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This edition of *Viral Hepatitis* is based on material presented at the Viral Hepatitis Prevention Board meeting on **Prevention of viral hepatitis in Italy: lessons learnt and the way forward.** Catania, Italy, November 7-8, 2002.

EDITORIAL

This issue of Viral Hepatitis takes a close look at some of the prevention and control measures for viral hepatitis that Italy has taken in recent years, and reviews key data from routine infectious diseases surveillance systems and from Italy's Integrated Epidemiological System for Acute Viral Hepatitis (SEIEVA).

Ten years on, following the introduction in 1991 of mandatory hepatitis B immunisation for infants and twelve-year-old adolescents, mandatory screening of HBsAg-positive women, and free-of-charge vaccination to high-risk groups, Italy has achieved outstanding progress in eliminating hepatitis B virus (HBV) transmission. If coverage rates are maintained at their current levels, elimination of HBV transmission in Italy may become a reality within the next few decades.

The incidence of hepatitis A has dropped in recent years, from 10/100,000 in 1985, to 2/100,000 in 2001. Nonetheless, outbreaks of hepatitis A virus infection continue to occur in southern areas of the country. As for other geographical regions of the world, the main risk factors are travel to endemic areas, consumption of raw or undercooked shellfish, and person-to-person transmission.

The prevalence of hepatitis C in Italy shows a north-south gradient, with an overall prevalence of 2-3%, and rates increasing with age, particularly among those over fifty years of age.

The VHPB recognises the important contributions that Italy has made in our understanding of viral hepatitis and how to control it. Italy was the first European country to introduce universal hepatitis B immunisation, an example that was generally followed by other countries. Its effective use of epidemiological surveillance data, research based on multidisciplinary expertise, and well-defined guidelines for control and prevention, should equally be considered as models to follow.

Pietro Crovari and Mark Kane,
on behalf of the Viral Hepatitis Prevention Board

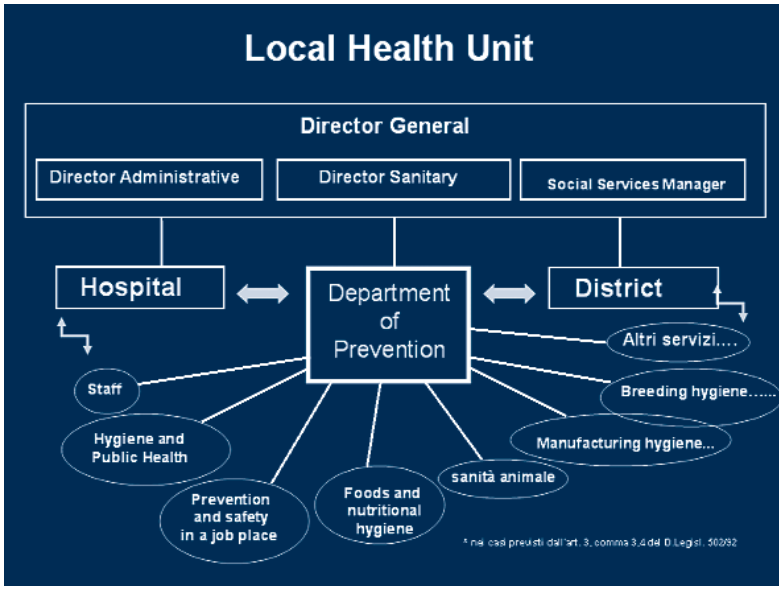
Prevention of viral hepatitis in Italy: lessons learnt and the way forward - a VHPB Symposium Report - Catania, Italy, November 7-8, 2002

Organisation of the health care system in Italy

For over twenty years, disease prevention has been at the core of Italian public health policy, dating back to 1978 when it was clearly mentioned in Italy's public health legislation for the first time. Health laws first came into force when Italy became established as a state and focused on control measures in public health. More recently, in the 1990s, there has been increased emphasis on epidemiological surveillance and risk assessment (D. legislativo N. 502/1992 and D. legislativo n. 229/1999).

Coinciding with this relatively recent legislation, Italy's National Health System is in the process of being restructured, moving from a bureaucratic model to a new federal system made up of open market services that are provided by Local Health Units, together with their respective Departments of Prevention.

The Italian Ministry of Health oversees each of the Regions and these, in turn oversee the Local Health Units. However, each Department of Prevention has autonomy with regard to financial and organisational decisions relating to hospital staff, hygiene and public health, prevention and safety in the workplace, food and nutritional hygiene, animal health, and hygiene in manufacturing and animal breeding.



Within each of the Departments of Prevention, epidemiological data provide the basis for risk assessment, evidence-based prevention programmes, as well as the foundation for cooperative ventures with other stakeholders in public health.

The Departments of Prevention thus form the cornerstone of Italy's public health system, liaising with other areas of the Local Health Units and hospitals, with the primary aims of:

- Promoting action at environmental, human and veterinary levels
- Preventing disease
- Enhancing quality of life.

Based on a presentation by Dr Maria Grazia Pompa, Communicable Diseases Unit, Agenzia Sanità Pubblica - Regione Lazio, Italy.

Integrated epidemiological system for acute viral hepatitis (SEIEVA)

In 1985, SEIEVA (*Sistema Epidemiologico Integrato dell'Epatite Virale Acuta* - Integrated epidemiological system for acute viral hepatitis) was set up to monitor epidemiological trends of acute viral hepatitis, and to identify epidemic clusters and risk factors associated with various types of hepatitis. The primary aims of this system are to formulate and to monitor the impact of acute viral hepatitis prevention strategies.

SEIEVA is coordinated through Italy's National Health Institute - the *Istituto Superiore di Sanità* (ISS) - in collaboration with Local Health Units. As of 2001, 137 such units throughout Italy were participating in SEIEVA, covering approximately 56% of the total population in Italy.

SEIEVA's methodology is based on *notification of cases*, where individuals who are diagnosed with acute viral hepatitis are reported to the Local Health Unit, whether they are hospitalised or not. Following notification, a public health official or physician from the Local Health Unit carries out an *interview* with the individual using a two-page *standardised questionnaire*. The questionnaire is designed to identify socio-demographic characteristics, the patient's exposure to parenteral risk factors within six months before the onset of the disease, and faecal / oral

risk factors within six weeks before disease onset. The questionnaire, which also includes the results of assays for *hepatitis markers*, is then sent to an *ISS computerised database* for data analysis.

Case definitions for acute hepatitis are based on clinical / biochemical criteria (i.e., acute illness compatible with hepatitis, and ALT levels 2.5 times the normal upper limit), and serological criteria for antigens / antibodies (HBsAg, IgM anti-HBc, IgM anti-HAV, anti-HCV, anti-delta, among others).

Incidence rates

The year 1991 represents an important benchmark in Italy's immunisation programme, marking the time that mandatory hepatitis B vaccination of infants and twelve-year-old adolescents was introduced. Mandatory screening of anti-HCV in blood banks was also introduced at that time.

However, infections caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) are still major public health concerns in Italy. While the incidence of these two infections has decreased during the last fifteen years,[1] new infections continue to occur.

More specifically, based on data delivered by SEIEVA in 2001, the incidence rates (number of cases per 100,000 population) for the different types of viral hepatitis have steadily decreased in the period 1985-2001: from 10 to 3 (hepatitis A), from 12 to 2 (hepatitis B), from 5 to 1 (non-A non-B), from 3 to 0.2 (type unknown), and from 30 to 6.2 (overall).

It is also important to note that the incidence of HBV was already decreasing before mandatory hepatitis B vaccination was introduced in 1991. From 1985 to 1999, the incidence of parenterally transmitted viral hepatitis decreased drastically, and, in addition to vaccination, may be attributed to various factors such as improved socio-economic conditions, smaller family size, introduction of blood bank screening, and increased use of disposable syringes. Nevertheless, the impact of the mandatory hepatitis B immunisation programme may become more evident in years to come, when vaccinated infants reach the age of major risk.

The prevalence of chronic HBV carriers is estimated at approximately 1% in the general population,[2-4] and high prevalence rates of HCV infection have been reported in certain areas of southern Italy, particularly among subjects over 50 years of age.[5-7]

Risk factors

According to SEIEVA data for the period 1998 and 2000, the major risk factors for HBV infection, with an odds ratio (OR) adjusted for sex, age, area of residence, educational level, among other variables, are:

Risk factors	Adjusted OR	95% CI
Blood transfusion	2.35	(0.56 - 9.92)
Intravenous drug use	6.78	(3.32 - 13.9)
Surgical intervention	2.44	(1.42 - 4.19)
Dental therapy	1.35	(0.99 - 1.84)
Other parenteral exposures	1.67	(1.26 - 2.33)
More than one sexual partner	1.75	(1.31 - 2.33)
Household contact with HBsAg-positive person	10.1	(4.52 - 22.7)

The high rate of hepatitis B transmission through household contacts highlights the importance of vaccination of family members, which has not reached sufficiently high levels, because HBsAg chronic carriers are often not aware of their carrier condition and because family members underestimate the risk of acquiring HBV.[8-9]

The greatest risk factors for HCV infection, according to SEIEVA data (1998-2000), are intravenous drug use, surgical interventions, blood transfusions, other parenteral exposures (such as ear piercing, tattooing, attending a manicurist or a chiropodist, barber shop shaving, acupuncture, electrolysis), dental therapy, and having more than one sexual partner. For hepatitis A infection, shellfish consumption and travel to high-endemic areas are the major risk factors.

