activities and to develop improved prevention methods. Prevention of spread of infection should be the main goal at the current time until cost effective therapies become available.[62]

Table I Global prevalence of HCV

WHO Region	Total population (Millions)	Hepatitis C Prevalence rate %	Infected population (Millions)
Africa	602	5.3	31.9
Americas	785	1.7	13.1
Eastern Mediterranean	466	4.6	21.3
Europe	858	1.03	8.9
South-East Asia	1500	2.15	32.3
Western Pacific	1600	3.9	62.2
Total	5811	3.1	169.7

Table II Common Terminology used in studies related to HCV genomic heterogeneity

Terminology	Definition	% Nucleotide similarity*
Genotype	Genetic heterogeneity among different HCV isolates	65.7 – 68.9
Subtype	Closely related isolates within each of the major genotypes	76.9 – 80.1

Quasispecies	Complex of genetic variants within individual isolates	90.8 - 99

* %Nucleotide similarity refers to the nucleotide sequence identities of the full length sequences of the HCV genome.[30]

Table III Epidemiology of the HCV genotypes

HCV Genotypes*	Geographical distribution	Clinical Significance
Ia	United States Northern Europe	Most common genotypes in the United States.\ May have a more aggressive clinical course than other genotypes and less likely to respond interferon treatment.
Ib	United States, Europe, Japan	Often transmitted by transfusion; may have a more aggressive clinical course than other genotypes and higher incidence of HCC; associated with recurrent hepatitis in patients with liver transplants. Less likely to respond interferon treatment.
2a, 2b	Europe, Japan, North America	With genotype 3, excellent treatment responses
2c	Northern Italy	
3a	India, Europe, United States	Associated with intravenous drug use; often associated with hepatic steatosis
4	North Africa, Middle East	
5	South Africa	
6	Hong Kong	
7, 8, 9	Vietnam	
10, 11	Indonesia	

* There has been disagreement about the number of genotypes into which HCV isolates should be classified. Investigators have proposed that genotypes 7 through 11 should be regarded as variants of the same group and classified as a single genotype, type 6. [33]

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Distribution of HCV genotypes among blood donors, patients with chronic liver disease, hepatocellular carcinoma, and patients on maintenance hemodialysis in Korea.

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Hepatitis C virus (HCV) is a single-stranded RNA virus related to the Flaviviridae family, and striking nucleotide sequence diversity has been reported among HCV isolates from different geographic areas. To study the distribution HCV genotypes among disease group in Korea, we subtyped HCV using the method of Okamoto et al. [(1992a): Journal of General Virology 73:673-679] and the reverse hybridization method (INNO-LiPA) on 138 patients who were HCV polymerase chain reaction (PCR)-positive: 30 blood donors, 30 with hepatocellular carcinoma (HCC), 33 with chronic hepatitis, 15 with liver cirrhosis, and 30 patients on maintenance hemodialysis in Korea. In 30 blood donors, HCV genotype 1b was most dominant (80%), followed by genotype 2a (13.3%), and 2b (6.7%). In 30 HCC cases, HCV genotype 1b was less frequent (60%), compared to blood donors, followed by genotype 2a (33.3%), and unclassified (6.7%). In 33 chronic hepatitis cases, HCV genotype 1b was also dominant (63.6%), followed by genotype 2a (30.3%), and 1a (6.1%). In 15 patients with liver cirrhosis, HCV genotype 1b was also dominant (60%), followed by genotype 2a (33.3%), and 1a (6.7%). In 30 patients on maintenance hemodialysis, HCV genotype 1b was dominant (86.7%), followed by genotype 2a (13.3%). In conclusion, among 138 HCV PCR-positive patients, type 1b was the prevailing type (71%), followed by type 2a (23.9%), type 1a (2.1%), type 2b (1.5%), and unclassified (1.5%) in Korea. The prevalence of type 1b in blood donors (80%) was higher than in patients with liver disease (61.5%) and the prevalence of type 1b was the lowest in patients with HCC (60%).

