

**The Hepatitis C Epidemic.
Burden, Determinants & Strategies:
A Roadmap for Pakistan.**

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The Netherlands**

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Analysis of Hepatitis C burden, determinants and prevention & control strategies globally and in Pakistan.

A thesis submitted in partial fulfillment of the requirement for the degree of Masters of Public Health

By Adnan Asghar, The Netherlands

Declaration:

When other people's work has been used (either from a printed source, internet or any other source) this has been carefully acknowledged and referenced in accordance with departmental requirements.

This thesis **The Hepatitis C Epidemic. Burden, Determinants & Strategies: A Roadmap for Pakistan** is my own work.

Signature:..........

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‘It’s closer than you think’

- Subtheme of World Hepatitis Day 2012

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Abbreviations:

SVR: sustained virologic response

WHO: world health organization

HCV: hepatitis C virus

HBV: hepatitis B virus

TB: tuberculosis

HIV: human immunodeficiency virus

AIDS: acquired immunodeficiency virus

ICER: incremental cost per quality-adjusted life year

HAART: highly active anti-retroviral treatment

RIBA: recombinant immunoblot assay

peg-IFN: pegylated-interferon

SVR: sustained virological response.

QALY: quality adjusted life years

HCC: hepatocellular carcinoma

MMT: Methadone maintenance therapy

NSI: Needle stick injury

NEP: Needle exchange program

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Abstract:

About 170 are chronically infected with hepatitis C (HCV) around the world and run the risk of developing liver cancer. In Pakistan, approximate 5% of the population are chronic carriers , affecting both genders from all age groups and social classes though certain groups suffer more. It is spread through contact with infected blood. While in developed countries this is through invasive drug use, in developing countries it through medical equipment.

Determinants, play a vital role in HCV transmission and spread and are often intertwined. However, the factors much like the disease are not well understood and not contextual. As a result, there is a need to understand these factors for formulate evidence-based interventions in an efficient and equitable manner. The interventions thus far have been combined with HIV and hepatitis B strategies, thus tackling multiple diseases at once. But interventions must be more holistic and include involvement from other sectors, e.g. urban affairs and housing to make a dent in prevalence. Furthermore, with populations becoming more mobile, so has the virus.

In the wake of the recent global response to viral hepatitis and recent WHO initiatives, this is the perfect time to use the momentum, develop a roadmap for Pakistan and mobilize resources and efforts. This thesis attempts to provide an understanding about the determinants and formulate a road map for Pakistan.

Estimated word count: 11,957

Chapter 1: Country Background.

Pakistan, an Islamic republic with parliamentary democracy, is a South Asian country with 180 million inhabitants. She gained her independence from the British on 14th August 1947, retained English as the official language though Urdu is the unofficial and widely spoken language. She covers a total area of 796,096 square kilometers, and borders Iran, Afghanistan, China and India (from east to west), with the Himalayan mountains run along the north, and the Indian Ocean bordering the south. It is a monsoon country with an annual rainfall between 76 and 127 cm. Main route of transportation is via roads (carry 96% of inland materials) , mobile coverage is 64.9% and rising.

There are 5 provinces Punjab, Sindh, Balochistan, NWFP (which recently formed Pakhtoonkhwa and FATA) and additional tribal areas of Azad Jammu and Kashmir. About 97% of the population are muslims. The major local ethnicities are Punjabi (44.7%), Pashtun (15.4%), Sindhi (14.1%), Saraiki (8.4%) Muhajir (7.6%), Baloch (3.6%), and remaining groups (6.3%). (1)

There are an estimated 1.7 million refugees, 97% are Afghans, and 420,500 internally displaced from NWFP. (2) The provinces are divided into 142 districts with further subdivided into Tehsils and finally villages or municipalities. Each province comprises of various ethnicities with their own language and dialects, traditions and customs. Islamabad is the capital while Karachi is the most populated city, at 16 million.