Conclusions

SEIEVA plays a vital role in determining Italy's public health prevention policies:

- by providing epidemiological data that are necessary for monitoring trends in acute viral hepatitis;
- for understanding the role that risk factors play in viral hepatitis transmission; and
- for helping to establish priorities and assessing the impact of viral hepatitis prevention programmes.

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Based on a presentation by Dr Alfonso Mele, Istituto Superiore di Sanità, Roma, Italy.

Epidemiology of hepatitis A virus infection in Italy

Epidemiology - global patterns

Hepatitis A is one of the most common infectious diseases worldwide, and is highly endemic in countries with poor sanitation. Hepatitis A virus (HAV) is usually transmitted through contaminated food or water, or from person to person. In Italy, the most important risk factors for acquiring HAV for all age groups are:[1]

- Eating undercooked or raw shellfish;
- Travel to endemic areas;
- Contact with a person with acute hepatitis A virus infection; and
- Drinking contaminated water.

The incubation period for hepatitis A is approximately three weeks, and infection is characterised by jaundice, fever, abdominal pain, diarrhoea, nausea, vomiting, and arthralgia.

Hepatitis A is often overlooked as a vaccine-preventable disease due to its low mortality rate.[2] Although approximately 1.4 million cases are reported yearly, this is considered an underestimate, and the actual incidence is 3 to 10 times higher.[3] Underestimates are due to subclinical infections that are very common during infancy, when most cases show no symptoms, and due to under-reporting of cases.

The epidemiology of HAV infection is closely related to the level of socio-economic development in a region. In industrialised countries, improved sanitation and living conditions have contributed to a decline in incidence and prevalence of HAV infection.[4] A consequence of this epidemiological shift is a greatly reduced risk of acquiring HAV infection during infancy, when most cases are asymptomatic and benign. This situation has led to an increasing proportion of susceptible adults, who have not developed immunity to the virus during childhood and in whom the infection may be particularly serious.[5]

The prevalence of anti-HAV antibodies in low- and intermediate-endemic regions is thus low in infancy and early childhood, and consequently the risk of acquiring the infection increases during adolescence and young adulthood - both age groups representing segments of the population that have not developed immunity to HAV infection.

Hepatitis A in Italy

Twenty to thirty years ago, hepatitis A was widespread in Italy, with increasing endemicity in the regions from north to south.[6] During that time, infections were acquired mostly in infancy and early childhood, with the majority of people developing long-lasting immunity very early in life. HAV infection was rarely seen in adulthood.

Since that time, improvements in clean water supply, sewage disposal and, more recently, vaccination, have led to a decline in circulation of HAV. In the northern regions of Italy, this has led to an anti-HAV prevalence rate of approximately 10% among those under 20 years of age,[2] leaving large cohorts of susceptible adults who have not developed immunity to the virus during childhood. However, in southern regions, such as Puglia and Campania, prevalence rates are still 40% in 18 year-olds, and more than 30% among those 20 to 30 years old.[2]

Hepatitis A epidemic in Puglia - lessons learnt

Cyclical outbreaks of hepatitis A occur in the southern regions of Italy. The incidence rates remain between 20 to 30 cases per 100,000 during the inter-epidemic intervals.[2]

The last outbreak occurred in Puglia between 1996 and 1997, a region with intermediate endemicity. At the beginning of the outbreak, there were 5,673 notified cases (incidence rate of 138.8 per 100,000), and at the end of the outbreak in December 1997 5,389 cases (incidence rate of 131.8 per 100,000).[2] Eighty-seven percent of notified cases resulted in hospitalisation, which was much higher than the 50% usually observed, suggesting that the notification rate was underestimated and that less severe cases had gone unreported.[2]

According to two case-control studies, data showed that the main risk factor in this outbreak was consumption of raw seafood, and that person-to-person contact would continue to maintain the outbreak between peaks.[7,8]

Economic burden to patients and health services

A study analysing the economic costs of the hepatitis A outbreak in Puglia showed huge costs to the individual patient, to public health services, and to society as a whole.[9] The mean cost of infection per patient (1996 rates) was US$662 - equivalent to 6.6% of the mean annual income. National Health Service costs totalled US$15.67 million, and costs to society (individual patient, National Health

Global patterns of hepatitis A virus transmission

Endemicity	*Disease rate*	*Peak age of infection*	*Transmission patterns*
High	Low to high	Early childhood	Person to person; outbreaks uncommon
Moderate	High	Late childhood / young adults	Person to person; food-borne and waterborne outbreaks
Low	Low	Young adults	Person to person; food-borne and waterborne outbreaks
Very low	Very low	Adults	Travellers; outbreaks uncommon

Service, and third parties combined) were estimated at US$24.45 million. This figure represented a cost of US$4,150 for the Italian economy per patient infected with hepatitis A during the outbreak.

In view of the high cost of cyclical hepatitis A outbreaks, the study concluded that a hepatitis A vaccination strategy be evaluated. This resulted in a recommendation in 1997 by the local government in Puglia to give infants (15-18 months) hepatitis A vaccine simultaneously with measles-mumps-rubella (MMR) vaccine. A combined hepatitis A and B vaccine was offered to adolescents at 12 years of age during the mandatory hepatitis B vaccination phase, consisting of 3 doses with 1 month between the first and second dose, and a period of 5 months between the second and third dose. Since introduction of the combined hepatitis A and B vaccination programme, 90% coverage has been achieved. The high cost of outbreaks has made immunisation strategies effective in reducing the burden of disease and economic costs to all concerned.

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Based on presentations by Dr Rosa Cristina Coppola, Department of Hygiene and Public Health, University of Cagliari, Italy, and Dr Pier Luigi Lopalco, Department of Internal Medicine and Public Medicine, Section of Hygiene, University of Bari, Italy.

Prevention of hepatitis A during outbreaks and post-exposure

Hepatitis A - an old disease of growing importance

A changing cultural environment presents opportunities for risk of new types of HAV exposure, such as dining out, increased interest in exotic and/or fast food, and a growing trend among young families to send children to day care at a younger age. Changing demographic patterns also contribute to possible new exposures characterised by the increasing numbers of people on the move from high / intermediate endemic countries to countries with low endemicity. Children from low endemic countries born to parents from areas of high endemicity may contract HAV if visiting their parents' birthplace, and may cause secondary infection upon their return.

General measures for preventing hepatitis A[1,2]

In household settings, strict personal hygne, such as thorough hand washing, is essential in helping to prevent spread of infectious disease. Such measures are especially important with regard to food preparation in the home and other culinary settings.

At the community level, the following measures are key to preventing transmission of HAV:

- Provision of safe drinking water;
- Proper disposal of sanitary waste;
- Thorough hand washing and safe food-handling techniques among food handlers;
- Surveillance of water beds for shellfish destined for human consumption; and
- Strict control measures to ensure that commercial distribution of shellfish from unsupervised areas is avoided.[3,4]

Impact of standard immune globulin use during hepatitis A outbreaks

Administration of immunoglobulin (Ig) may be a useful measure in reducing the circulation of the hepatitis A virus during epidemics. However, Ig is often not sufficient to bring outbreaks under control, especially those that occur in day care centres or in closed communities characterised by toilet facilities shared by many people or where high levels of promiscuity are present.

An efficacy of about 85% has been demonstrated in post-exposure prophylaxis when Ig was given within 14 days after exposure.[5] However, Ig was often unable to stop community-wide outbreaks, probably due to its limited time of protection compared with the usual length of an epidemic. Ig is often difficult to obtain in large stock for use in the general population, and is not always well accepted since it is obtained from human blood. Also the concentration of anti-HAV in Ig has declined during the last few decades due to decreased circulation of the virus.

Impact of hepatitis A vaccine in pre-exposure prophylaxis

Hepatitis A vaccine is one of the most immunogenic vaccines available, and its efficacy in pre-exposure prophylaxis has been documented by several studies. Vaccination has been used during the course of outbreaks and for the prevention of secondary cases.[6,7] Active prophylaxis has usually shortened the course of outbreaks where coverage of a well-defined target population was high. No clinical trials are available on the effectiveness of hepatitis A vaccination compared with human Ig during outbreaks.

The only clinical trial of vaccine used for post-exposure prophylaxis has shown good efficacy (about 80%). In communities experiencing recurrent epidemics, the use of hepatitis A vaccine also seems justified by the high secondary attack rates, and the consequent acceptable cost-effectiveness profile. However, in

areas where hepatitis A represents a public health problem, the implementation of routine vaccination of children and/or adolescents seems, in the long term, the most reasonable way to bring outbreaks under control.

Summary of actions when an outbreak occurs

1. Rapid identification of the source of the outbreak;
2. Rapid identification of the population to be targeted by vaccination (e.g., contacts of cases and people present in institutions where infection has occurred);
3. Rapid communication campaign informing people about the infection, how it is spread, possibility of prevention by vaccination and good hygiene measures;
4. Rapid creation of an action programme task force;
5. Rapid administration of the first vaccine dose to the target population;
6. Maintenance of records of vaccinated people; and
7. Documented review of the campaign detailing:
   - Initial number of cases;
   - Ratio of numbers immunised versus the target population;
   - Time necessary to bring the outbreak under control;
   - Number of cases occurring in vaccinated persons and the timing of their vaccination; and
   - Number of boosters administered.