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Hepatitis C virus genotypes in Korea and their relationship to clinical outcome in type C chronic liver diseases.

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OBJECTIVES: The relationship between HCV genotype and the development of more serious liver disease has not been clearly established. This study was to investigate the distribution pattern of HCV genotypes in Korea and their relationship to the viremic level and to progression of chronic liver disease.
METHODS: Study population was 217 patients with type C chronic liver disease. They were divided into 4 groups; 83 patients with near-normal ALT (group 1), 64 patients with elevated ALT (group 2), 20 patients with decompensated liver cirrhosis (group 3) and 50 patients with hepatocellular carcinoma (group 4). HCV genotypes were determined by reverse transcription polymerase chain reaction (RT-PCR) using mixed primer sets, and then the fidelity of genotyping was confirmed by cloning and sequencing. HCV RNA concentration was measured by quantitative competitive RT-PCR for 23 patients in group 2.
RESULTS: The genotypes could be determined in 166 (76%) out of 217 patients. Type 1b and type 2a were predominantly occurring over the other types in somewhat similar frequency (45% and 51%, respectively). The genotype distribution of type 1b and 2a among four different groups showed 42% and 54% in group 1, 49% and 45% in group 2, 53% and 47% in group 3 and 41% and 57% in group 4; thus there was no significant difference in genotype distribution among 4 different disease groups. However, the viremia levels in patients with genotype 1b infection were significantly higher than those with genotype 2a.
CONCLUSION: Genotype 2a infection is as prevalent as genotype 1b in Korea, and genotype 2a infection may pose no less risk for progression of disease despite lower replication level than genotype 1b infection.

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Conflict of Interest: None

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Colorado Immunization Manual

* SEE "SECTION - PAGE : 9-4" *

SECTION 9

Administration Techniques

SECTION 9

Administration Techniques

CONTENTS

ADMINISTRATION OF VACCINES

(MMWR February 8, 2002; 51 [RR-2]: 11–14)

Infection Control and Sterile Technique

Persons administering vaccines should follow necessary precautions to minimize risk for spreading disease. Hands should be washed with soap and water or cleansed with an alcohol-based waterless antiseptic hand rub between each patient contact. Gloves are not required when administering vaccinations, unless persons administering vaccinations are likely to come into contact with potentially infectious body fluids or have open lesions on their hands. Syringes and needles used for injections must be sterile and disposable to minimize the risk of contamination. A separate needle and syringe should be used for each injection. Changing needles between drawing vaccine from a vial and injecting it into a recipient is unnecessary. Different vaccines should never be mixed in the same syringe unless specifically licensed for such use.

Disposable needles and syringes should be discarded in labeled, puncture-proof containers to prevent inadvertent needle-stick injury or reuse. Safety needles or needle-free injection devices also can reduce the risk for injury and should be used whenever available (see Occupational Safety Regulations).

Recommended Routes of Injection and Needle Length

Routes of administration are recommended by the manufacturer for each immunobiologic. Deviation from the recommended route of administration might reduce vaccine efficacy (*53,54*) or increase local adverse reactions (*55–57*). Injectable immunobiologics should be administered where the likelihood of local, neural, vascular, or tissue injury is limited. Vaccines containing adjuvants should be injected into the muscle mass; when administered subcutaneously or intradermally, they can cause local irritation, induration, skin discoloration, inflammation, and granuloma formation.

Subcutaneous Injections

Subcutaneous injections usually are administered at a 45-degree angle into the thigh of infants aged <12 months and in the upper-outer triceps area of persons aged ≥12 months. Subcutaneous injections can be administered into the upper-outer triceps area of an infant, if necessary. A 5/8-inch, 23–25-gauge needle should be inserted into the subcutaneous tissue.