Disparities in health are seen based on geographical region and within districts. For decades, political leaders from Sindh and Punjab, have been elected to office. This led to focus and development the 2 provinces. Balochistan, remains least developed and afflicted by tribal conflicts.

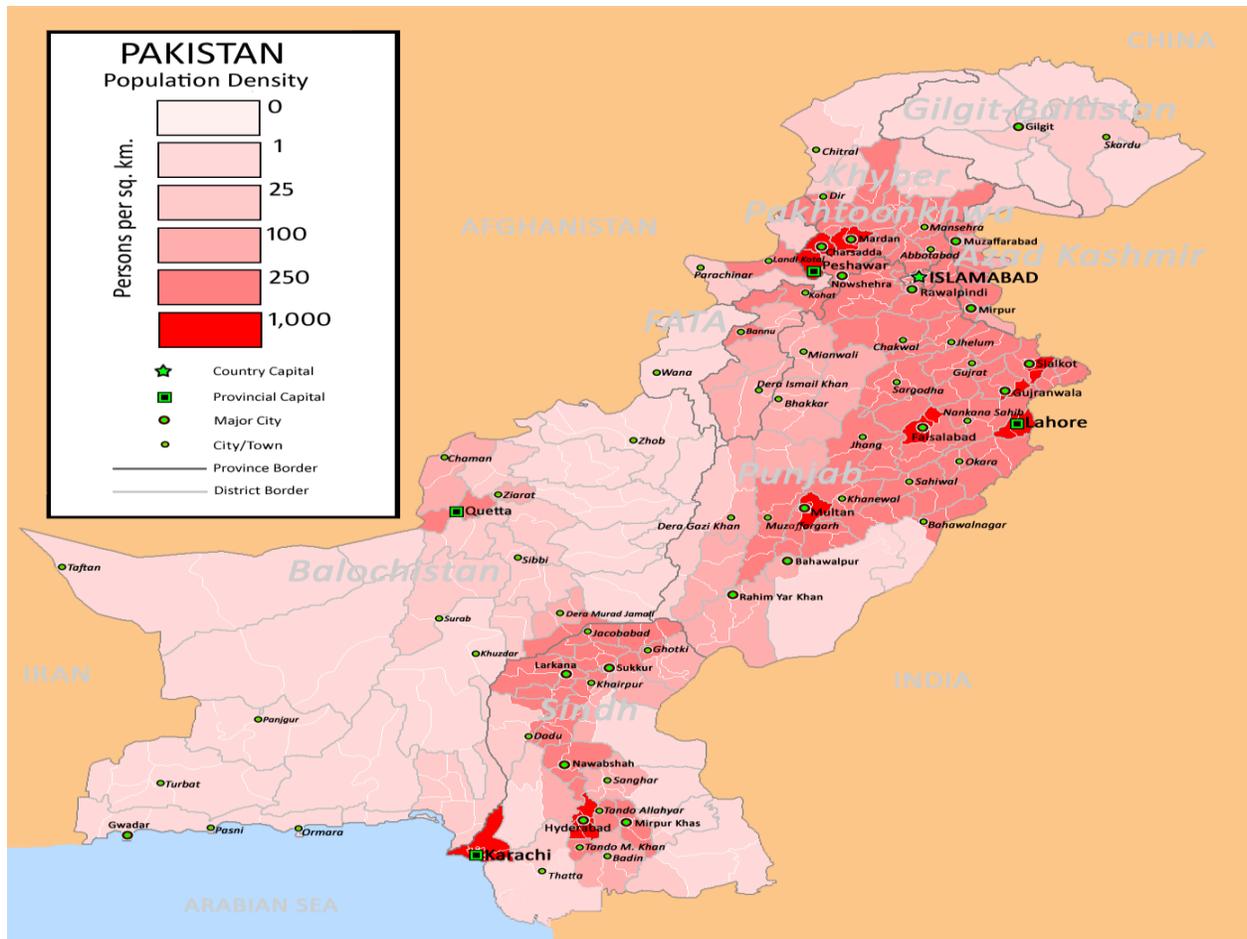


Figure 1. Population density map of Pakistan (12)