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Based on a presentation by Dr Paolo Bonanni, Public Health Department, University of Firenze, Italy.

The new Italian guidelines for the use of hepatitis A vaccine

Methodology

The methodology used in drawing up these guidelines is based on evidence available in peer-reviewed literature and on the expert opinions of a multi-disciplinary team regarding the possible use of hepatitis A vaccine. The guidelines are intended to assist public health physicians and clinicians in controlling HAV infection, and in counselling patients and their contacts.

The scientific evidence is based on papers that appear in various online databases, such as Medline, Embase, and The Cochrane Controlled Trial Register. These papers were evaluated for their content and scientific relevance. Conclusive data were then extracted and synthesised, and provided the basis for recommendations of hepatitis A vaccine in Italy.

Although these proposed recommendations have been drawn up in the context of the Italian epidemiology of hepatitis A, the evidence and discussion material may be useful for implementing hepatitis A vaccination in other western countries.

Summary of the guidelines

1. Effectiveness and safety of hepatitis A vaccine

Seven papers were examined for systematic review of this issue, concluding that the effectiveness of hepatitis A vaccine was 86% in pre-exposure, and 82% in post-exposure prophylaxis. No serious adverse reactions were reported.

2. Economic evaluation

From an economic point of view, mass vaccination is useful only during the course of outbreaks. Vaccination of contacts of acute hepatitis A cases should be applied as a routine measure.

3. Assessment of various risk groups for hepatitis A virus infection

- *Travellers*
  Evidence regarding the risk of acquiring hepatitis A dates back to studies carried out during the 1980s and early 1990s. Although socio-economic improvements have occurred in many regions of the world, travel is still considered a risk factor. The degree of risk depends on the level of endemicity of the visited area, and the level of preventive hygiene measures that are taken.
- *Health care workers*
  There is no evidence that health care workers constitute a risk group for HAV infection. This conclusion is based on the documented effectiveness of universal precautionary measures in protecting against HAV occupational exposures in a group where there is no evidence of a higher antibody seroprevalence than in the general population.
- *Sewage workers*
  There is evidence that sewage workers are exposed to a higher personal risk of HAV infection that is related to their profession, even when observing adequate hygienic precautions. However, they do not represent a risk for the community, and no epidemics have been described where sewage workers were reported to be the source of infection.
- *Food handlers*
  Food handlers can contract HAV from contaminated food and, once infected, may be the source of further infections. However, there is no evidence that they are a risk group, as the contamination of food by infected food handlers or infection by contaminated food manipulation is easily avoidable by observing the most common and basic standards of hygiene.

- *Day care personnel*
  Not only children in day care but also family members and day care personnel are at risk for HAV infection. For both groups, the risk is related to close contact with children, the risk being higher within families than among personnel. Transmission can be easily avoided by observing the generally adopted standards of hygiene. Therefore, there is no strong evidence to consider day care centre personnel as a risk group for HAV infection.
- *Institutionalised persons*
  Outbreaks of hepatitis A in institutions for persons with physical and, above all, those with mental disabilities, have been reported. The age of the residents and their length of stay in an institution were both related to the risk of acquiring HAV, which was demonstrated by higher antibody prevalence. Although there is evidence of risk of contracting HAV among institutionalised subjects, staff members may easily protect themselves from exposure to HAV by following standard precautionary measures.
- *Haemophiliacs*
  Hepatitis A outbreaks among haemophiliacs treated with solvent / detergent inactivated factors VIII/IX concentrates have been described in the past, but in the last several years, no more cases of HAV infection have been reported, due to improved inactivation methods, and the use of products obtained through genetic recombination techniques. Seroprevalence and case-control studies do not show an increased risk of hepatitis A among haemophiliacs.
- *Drug addicts*
  Epidemics that occur regularly among drug addicts and homosexual men have been described, and it has been pointed out that these groups may become important sources of hepatitis A virus infection even if drug addicts are not recognised as sources of epidemics in the general population. The HAV infection prevalence is slightly higher in drug addicts than in various control populations. However, the transmission is related to socio-economic factors, sexual promiscuity, syringe exchange and contamination of instruments used to prepare the drugs.
- *Sexual promiscuity*
  The hypothesis of considering homosexuals as a potential group at risk of acquiring HAV dates back to the early 1990s, and arises from the demonstration of a peak incidence of hepatitis A in males 20-39 years of age, and the description of many outbreaks among homosexuals. The risk of acquiring HAV infection is linked to oral / anal sexual practices and sexual promiscuity. Prevalence studies do not show significant differences in anti-HAV prevalence between homosexuals and control groups.
- *Patients with chronic liver disease*
  Even if not all of the papers examined in the systematic review of the literature are of high quality, it appears that patients with chronic liver disease show a greater risk of complications of HAV infection. Therefore, hepatitis A vaccination is recommended to patients with advanced chronic liver disease.

Outbreaks

In closed communities, such as day care centres, where most subjects are susceptible and the risk for person-to-person transmission is high, vaccine is recommended for family members, schoolmates, and personnel, following a single case of infection. In older age groups, vaccination is recommended if a secondary case is demonstrated.

- *Post-exposure prophylaxis*
  There is only a recent trial regarding the effectiveness of vaccine as post-exposure prophylaxis (82%). The vaccine should be administered not later than eight days after the exposure and is preferred above the use of gamma-globulins.

Based on a presentation by Dr Elisabetta Franco, Department of Public Health, University of Roma Tor Vergata, Italy.

Epidemiology of hepatitis B virus infection in Italy

Hepatitis B virus is one of the most infectious agents worldwide, with approximately 400 million carriers globally. In Italy, HBV and HCV are among the leading causes of acute and chronic liver disease, resulting in several thousand deaths each year from cirrhosis and hepatocellular carcinoma.[1]

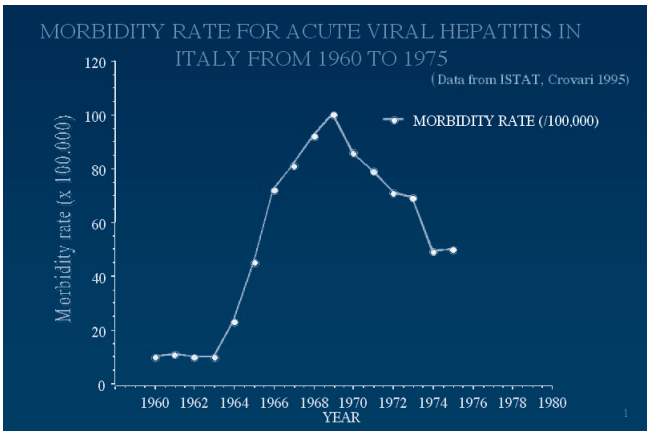
Evolution of HBV infection in Italy

Up until the mid-1970s, hepatitis B morbidity rates were high, and can be mainly attributed to:

- Use of unscreened blood and blood products;
- Re-use of inadequately sterilised medical equipment;
- High birth rate and large family size; and
- Increase in intravenous drug use.

During the 1980s, HBV infection in Italy began to decrease, mainly due to:

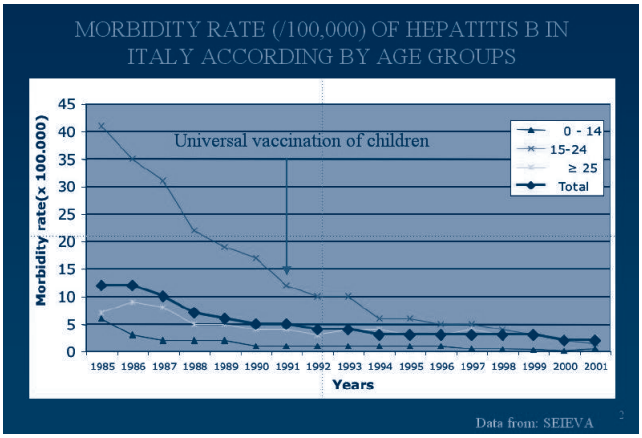
- Improved health care, such as:
  - Use of disposables;
  - RIA and EIA testing for blood screening; and
  - Better education of health care workers.
- Better living standards and reduction of average family size;
- The 'AIDS effect' contributing to safer sexual practices; and
- Selective immunisation of:
  - Newborns to HBsAg-positive women;
  - Household contacts of HBV carriers; and
  - Health care workers.



The 1990s saw an even further reduction in HBV infection, following Italy's decision to implement mandatory universal immunisation for infants and 12-year-old adolescents, together

with mandatory HBsAg screening of women. Hepatitis B vaccination was also offered free of charge to high-risk groups. Since the mandatory hepatitis B vaccination programme began in 1991, more than 10 million children in Italy have been immunised with an outstanding record of safety and efficacy.[2] Globally, the coverage rate is approximately 95%, with somewhat lower acceptance rates in the south compared with northern regions.

During the period 1991-1999, data show that the number of new cases of hepatitis B dropped by about 40%, compared with data for 1988-1991.