Intramuscular Injections

Intramuscular injections are administered at a 90-degree angle into the anterolateral aspect of the thigh or the deltoid muscle of the upper arm. The buttock should not be used for administration of vaccines or toxoids because of the potential risk of injury to the sciatic nerve (*58*). In addition, injection into the buttock has been associated with decreased immunogenicity of hepatitis B and rabies vaccines in adults, presumably because of inadvertent subcutaneous injection or injection into deep fat tissue (*53,59*).

For all intramuscular injections, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves and blood vessels or bone (*54,60–62*). Vaccinators should be familiar with the anatomy of the area into which they are injecting vaccine. An individual decision on needle size and site of injection must be made for each person on the basis of age, the volume of the material to be administered, the size of the muscle, and the depth below the muscle surface into which the material is to be injected.

Although certain vaccination specialists advocate aspiration (i.e., the syringe plunger pulled back before injection), no data exist to document the necessity for this procedure. If aspiration results in blood in the needle hub, the needle should be withdrawn and a new site should be selected.

Infants (persons aged <12 months). Among the majority of infants, the anterolateral aspect of the thigh provides the largest muscle mass and is therefore the recommended site for injection. For the majority of infants, a 7/8–1-inch, 22–25-gauge needle is sufficient to penetrate muscle in the infant's thigh.

Toddlers and Older Children (persons aged ≥12 months–18 years). The deltoid muscle can be used if the muscle mass is adequate. The needle size can range from 22 to 25 gauge and from 7/8 to 1¼ inches, on the basis of the size of the muscle. For toddlers, the anterolateral thigh can be used, but the needle should be longer, usually 1 inch.

Adults (persons aged >18 years). For adults, the deltoid muscle is recommended for routine intramuscular vaccinations. The anterolateral thigh can be used. The suggested needle size is 1–1½ inches and 22–25 gauge.

Intradermal Injections

Intradermal injections are usually administered on the volar surface of the forearm. With the bevel facing upwards, a 3/8–3/4-inch, 25–27-gauge needle can be inserted into the epidermis at an angle parallel to the long axis of the forearm. The needle should be inserted so that the entire bevel penetrates the skin and the injected solution raises a small bleb. Because of the small amounts of antigen used in intradermal vaccinations, care must be taken not to inject the vaccine subcutaneously because it can result in a suboptimal immunologic response.

Multiple Vaccinations

If ≥2 vaccine preparations are administered or if vaccine and an immune globulin preparation are administered simultaneously, each preparation should be administered at a different anatomic site. If ≥2 injections must be administered in a single limb, the thigh is usually the preferred site because of the greater muscle mass; the injections should be sufficiently separated (i.e., ≥1 inch) so that any local reactions can be differentiated (*55,63*). For older children and adults, the deltoid muscle can be used for multiple intramuscular injections, if necessary. The location of each injection should documented in the person's medical record.

Jet Injection

Jet injectors (JIs) are needle-free devices that drive liquid medication through a nozzle orifice, creating a narrow stream under high pressure that penetrates skin to deliver a drug or vaccine into intradermal, subcutaneous, or intramuscular tissues (*64,65*). Increasing attention to JI technology as an alternative to conventional needle injection has resulted from recent efforts to reduce the frequency of needle-stick injuries to health-care workers (*66*) and to overcome the improper reuse and other drawbacks of needles and syringes in economically developing countries (*67–69*). JIs have been reported safe and effective in administering different live and inactivated vaccines for viral and bacterial diseases (*69*). The immune responses generated are usually equivalent to, and occasionally greater than, those induced by needle injection. However, local reactions or injury (e.g., redness, induration, pain, blood, and ecchymosis at the injection site) can be more frequent for vaccines delivered by JIs compared with needle injection (*65,69*).

Certain JIs were developed for situations in which substantial numbers of persons must be vaccinated rapidly, but personnel or supplies are insufficient to do so with conventional needle injection. Such high-workload devices vaccinate consecutive patients from the same nozzle orifice, fluid pathway, and dose chamber, which is refilled automatically from attached vials containing ≤50 doses each. Since the 1950s, these devices have been used extensively among military recruits and for mass vaccination campaigns for disease control and eradication (*64*). An outbreak of hepatitis B among patients receiving injections from a multiple-use–nozzle JI was documented (*70,71*), and subsequent laboratory, field, and animal studies demonstrated that such devices could become contaminated with blood (*69,72,73*).