At the present time, the level of acute hepatitis B infection is at an all-time low. However, there are still new infections occurring and there is also a shift in the prevalence of HBsAg-positive subjects towards more advanced age groups. The steady decrease in incidence of HBV infection over a period of time is consistent with data that show prevalence rates of serological markers low among children and young adults, but significantly higher among those between 50 and 60 years of age, particularly in southern Italy.[3]

What the future holds

The main objectives for Italy's public health programmes in the coming years will be to consolidate and improve the results that have been achieved thus far in controlling and preventing viral hepatitis. Public health strategies will include:

- Maintaining mandatory vaccination of infants;
- Maintaining HBsAg testing for pregnant women;
- Increasing vaccination coverage in adults at risk;
- Maintaining a high safety level of invasive treatments for both medical and non-medical purposes;
- Increasing health education of the general public on sexually transmitted diseases;
- Considering the use of booster doses of hepatitis B vaccine;
- Maintaining / increasing surveillance; and
- Continuing / accelerating research into HBV infection.

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Based on a presentation by Dr Pietro Crovari, Department of Health Sciences, University of Genova, Italy.

Epidemiology of hepatitis B core / pre-core mutants in Italy

Chronic hepatitis B (CHB) may be separated into two major forms: the HBeAg-positive and the HBeAg-negative.[1] HBeAg-negative CHB has also been referred to as 'anti-HBeAg-positive CHB' as well as 'pre-core mutant CHB,' but the term 'HBeAg-negative CHB is more widespread.[2]

HBeAg-negative CHB is prevalent in certain areas of the world, such as southern Europe, the Middle East and Asia, and is a potentially severe and progressive form of CHB.[2,3] It was first identified in 1980 in the Mediterranean area,[4,5] and has shown increased prevalence in Italy, due to:

- Reduction of HBeAg-positive cases;
- Long-lasting unresolved disease inducing progressive accumulation of cases in the population; and
- Increased diagnostic accuracy through use of more sensitive assays, and more diagnostic accuracy by clinicians.

In the Mediterranean Basin, 30% to 80% of patients with CHB are HBeAg-negative, compared with other areas of the world, such as northern Europe and the USA where only 10% to 40% of CHB patients are lacking HBeAg.[1,6]

HBeAg-negative CHB the infection is sustained by HBV mutants, unable to produce HBeAg because of a translational stop codon at nucleotide 1896 of the pre-core region.[7] The mutation does not hamper the replication efficiency of the virus and its selection seems to be favoured by some genotypes, such as genotype D, prevailing in southern Europe. Pre-core mutants may be present in the early stages of CHB with the wild type (i.e., HBeAg-positive HBV), and then become selected in the natural course of chronic infection during or after HBeAg seroconversion.[6]

In reports from southern Europe, response to interferon alpha therapy of HBeAg-negative CHB was effective, improving the outcome of the disease in several patients. However, these results mainly concern the pre-core mutant of genotype D and do not necessarily apply to other geographical areas where other virologic forms of HBeAg-negative CHB may prevail.[2]

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Based on a presentation by Dr Maurizia Brunetto, Department of Gastroenterology, University of Pisa, Italy.

Impact of hepatitis B virus S-gene mutants on the efficacy of vaccination

Many mutations that occur during replication of the hepatitis B virus are highly detrimental or lethal for the virus itself and are not maintained in the virus population. A proportion of mutants may survive but only if they confer some advantage over pre-existing strains. The immune responses of the host as well as prophylactic and therapeutic interventions may select variants that arise during the process of replication.

Neutralising (protective) antibodies that are induced by vaccines are mainly targeted towards the *a* determinant. Evidence indicates that amino acid substitutions within this region of HBsAg can lead to conformational changes that allow the mutated HBV to escape vaccine-induced antibodies.

The emergence of an HBV variant possibly able to escape the vaccine-induced response was first suggested in Italy some 15 years ago.[1] Forty-four of 1,590 vaccinated people (2.8%), including babies born to HBsAg-positive mothers, became HBV infected despite immunisation. All cases showed co-existence of HBsAg and anti-HBs.

Sequence analysis from one of these cases revealed substitution from *Gly* to *Arg* at position 178 of the *a* determinant.[2] The same mutation (G145R) was observed in a patient who underwent transplantation for end-stage HBV-induced hepatitis and who was subsequently treated with monoclonal anti-*a* to prevent reinfection of the homograft.[3]

The G145R mutation as well as other less frequently occurring mutations within the HBsAg *a* determinant were also found in successfully vaccinated babies in Singapore, Thailand, China, Japan, Brazil, the Gambia, and the USA.

In a study carried out in Singapore,[4] 41 breakthrough infections occurred in 345 infants (11.9%) born to HBsAg / HBeAg carrier mothers who were given HBIg plus vaccine at birth, the most frequent mutant being G145R.

A study in Taiwan[5] showed an increase in the prevalence of HBV mutants (mostly G145R) reported in Taiwan over 10 years after the introduction of universal vaccination, as shown below.

Year	Prevalence (%) of HBV mutants
1984	7.8
1989	19.6
1990	28.1

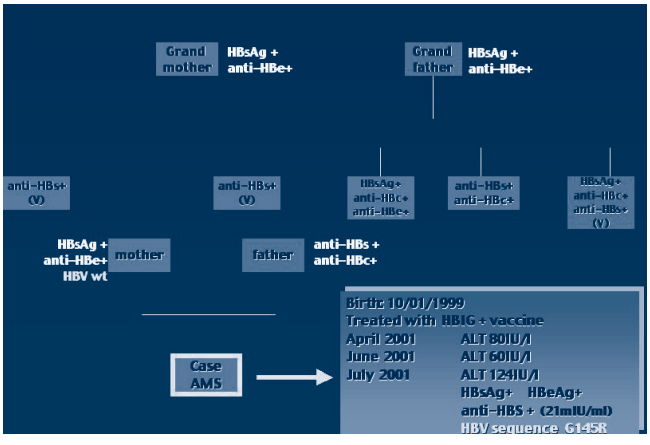
Emergence of HBV S-gene mutants secondary to vaccination
Based on the assumption that current vaccines containing S protein do not cross-protect against S-gene mutants, a mathematical model predicted the disappearance of wild type HBV and the emergence of G145R in approximately 100 years.

On the other hand, a study[6] carried out at the National Institutes of Health (USA) on four chimpanzees vaccinated with licensed recombinant vaccines, showed that immunised animals were protected when challenged with G145R.

HBV S-gene mutants in Italy
There are very few studies that have been carried out in Italy designed to detect HBV S-gene mutants in those vaccinated and in chronic HBsAg carriers. However, occasional breakthrough infections due to the G145R mutant or to less frequent S-gene mutants have been described, both in liver transplant recipients[7] and in children born to HBsAg-positive mothers.[8]

Effectiveness of vaccination in babies born to HBsAg-positive mothers in Italy
HBIg plus hepatitis B vaccine was given to 522 babies at birth. The results, 5 to 14 years after immunisation, showed:

- 97% of the children had protective anti-HBs;
- 14 children (2.7%) had seroconverted to anti-HBc;
- 3 children had become HBsAg carriers; and
- 1 child carrier had a double mutation with substitution of proline to serine at codons 120 (P120S) and 127 (P127S) within the *a* determinant.



HBV S-gene mutants - mere curiosity or a potential public health problem?

HBV S-gene mutants have been identified in successfully immunised people worldwide. There is evidence that such mutants may escape detection by assays based on monoclonal antibodies. G145R is replication competent, stable, and may persist in the host for years. S-gene mutants appear to have a greater chance to emerge after post-exposure prophylaxis with HBIg and hepatitis B vaccine.

In Italy there is no evidence, at present, that S-gene mutants may pose a threat to the established programme of hepatitis B vaccination. However, epidemiological monitoring of viral mutations, documentation of the natural history and disease progression caused by mutants, and their person-to-person transmissibility in both susceptible and immunised individuals deserve further study.

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Based on a presentation by Dr Alessandro Zanetti, Institute of Virology, University of Milano, Italy.

Programme of hepatitis B vaccination targeted to risk groups

In 1983, Italy introduced an immunisation programme targeted to people at high risk for acquiring HBV, defined as:

- Household contacts of HBsAg carriers;
- Health care workers;
- Polytransfused patients;
- Dialysis patients;
- Injecting drug users; and
- Male homosexuals.

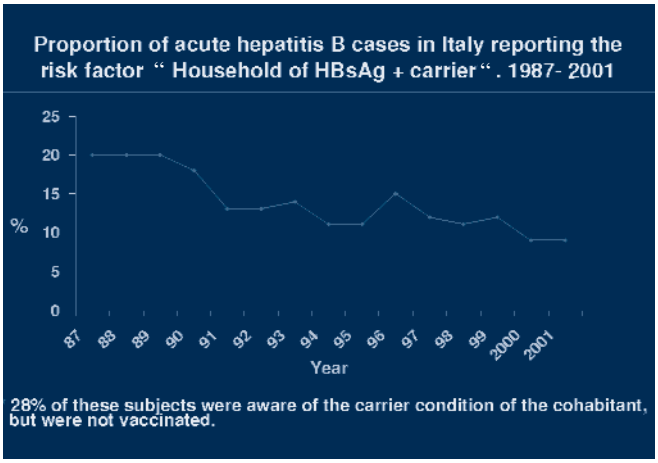
The hepatitis B vaccine has been strongly recommended to high-risk groups in Italy since 1984. Nonetheless, until 1991 the only major risk group that reported widespread use of the vaccine was health care workers, who accounted for only a small proportion of reported cases.[1] Hepatitis B vaccination coverage data for health care workers in 1996 are shown below, highlighting regional differences between north and south.