No U.S.-licensed, high-workload vaccination devices of unquestioned safety are available to vaccination programs. Efforts are under way for the research and development of new high-workload JIs using disposable-cartridge technology that avoids reuse of any unsterilized components having contact with the medication fluid pathway or patient's blood. Until such devices become licensed and available, the use of existing multiple-use–nozzle JIs should be limited. Use can be considered when the theoretical risk for bloodborne disease transmission is outweighed by the benefits of rapid vaccination with limited personnel in responding to serious disease threats (e.g., pandemic influenza or bioterrorism event), and by any competing risks of iatrogenic or occupational infections resulting from conventional needles and syringes. Before such emergency use of multiple-use–nozzle JIs, health-care workers should consult with local, state, national, or international health agencies or organizations that have experience in their use.

In the 1990s, a new generation of low-workload JIs were introduced with disposable cartridges serving as dose chambers and nozzle (*69*). With the provision of a new sterile cartridge for each patient and other correct use, these devices avoid the safety concerns described previously for multiple-use–nozzle devices. They can be used in accordance with their labeling for intradermal, subcutaneous, or intramuscular administration.

Methods for Alleviating Discomfort and Pain Associated with Vaccination

Comfort measures and distraction techniques (e.g., playing music or pretending to blow away the pain) might help children cope with the discomfort associated with vaccination. Pretreatment (30-60 minutes before injection) with 5% topical lidocaine-prilocaine emulsion (EMLA ® cream or disk [manufactured by

AstraZeneca LP]) can decrease the pain of vaccination among infants by causing superficial anesthesia (*74,75*). Preliminary evidence indicates that this cream does not interfere with the immune response to MMR (*76*). Topical lidocaine-prilocaine emulsion should not be used on infants aged <12 months who are receiving treatment with methemoglobin-inducing agents because of the possible development of methemoglobinemia (*77*). Acetaminophen has been used among children to reduce the discomfort and fever associated with vaccination (*78*). However, acetaminophen can cause formation of methemoglobin and, thus, might interact with lidocaine-prilocaine cream, if used concurrently (*77*). Ibuprofen or other nonaspirin analgesic can be used, if necessary. Use of a topical refrigerant (vapocoolant) spray can reduce the short-term pain associated with injections and can be as effective as lidocaine-prilocaine cream (*79*). Administering sweet-tasting fluid orally immediately before injection can result in a calming or analgesic effect among certain infants.

Nonstandard Vaccination Practices

Recommendations regarding route, site, and dosage of immunobiologics are derived from data from clinical trials, from practical experience, and from theoretical considerations. ACIP strongly discourages variations from the recommended route, site, volume, or number of doses of any vaccine.

Variation from the recommended route and site can result in inadequate protection. The immunogenicity of hepatitis B vaccine and rabies vaccine is substantially lower when the gluteal rather than the deltoid site is used for administration (*53,59*). Hepatitis B vaccine administered intradermally can result in a lower seroconversion rate and final titer of hepatitis B surface antibody than when administered by the deltoid intramuscular route (*80,81*). Doses of rabies vaccine administered in the gluteal site should not be counted as valid doses and should be repeated. Hepatitis B vaccine administered by any route or site other than intramuscularly in the anterolateral thigh or deltoid muscle should not be counted as valid and should be repeated, unless serologic testing indicates that an adequate response has been achieved.

Live attenuated parenteral vaccines (e.g., MMR, varicella, or yellow fever) and certain inactivated vaccines (e.g., IPV, 23-valent pneumococcal polysaccharide, and anthrax) are recommended by the manufacturers to be administered by subcutaneous injection. Pneumococcal polysaccharide and IPV are approved for either intramuscular or subcutaneous administration. Response to these vaccines probably will not be affected if the vaccines are administered by the intramuscular rather then subcutaneous route. Repeating doses of vaccine administered by the intramuscular route rather than by the subcutaneous route is unnecessary.

Administering volumes smaller than those recommended (e.g., split doses) can result in inadequate protection. Using larger than the recommended dose can be hazardous because of excessive local or systemic concentrations of antigens or other vaccine constituents. Using multiple reduced doses that together equal a full immunizing dose or using smaller divided doses is not endorsed or recommended. Any vaccination using less than the standard dose should not be counted, and the person should be revaccinated according to age, unless serologic testing indicates that an adequate response has been achieved.

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An outbreak of hepatitis B associated with jet injections in a weight reduction clinic.

Canter J, Mackey K, Good LS, Roberto RR, Chin J, Bond WW, Alter MJ, Horan JM.

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From January 1984 through November 1985, 31 clinical cases of hepatitis B occurred among attendees of a weight reduction clinic (clinic 1). Before the onset of illness, each case-patient had received a series of injections of human chorionic gonadotropin administered by jet injectors at clinic 1. Clinical history, risk factor assessment, serologic evaluation, and review of clinic injection records were obtained on 287 (84%) of 341 persons who had attended clinic 1 in the first 6 months of 1985. Of this cohort, 21% (60/287) had evidence of acute infection with hepatitis B virus (either documented clinical cases or antibody to hepatitis B core antigen, IgM positive). Of persons who had been given human chorionic gonadotropin at the clinic during the period studied, 24% (57/239) of those receiving human chorionic gonadotropin only by jet injector experienced acute hepatitis B virus infection. None of the 22 persons who had received injections only by syringe experienced hepatitis B virus infection. Stopping the use of the jet injectors on July 2, 1985, at clinic 1, was associated with the termination of this outbreak. This investigation demonstrated that jet injectors can become contaminated with hepatitis B virus and then may be vehicles for its transmission.

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[redacted]

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Preventing contamination between injections with multiple-use nozzle needle-free injectors: a safety trial.

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Multiple-use nozzle jet injectors (MUNJIs), a type of needle-free injector, use a high-pressure stream to penetrate skin and deliver medicament. Concerns for their potential to transmit blood borne pathogens led to development of a hybrid MUNJI for use in mass immunizations. The HSI-500, referred to here as a protector cap needle-free injector (PCNFI), utilizes a disposable cap as a shield between the reusable injector nozzle and the skin to reduce the risk of contamination. This study aimed to determine the presence of hepatitis B virus (HBV) contamination in post-injection ("next person") samples immediately following injection in HBV-carrier adults. Tolerability and pain were also assessed. The study ended early because the PCNFI failed to prevent contamination in the first batch tested (8.2% failure rate). The injections were very well tolerated, with most followed by no bleeding (81.2%) or mild bleeding (7.8%). 55.2% of participants experienced no pain while 42.3% experienced mild pain following injection.

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A model to assess the infection potential of jet injectors used in mass immunisation.

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Jet injectors are needleless injectors that penetrate skin with high-pressure fluid. They have potential advantages over needles and syringes in mass immunisation programs, but concerns over their capacity to transfer blood-borne viruses have been a barrier to acceptance. Hepatitis B infection can transmit in 10 pl of blood; detection of such low volumes presents severe difficulties to such assessments. A model to assess jet injector safety was developed using injection of an inert buffer into calves and assaying the next injector discharge, representing the next dose of vaccine, for blood using a highly sensitive ELISA. Four injectors were tested: two with reusable heads and direct skin contact, one with single-use injector heads and one where the injector head discharged at a distance from the skin. All injectors tested transmitted significant (over 10 pl) volumes of blood; the volumes and frequency of contamination varied with injector. The source of the contamination was consistent with contamination by efflux of injected fluid and blood from the pressurised pocket in tissue that is formed during injection. This insight should inform the design of safe jet injectors.

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