Hepatitis B vaccination coverage among health care workers in Italy, 1996[2]

Geographical area	*Number of subjects studied*	*Coverage (%)*
Ferrara (North)	903	77.6 [a]
Rome (Central)	1327	67.7 [b]
Naples (South)	927	44.3 [c]
Total	3157	64.5

a *vs.* c: P < 0.01; b *vs.* c: P < 0.01

Between 1987 and 1989, household contact with HBsAg chronic carriers was reported by 20% of hepatitis B cases, with that figure falling to 12% between 1997 and 1999. The proportion of those cases for children was 37% and 25%, respectively, emphasising the importance of household transmission of HBV, particularly at an early age.[1] However, sufficiently high levels of vaccination of household contacts has not been achieved due to the fact that HBsAg carriers are often unaware of their carrier condition, and because household contacts may underestimate the risk of acquiring HBV.[3-4]



Between 1997 and 1999, the highest incidence rates for hepatitis B were observed in the 15-24 year-old age group, and were attributed to high-risk behaviour such as multiple sex partners and drug use. During that time period, sexual exposure accounted for the majority of reported cases of hepatitis B.

There was a marked increase in frequency observed during 1997-1999 due to other parenteral exposures in the 0-14 year-old age group. These subjects had not reached the age of vaccination yet and had not been immunised at birth since they were born after 1991.

Between 1997 and 1999, a significant proportion of individuals with hepatitis B virus infection reported a history of surgical intervention, dental treatment, and other parental exposures,[5-7] all of which may be considered responsible for a large number of cases, particularly among adults in the general population who routinely undergo such procedures.

More recent data highlight the success of Italy's immunisation policy for hepatitis B vaccination of newborns of HBsAg-positive mothers in 2001. From among 11,858 women selected, 10,881 pregnant women (91.5%) were screened for HBsAg, and 182 (1.7%) tested positive. This pre-natal screening led to 95% immunisation coverage for infants born to the 182 HBsAg-positive mothers.

Some of the factors associated with not adhering to HBsAg screening among pregnant women in Italy include age, years of schooling, family size, whether they are seen in a public or private hospital, and geographical area. Data from 2001 show a lower percentage of foreign-born women participating in the screening programme than Italian mothers - 88% versus 93%, respectively. However, 100% of newborns of foreign-born HBsAg-positive mothers were immunised, compared with 92.8% newborns of Italian mothers. Nonetheless, data showed more than 86% overall effectiveness of the programme for both groups of women.

Conclusions

Information and educational campaigns concerning HBV transmission should continue to be an important tool in Italy's public health efforts to reach groups at high risk for hepatitis B virus infection. Further, sterilisation and strict maintenance procedures for instruments used in aesthetic or dental treatments, and invasive medical procedures should be carefully monitored, with disposable materials being used whenever possible.

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Based on a presentation by Dr Tommaso Stroffolini, Istituto Superiore di Sanità, Roma, Italy.

Evaluation framework of viral hepatitis prevention programmes: examples in Italy - impact of ten years of universal hepatitis B vaccination programmes

Italy was one of the first industrialised countries to introduce universal hepatitis B vaccination. Based on epidemiological and economic data, it was decided to adopt a double cohort policy of mandatory immunisation for infants and 12-year old adolescents, together with free-of-charge vaccination for high-risk groups. The aim of the programme was to reduce and, eventually, to eliminate transmission of HBV by 'rapidly creating 24 generations of immune subjects within the first 12 years of implementation'.[1] The law introducing mandatory vaccination (No. 165) was issued in May 1991, but the programme was not fully implemented for the entire country until the beginning of 1992.

Implementing and monitoring vaccination coverage

Following the implementation of a universal immunisation programme, the next step was to monitor the coverage. In principle, hepatitis B vaccination coverage levels should be available through data reported by each Local Health Unit of the Department of Prevention that, in turn, reports to each Regional Health Authority. However, data collection is not always complete, and how it is performed varies by region. For this reason, *ad hoc* surveys were carried out in 1993 and 1998 on children born in different regions of Italy in 1991 and 1996. Another study was also performed in Tuscany among 22,000 children and adolescents from various municipalities representative of the entire region.

In the first few years following introduction of the vaccination programme, high coverage with three doses of the hepatitis B vaccine was documented.[2,3] Since the introduction of the programme, coverage is approximately 90% overall in Italy, and even higher (approximately 95%) in many areas of the country. The incidence of acute hepatitis B, which had already begun to decline before 1991, has decreased even further due to routine vaccination programmes. This has been the case particularly for adolescents and young adults who have received hepatitis B mandatory vaccination. In older subjects, however, epidemiological data show that the incidence has changed very little during the last years. This situation highlights the importance of complementing routine immunisation with measures that focus on communication and education programmes to groups at high risk.

Excellent safety record of hepatitis B vaccines

There is increasing interest among the general public in Italy with regard to safety issues and the acceptance of routine immunisation. While minor side effects are evident during clinical trials before vaccines are registered, rare and possible serious adverse events are detected during large-scale post-marketing surveillance studies. Italy's system of passive surveillance of adverse events following hepatitis B vaccination demonstrates the vaccine's excellent safety record.[1]

As well as initiating a policy of routine immunisation for infants and adolescents, Italy also adopted a policy for mandatory HBsAg screening of pregnant women. The results of long-term surveillance studies of children who were born to HBsAg-positive women show that the number of infections among vaccinees was very limited, asymptomatic, and nearly always self-limiting.[1]

With regard to mutant viruses, there was no evidence suggesting that they pose a threat to Italy's universal vaccination programmes.[1]

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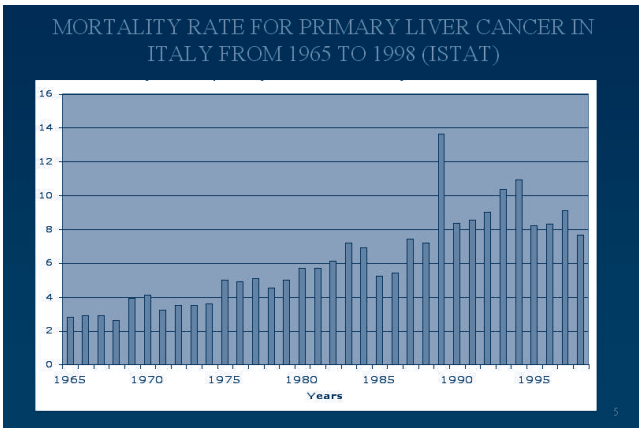
Based on a presentation by Dr Tommaso Stroffolini, Istituto Superiore di Sanità, Roma, Italy.

Epidemiology of hepatitis C virus infection in Italy

The prevalence of HCV infections in the world is estimated to be 3% of the general population. Approximately 170 million persons worldwide are carriers of HCV, resulting in approximately half a million deaths per year. Due to the slow and insidious nature of the disease, and the large reservoir of previously infected individuals, the number of patients who develop complications due to HCV infection and end-stage liver disease, is expected to increase during the next 10 to 20 years.[1] In Italy, HCV infections continue to represent a major public health problem.



Although earlier studies indicated that no more than 1% of the general population in Italy was infected with HCV, recent field studies involving open populations suggest that the global prevalence in Italy is much higher than previously estimated. The prevalence in the general population is now estimated to be 2-3%, and as high as 12% to 26% in certain areas of the country. The incidence of HCV infection has declined during the last 15 years.[2] However, new infections still occur. Currently, the incidence of acute hepatitis C in Italy is approximately 1/100,000 annually, but the total number of new infections per year is at least 10 times higher[3] since most infections are asymptomatic.

A number of factors have led to the decrease in incidence during the last ten years, mainly due to:

- Use of disposable syringes and needles;
- Screening for safe blood and blood products; and
- Implementation of universal precautions in medical settings.

The most common risk factors identified among patients with hepatitis C in Italy[4] are:

- Intravenous drug use and other parenteral exposures (e.g., ear piercing and tattooing);
- Surgery;
- Hospitalisation; and
- Dental treatment.

However, between 30% and 40% of cases have been diagnosed without parenteral exposure. Recently, a study[5] has shown that blood microtransfusions carried out in the 1960s may account for HCV infections in persons with unidentified risk factors.

Targets under sero-epidemiological investigation

Blood donors[6,7]

- The prevalence of HCV-positive patients in blood donors in Italy was initially estimated at approximately 1%.
- The incidence of post-transfusion cases has dropped from 7/1,000,000 in 1986 to 1.1/1,000,000 in 1991 since the introduction of screening tests.
- The incidence was further reduced to 0.4/1,000,000 in 1993 by using second-generation EIA anti-HCV assays.

Subjects receiving haemoderivatives (FVIII, FIX)[8,9]

- Up to 85% of haemophiliac and 61% of thalassaemic patients test positive for anti-HCV.
- At present, donor screening and the virucidal treatment of blood products have minimised the risk of infection through transfusion of blood or its derivatives.

Intravenous drug users / lifestyle

- Intravenous drug use remains the main mode of transmission.[10] Between 60% and 92% of drug users are anti-HCV positive.[11]
- Tattooing, piercing, etc. with shared needles is also a route of transmission.[12]

Haemodialysis patients

Approximately 30% of haemodialysis patients test anti-HCV positive.[7,13]

Health care workers

The majority of percutaneous exposures in health care workers involves needle devices and sharp instruments. Nurses, housekeepers, training personnel, surgeons, and laboratory workers appear to be the groups at highest risk for infection with

blood-borne pathogens - data from SIROH-EPINet.[14]

Pregnant women

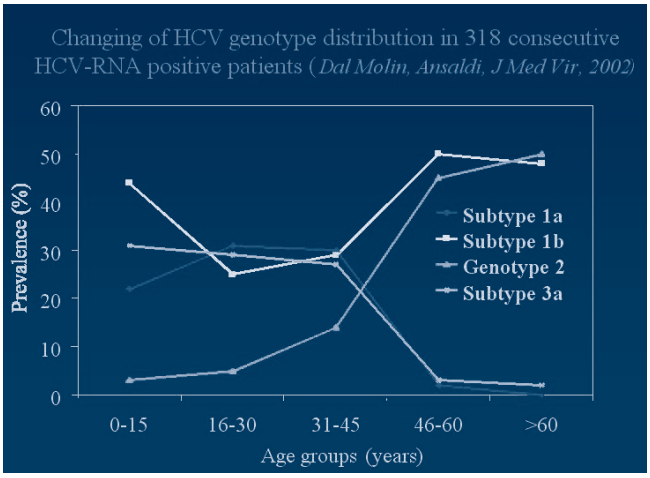
The HCV seroprevalence in pregnant women was regularly examined in women at childbirth and in voluntary pregnancy interruptions in Liguria, in 1996, 1997, and 1998.

Vertical / perinatal transmission

- Mode of delivery (caesarean section / vaginal) does not appear to influence the rate of HCV transmission from mother to child.
- There is an increased risk of neonatal infection from HCV-infected mothers in the presence of maternal HIV co-infection.[15,16]
- This risk is usually higher in mothers with $>10^6$ genome copies of HCV/ml.[17]
- There is no association between breast-feeding and HCV transmission from mother to child.

Changing epidemiology of HCV in Italy

The most prevalent genotype in Italy is genotype 1b, followed by 2a / 2c, 1a, and 3a.[18] Recently, however, changes have been observed in the incidence of these genotypes.[19] The changing epidemiology of HCV in Northeast Italy is characterised by the introduction of subtypes 1a and 3a (predominant among injecting drug users), and a marked reduction of genotype 2.[19] Logistic regression has shown that injecting drug use and age are independent determinants of genotype distribution[19].



Continued epidemiological surveillance using HCV genotyping in Italy will help to identify the source of outbreaks, and help to establish associations between viral genotype and liver damage, the response to antiviral treatment, and clinical management.

Conclusions

The annual rate of new HCV infections in Italy suggests that control of these infections has not yet been achieved. Given the serious long-term complications of HCV infection, it is clear that in order to reduce further the rate of these infections, strict application of recommended preventive measures will be required. It is also expected that the development and availability of a hepatitis C virus vaccine, together with new therapeutic options, will lead to improved prevention and control of HCV infection.

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Based on a presentation by Dr Pietro Crovari, Department of Health Sciences, University of Genova, Italy.

Molecular tracing of HCV: options for control of hospital transmission

Neither the magnitude of nosocomial transmission … nor the mechanisms involved in HCV transmission are well understood'.[1]

While studies have been carried out to determine the modes of HCV nosocomial transmission, a number of questions remain as to the exact mode of transmission, the efficacy of some preventive measures, and the isolation of HCV-positive patients.

However, the following risk factors are believed to contribute to HCV transmission in nosocomial settings:

- History of blood transfusion;
- Timing of haemodialysis;
- Multiple medical, surgical, or endoscopic procedures;
- High prevalence of HCV-infected patients attending the unit;
- Understaffing.

Investigation on haemodialysis patients

HCV transmission was studied in patients at a haemodialysis unit in May 1996. Newly infected patients that were HCV-RNA-positive, and viraemic patients already infected in May 1996, were retrospectively investigated by sequencing the highly conserved 5' untranslated region (5' UTR) of the viral genome, to identify the route and the mechanisms of transmission. This region is supposed to be less susceptible to mutations under immunological pressure, thus representing a fingerprint of the virus.

In order to investigate the occurrence of monitor contamination, strains infecting the new cases and those infecting patients who were already anti-HCV-positive who dialysed in the same console and during the previous shifts, were compared. No correlation was observed. The investigation included the collection of information on the use of multi-dose medication vials, staff training, the use of gloves, and environmental decontamination or other methods of infection control.

Exposure to blood and potentially contaminated items could not be anticipated in every situation, and opportunities for cross-contamination from chronically infected patients were rarely observed.

Conclusions

- The molecular data obtained from the study strongly suggest patient-to-patient transmission of HCV in haemodialysis units.
- The main pitfall of the use of the 5' UTR sequence is that only five different isolates were found in haemodialysis patients by application of this method. Despite this limitation, evidence was found for nosocomial transmission.
- It was shown that measures to treat anti-HCV positive patients in dedicated areas failed. The sequencing data allowed investigators to exclude console contamination.
- There was no evidence for blood or blood-product contamination.
- The data from this study highlight the importance of strict enforcement of standard precautions to prevent HCV transmisison in haemodialysis units - during the process of haemodialysis, exposure to blood can be routinely anticipated, and gloves are required whenever caring for a patient or touching the equipment.
- Medications should not be prepared in the same room as the ones being used for treatment of patients, and common trolleys should not be used to distribute medication.
- Training and educational programmes for all health care workers should be improved in order to reduce risk and prevent transmission of infections among chronic haemodialysis patients.

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Based on presentations by Dr Filippo Ansaldi and Dr Giancarlo Icardi, University of Genova, Italy.

Residual risk of transfusion-transmitted HBV, HCV, and HIV infections in Italy

The residual risk of transfusion-transmitted viral infections (TTIs) is mostly related to the use of blood donated during the window period in which an acutely infected donor may harbour infectious viral particles in the absence of symptoms and antigens / antibodies. The probability of transmitting blood-borne viruses through the transfusion of screened blood is related to the length of the pre-seroconversion window, and to the incidence of HBV, HCV, and HIV infections among the donors.

Prevention strategies for blood transfusion safety include:

- Selection of period, volunteer, unpaid donors;
- Evaluation of donor's medical and personal history;
- Confidential exclusion of suspected blood units;
- Implementation of donor screening;
- Viral inactivation; and
- Proper use of blood, blood components, and derivatives.

The magnitude of residual risk may differ by country depending on the sensitivity of screening assays and the levels of HBV, HCV, and HIV endemicity. In most industrialised countries, the rates of TTIs are so low as to render impossible their measurement through most specific studies, although some mathematical models have been developed.

Study of transfusion-transmitted viral infections in Lombardy

Between January 1996 and December 2000, a study was carried out in the region of Lombardy to assess the risk of transmitting HBV, HCV, and HIV by transfusion of screened blood. Another study objective was to estimate the additional reduction in risk that may be achieved through the implementation of direct viral detection assays. The sample comprised 2,411,800 unpaid donor volunteers, with a mean of 223,500 donors per year. Laboratory measurements were carried out using third-generation EIA and supplemental assays.

The results of the study demonstrated that the risk of acquiring HBV, HCV, or HIV through transfusion is extremely low. Nevertheless, the safety of blood supply remains a major source of public concern, requiring a continuous effort to reach zero risk. Advances in viral inactivation technologies and the introduction of nucleic acid amplification technology (NAT) offer the potential to increase the safety of blood supply.

Assays for the detection of HIV p24 Ag and HCV cAg can represent alternatives to NAT that are easy to perform, compatible with the current EIAs, and possibly less expensive. In the case of HIV, NAT is clearly more sensitive than the p24 assay. In the case of HCV, NAT and HCV cAg show comparable clinical sensitivity (mean difference 1-2 days, range 0-10 days).

The risk of transmitting HBV, HCV, and HIV by transfusion of screened blood collected from period donors, properly selected through volunteers with appropriate medical history, is currently very low. It can be reduced even further with the introduction of direct viral detection assays.[1]

The need for such assays may vary by country depending on:

- HBV, HCV and HIV endemicity;
- Health care resources;
- Potential benefits and costs; and
- Ethical and legal issues that may have an impact on policy decision making.

The yield of NAT for HCV in different European countries

Country	*Observed cases*	*Cases / 10^6 population*
Netherlands	0/1,800,000	0
United Kingdom	3/7,000,000	0,4
Germany	6/3,600,000	1,7
Spain	2/1,000,000	2
Italy	3/1,679,935 (NAT+Ag) 3/829,855 (NAT only)	1,8 3,6

European legislation regarding NAT

On 1 July 1999, the European Agency for the Evaluation of Medicinal Products (EMEA) recommended that all plasma products intended for fractionation be tested for HCV using NAT. Since then, much of the recent European legislation relating to blood safety and HCV screening supports the use of NAT. In Italy, NAT has been mandatory since June 2002.

Testing options and their cost-effectiveness

PCR testing performed in parallel with antibody screening, either on pools or on single donations, is not currently a cost-effective option for the detection of HCV in blood donors.[2]

The cost-effectiveness of adding minipool NAT to current screening, although high, may not be unreasonable when considered within the context of other preventive health care interventions (e.g., HIV p24 Ag testing, universal precautions for HIV, and autologous blood donations), and the desire for a zero tolerance level for infections from blood transfusions.[3]

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Based on a presentation by Dr Alessandro Zanetti, Institute of Virology, University of Milano, Italy.

Clinical patterns, epidemiology, and disease burden of hepatitis delta virus chronic liver disease

Background: epidemiology of hepatitis delta virus infections in the 1980s

It was not until the 1980s that the epidemiological patterns of hepatitis delta virus (HDV) infection were identified.[1] Endemicity was high in the developing countries of South America and Africa where HDV was transmitted primarily by super-infection in areas where HBV was highly endemic. In these countries, HDV infection occurred mostly among children perinatally infected with HBV. By adulthood most of these carriers had also contracted HDV.[2]

HDV endemicity was low in temperate and cold regions of the world where HBV prevalence is low. However, HDV was also low in some subtropical and temperate areas where HBV rates are high, such as Japan and Southeast Asia. In these areas, HDV infection was acquired primarily through parenteral exposure to HBV among injecting drug users (IDUs). In such cases, HDV infection was acquired by co-infection through blood and unsafe sexual contacts with other infected IDUs. HDV infection only rarely occurred in the general population, and then it was usually found among immigrants from high HDV-endemic areas, and in the form of chronic hepatitis D acquired by super-infection.

The endemicity of HDV was intermediate in southern Europe. Italy provided the prototype for this pattern, which resulted from an endemic pattern in the general population and an epidemic pattern within groups at risk of HBV infection, with IDUs in urban areas being the largest risk group. Other less conspicuous risk groups included haemophiliacs receiving clotting products from pooled plasma, institutionalised patients, prisoners, sex workers and haemodialysis patients.[1] In the general population, HDV was transmitted primarily through super-infection. Co-habitation with an anti-HDV-positive subject was the single most important risk factor for HDV transmission.

Living in a large family, as well as being an HBsAg carrier, distinctly increased the risk of acquiring HDV.[3] As large families were common in southern Italy during that time, residence in the south of Italy was considered a significant risk factor. Spread of the virus in Italy was slow and sporadic, occurring primarily among those living in overcrowded family units in the south of the country. As underlying HBV infection was not acquired perinatally but in childhood, co-infection with HDV was delayed and began to occur among adolescents and young adults.

Current epidemiological situation[4-6]

There is a scarcity of epidemiological data regarding HDV in areas of high endemicity. In addition, the small number of cases and their disparate clinical characteristics make data comparison difficult. However, it appears to be unlikely that the pattern of HDV infection has changed in endemic areas of the developing world since none of the factors that determine transmission and circulation has been modified in the last ten years. The reduction of HBV infection and the shrinking HBsAg pool among IDUs may have had some impact on reducing HDV infection in IDU communities. The fact that HDV has received limited interest in recent years may reflect a diminished clinical role of this infection within high-risk groups.

In southern Europe, spectacular changes have occurred in the epidemiological and clinical features of HDV infection, best characterised by what has occurred in Italy where circulation of HDV has significantly declined. The decrease of HDV infection may be attributed to control of HBV infection through:

- Improved public health standards
- Universal HBV vaccination[7]
- Measures to contain the spread of HIV, which is transmitted in the same way as HBV and HDV.

The fear of HIV/AIDS has brought with it a reduction of HDV transmission through sexual contacts. Also, a reduction of family size has been brought about by social and economic changes in southern Italy. Both of these factors have had an impact on reduction of HDV infection. However, available data suggest that the prevalence of HDV infections has not significantly diminished in Italian IDUs. So, although there has been a consistent numerical shrinkage, drug-using communities continue to represent a pool of HBsAg carriers that allows significant transmission of HDV.

Changing clinical patterns of HDV

In the 1980s, although medical scrutiny worldwide suggested that HDV infections could result in a wide spectrum of liver disorders and sub-clinical infections without signs of liver damage, in most clinical studies a significant association had emerged between HDV infection and severe acute and chronic liver damage.[1,2,8-10]

Data from Italian medical centres show that the proportion of HDV-positive to total HBsAg-positive chronic persistent hepatitis, chronic active hepatitis and cirrhosis diminished between the 1980s and 1990s when comparing similar histological varieties of HBsAg liver disorders:[11]

Clinical manifestation	Proportion of HDV-positives	
	1980s	1990s
HBsAg chronic persistent hepatitis	10.6%	2.0%
Chronic active hepatitis	34.5%	7.1%
Cirrhosis	42.5%	11.7%

The occurrence of new hepatitis D pathologies has greatly diminished due to the diminished circulation of HDV, and the medical scenario is now dominated by advanced fibrotic HDV disorders.

In Torino, the proportion of cirrhotic to non-cirrhotic patients increased from 30% in the period 1977-1986 to 70% between 1996 and 2000, the latter representing cohorts of patients who survived the immediate medical impact of hepatitis D and who are now seeking care for end-stage decompensated liver disease. These patients do not respond to interferon and are unlikely to achieve long-term benefits from any existing medical therapy. Ultimately, only liver transplantation offers therapeutic hope. In Europe, the proportion of HDV transplants over the total number of cirrhotic transplanted patients has amounted to 5% during the last decade,[12] a percentage which largely exceeds the current epidemiological impact of HDV infection whose prevalence in the general HBsAg carrier population is less than 1 in 100.

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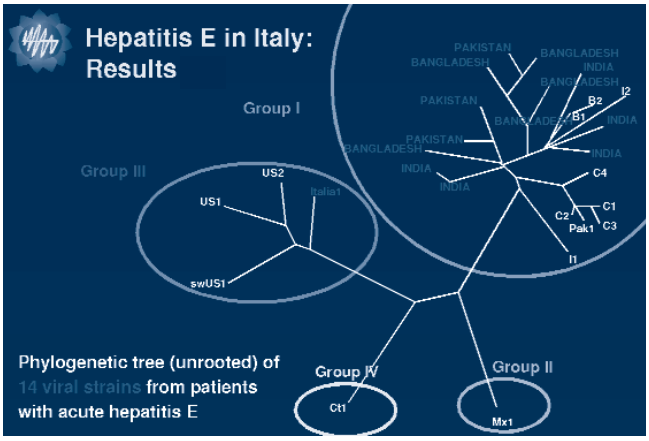
Based on a presentation by Dr Mario Rizzetto, Department of Gastroenterology, Azienda Ospedaliera S. Giovanni Battista, Torino, Italy.

Hepatitis E virus infection in Italy

In Italy, hepatitis E virus (HEV) is only a minor cause of viral hepatitis.[1] Hepatitis E is generally diagnosed in travellers from endemic areas. However, sporadic cases of acute hepatitis E not associated with travel have been reported in Sicily.[2]

Between January 1994 and December 2001, a study was carried out among 310 patients with acute non-A, non-C hepatitis, at the University of Milano's Institute of Virology. The aim of the study was to identify risk factors for acute hepatitis E infection during the six-month period preceding onset of the illness. The methodology consisted of personal interviews with each of the patients using a pre-coded questionnaire. Hepatitis E was defined by the presence of HEV-RNA in sera and/or stools; positivity for IgM anti-HEV and/or seroconversion to IgG anti-HEV. The study results showed that HEV was the aetiological cause in approximately 14% of patients with acute non-A, non-C hepatitis, 95% of whom exhibited a benign course of the disease.

A new HEV strain was also identified in an individual who had never indicated travel or contact with individuals associated with endemic areas, further suggesting that this virus may be native to Italy.[3,4]



Other studies of anti-HEV prevalence rates show that within the healthy population, anti-HEV is evident in approximately 1% of the population in northern Italy, and up to 5% in southern Italy and the Islands.

Anti-HEV is rarely seen in children, and appears to increase in frequency with age, which suggests that there may be a cohort effect with infections acquired in the past.[5]

Preventing hepatitis E virus infection includes public health measures to control the transmission of enteric infections, particularly to ensure the supply of clean water. Other prevention measures include the following precautions to travellers to endemic areas:

- Avoid drinking water of unknown origin;
- Avoid eating uncooked shellfish, vegetables, and unpeeled fruit;
- Ensure high standards of personal hygiene.

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Based on presentations by Dr Alessandro Zanetti, Institute of Virology, University of Milano, Italy, and Dr Rosa Cristina Coppola, Department of Hygiene and Public Health, University of Cagliari, Italy.

Conclusions of the meeting

The Viral Hepatitis Prevention Board met in Catania, Italy, November 7-8, 2002, to review Italy's progress in preventing and controlling viral hepatitis. The specific meeting objectives were:

- To review Italy's surveillance systems for infectious diseases;
- To establish an up-to-date epidemiological overview of viral hepatitis in Italy;
- To evaluate Italy's current prevention and control measures for viral hepatitis; and
- To consider Italy's public health programmes as possible models for other European countries to follow in their prevention and control programmes for viral hepatitis and other infectious diseases.

IMMUNISATION

During the 1970s, hepatitis B had become a major public health problem in Italy, which led to extensive research being carried out among scientists, doctors, and public health experts to help tackle the problem. However, Italy's improved standards of living and medical care, together with a changing demography and behavioural changes, led to a decrease in levels of hepatitis B virus infection, starting from the end of the 1970s. During the 1980s, prevention programmes were put into place, such as screening and free-of-charge immunisation for high-risk groups, which helped to lower hepatitis B virus infection levels.

1. Immunisation policies in Italy are specified in national laws or guidelines. However, each region prepares its local / regional health plans accordingly, and adapts them to local priorities. The regions also provide the funding for their immunisation programmes.

2. Mandatory hepatitis B vaccination for all infants and 12-year-old adolescents, together with mandatory screening of pregnant women, was introduced in 1991.

SURVEILLANCE

At the national level, there is a mandatory system of notifiable infectious diseases, which includes all types of viral hepatitis. The specification of the types was introduced in 1987. SEIEVA (*Sistema Epidemiologico Integrato dell'Epatite Virale Acuta* - Integrated epidemiological system for acute viral hepatitis) was set up in 1985 to monitor epidemiological trends of acute viral hepatitis and to identify epidemic clusters and risk factors associated with various types of hepatitis. The system is based on voluntary participation, and its primary aims today are to monitor the impact of acute viral hepatitis prevention strategies.

EPIDEMIOLOGY

Hepatitis A

Improvements in clean water supply and sewage disposal, and vaccination have led to a decline in HAV circulation. In northern regions of Italy, the anti-HAV prevalence rate is approximately 10% among those under 20 years of age, leaving large cohorts of susceptible adults who have not developed immunity to the virus in childhood. In southern regions, such as Puglia and Campania, prevalence rates are as high as 40% in 18 year-olds, and over 30% among those 20 to 30 years old.

Continued outbreaks of HAV infection account for huge economic costs to infected patients, public health services, and society as a whole. In 1997, Puglia introduced hepatitis A vaccination for infants 15 to 18 months old, to be given simultaneously with measles-mumps-rubella (MMR) vaccine, and for 12-year-old adolescents, to be given together with the mandatory hepatitis B vaccine.

The high cost of outbreaks has made immunisation strategies effective in reducing the burden of disease and economic costs to all concerned.

Hepatitis B

HBV infection rates continue to decline in Italy. Since universal immunisation for infants and 12-year-old adolescents was introduced in 1991, together with mandatory screening of pregnant women, vaccination coverage is ca 90% overall in Italy, and ca 95% in some regions.

The incidence of acute hepatitis B had already begun to decline before 1991, and has decreased even further since the introduction of routine vaccination programmes, particularly for adolescents and young adults who have received hepatitis B mandatory vaccination. However, epidemiological data show that the situation has changed very little among older subjects - a situation that highlights the importance of combining routine immunisation with communication and education programmes aimed at high-risk groups.

With regard to HBV mutants, there is no evidence to suggest that they pose a threat to Italy's universal vaccination programme.

If hepatitis B vaccination coverage rates are maintained at their current levels, elimination of HBV transmission in Italy could become a reality within the next few decades.

Hepatitis C

The prevalence in the general population is now estimated to be 2-3%, and as high as 12% to 26% in certain areas of the country. New HCV infections continue to occur and given the long-term serious complications, it is clear that in order to reduce further their rate, strict application of recommended preventive measures will be required.

The incidence of acute hepatitis C virus infection in Italy is approximately 1/100,000 annually, but the number of new infections per year is at least 10 times higher, since most infections are asymptomatic. The incidence of HCV infection in Italy has decreased during the last 15 years due to:

- Use of disposable syringes and needles;
- Screening for safe blood and blood products; and
- Implementation of universal precautions in medical settings.

Targets under sero-epidemiological investigation:

- Blood donors;
- Subjects receiving haemoderivatives (blood products, i.e., FVIII, FIX);
- Intravenous drug users / lifestyle;
- Haemodialysis patients;
- Health care workers;
- Pregnant women; and
- Vertical / perinatal transmission.

Molecular investigations strongly suggest patient-to-patient transmission of HCV in nosocomial settings. Standard precautions to treat anti-HCV positive patients in dedicated areas need to be strictly enforced.

- During the process of haemodialysis, exposure to blood can be routinely anticipated, and gloves are required whenever caring for a patient or touching the equipment.
- Medications should not be prepared in the same room as the ones that are being used for treatment of patients.
- Common trolleys should not be used to distribute medication.

- Training and educational programmes for all health care workers should be improved in order to reduce risk and prevent HCV transmission of infections among chronic haemodialysis patients.

It is expected that the development and availability of a hepatitis C virus vaccine, together with new therapeutic options, will lead to improved prevention and control of HCV infection.

Residual risk of transfusion-transmitted HBV, HCV, and HIV infections

The risk of transmitting HBV, HCV, or HIV by transfusion or screened blood collected from period donors, properly selected through volunteers with appropriate medical history, is currently very low. Transmission prevention strategies for blood transfusion safety include:

- Selection of period, volunteer, unpaid donors;
- Evaluation of donor's medical and personal history;
- Confidential unit exclusion;
- Implementation of donor screening;
- Viral inactivation; and
- Proper use of blood, blood components, and derivatives.

Residual risk can be reduced even further with the introduction of direct viral detection assays. The need for such assays may vary by country depending on:

- HBV, HCV, and HIV endemicity;
- Health care resources;
- Potential benefits and costs; and
- Ethical and legal issues that may have an impact on policy decision making.

On 1 July 1999, the European Agency for the Evaluation of Medicinal Products (EMEA) recommended that all plasma products intended for fractionation be tested for HCV using nucleic acid amplification technology (NAT). Since then, much of the recent European legislation relating to blood safety and HCV screening supports the use of NAT. In Italy, NAT has been mandatory since June 2002.

Hepatitis D

In southern Europe, spectacular changes have occurred in the epidemiological and clinical features of HDV infection. In Italy the decrease of HDV infection may be attributed to control of HBV through:

- Improved standards of public health;
- Universal HBV vaccination;
- Measures to contain the spread of HIV, which is transmitted in the same way as HBV and HDV.

Hepatitis E

In Italy, HEV is only a minor cause of viral hepatitis. Hepatitis E is generally diagnosed in travellers from endemic areas. However, sporadic cases of acute hepatitis E not associated with travel have been reported in Sicily.

Within the healthy Italian population, studies of anti-HEV prevalence rates have shown that anti-HEV is evident in approximately 1% of the population in northern Italy, and up to 5% in southern Italy and the Islands.

Anti-HEV is rarely seen in children, and appears to increase in frequency with age, suggesting that there may be a possible cohort effect with infections acquired in the past.

Preventing hepatitis E virus infection includes public health measures to control the transmission of enteric infections, particularly to ensure the supply of clean water. Other prevention measures include the following precautions to travellers to endemic areas:

- Avoid drinking water of unknown origin;
- Avoid eating uncooked / undercooked shellfish;
- Avoid eating uncooked vegetables and unpeeled fruit; and
- Ensure high standards of personal hygiene.

CURRENT PREVENTION AND CONTROL STRATEGIES

Public health is held in high regard by the general public in Italy. Prevention and control strategies against infectious diseases also have clear political support.

Effective routine surveillance systems and data from SEIEVA provide Italy with reliable feedback, and flexibility in responding to disease outbreaks through:

- Rapid identification of the source of infection
- Rapid identification of the population to be targeted by vaccination (e.g., contacts of cases and people present in institutions where infection has occurred);
- Rapid communication campaigns informing people about the infection, how it is spread, the possibility of prevention by vaccination, and good hygiene measures;
- Rapid creation of a task force in charge of the action programme;
- Rapid administration of the first vaccine dose to the target population;
- Maintenance of records of vaccinated people; and
- Documented review of the campaign detailing:

  - Initial number of cases;
  - Ratio of numbers immunised versus the target population;
  - Time necessary to bring the outbreak under control;
  - Number of cases occurring in vaccinees and the timing of their vaccination; and
  - Number of boosters administered.

LESSONS LEARNT

1. Departments of Prevention need clear and agreed mandates together with effective training of staff.

2. Prevention plans need to be evidence-based.

3. The need for immunisation is evident.

4. Risk factors still contribute to transmission especially through failure of standard precautions in medical practice and interventions.

5. Outbreaks in nosocomial settings may be underestimated.

6. Successes in disease prevention must take into account an accurate assessment and interplay of socio-economic conditions, improved hygiene measures and immunisation.

7. Increase coverage through mandatory immunisation programmes.

8. Continue efforts to reach members of risk groups who remain unvaccinated despite availability of free vaccine.

RECOMMENDATIONS FOR FUTURE ACTIONS

1. Continue to increase awareness of vaccine-preventable diseases and develop actions to help persuade HBsAg-positive mothers to have their children immunised.

2. Conduct epidemiological studies on:
(a) Transmissibility of and susceptibility to HBV escape mutants; (b) Factors underlying the increase in anti-HBe-positive chronic hepatitis B; (c) Seroprevalence studies of HAV, including documentation of occupational risks.

3. Continue education programmes aimed at improving hygiene and food preparation to prevent HAV and HEV infections, and other food-borne diseases.

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