Post Flood assessment, following the heavy monsoon floods in July 2010, showed that direct effects were felt by 14.1 million people, mostly the labor class and farmers 1.1 million people lost their house with a damage of 2 million hectares of crops throughout Punjab, Balochistan and Sindh, leading to an estimated damage of US\$43 billion that Pakistan still has yet to recover from. (3)

1.1 Health

Male to female ratio is 1.07. Total Fertility rate is 3.4 children per woman (has been dropping), with contraception prevalence of 27% (a drop of 3% since last year). Crude birth rate of 27.5 per 1,000. Life expectancy is 65.8 years for men and 66.1 years for women. Crude death rate and infant mortality have declined to at 7.2 per 1000 and 69 per 1,000 respectively. (4)

Maternal mortality ratio is 260 / 100,000 live births. Antenatal care (ANC) coverage is 61%, 47% vaccination coverage. Hepatitis B (HBV) vaccination coverage is 54.5%. **(5)** Access to clean water (92%) and improved sanitation (48%) has increased.

Approximately 43.4% is under the age of 15, 36% live in urban areas, adult literacy rates for men and women are 69% and 45% respectively, total labor force is 56.33 million, 73.8% work in the informal sector, higher in rural sector (76.5%) than the urban sector (71.2%). Minimum labor wage is Rs. 8,000/- and 5.6% of the workforce is unemployed.

1.2 Economy & Health

Pakistan is a low-middle income country with a GDP per capita of \$2,800 and GDP growth of 3.7% (2011-2012). The total expenditure on health (TEH) as % of GDP is 2.2%. General governmental expenditure on health (GGHE) as % of GDP is 38.5% and GGHE as % of General governmental expenditure is 3.6%, social security funds as % of GGHE is 3.8, out of pocket expenditure is 82%. The largest sector is agriculture, which utilized 45% of the labor force. Expatriate remittance is estimated close to US\$8 billion annually. Health care insurance coverage, primarily through employer-employee insurance, is limited to only a quarter of the population. An estimated 22.3% of the population live below the poverty line.

1.3 Security Protection Schemes

Social safety nets, primarily through the federal Benazir Income Support Programme (BISP) initiative, have 6 running programs, namely "Graduation Initiatives", "Waseela-e-Haq", "Waseela-e-Rozgar", "Waseela-e-Sehat" and "Waseela-e-Taleem", covering 7 million residents. Federal Zakat funds, Pakistan Poverty Alleviation Fund and NGO initiatives, e.g. Nya Jeevan, provide additional coverage to poor communities. "Employment Old Age Benefits" provides elderly pension and benefits. Workers Welfare Fund provides grants to industrial workers.

1.4 Health care

The health care system (HCS) is reversing the process of devolution, previously passed as per 18th Amendment on June 2011 which abolishing the federal ministry of health (MOH), shifting powers from District

Department of Health (DOH) to Provincial DOH. Regulation is through the Pakistan Medical and Dental Council (PMDC).

There are currently approximately 972 hospitals, 4,842 dispensaries, 5,374 basic health units (BHU) and 909 maternity and child health centers (MCHC). There are about 149,201 doctors, 10,958 dentists, 76,244 nurses and 108,137 hospital beds, with an approximate 1,206 person-doctor ratio, 16,426 person-dentist and 1,665 person-hospital bed ratio. (4) About 65% of deliveries are conducted at home, (6) mostly by Traditional birth attendants (TBA), or midwives(90%).

Public HCS infrastructures are heavily under-utilized (30%), comprising of primary care units entailing BHU serving 10,000-20,000 residents and Rural Health centers (RHS) serving 25,000-50,000 residents. BHU and RHS support grass root community programs such as Lady Health Worker (LHW) programs and Village Based Family Planning Worker (VBFPW), providing a wide variety of services including family planning, ANC, EPI, IMCI, TB and malaria control and referrals to higher tiers. Secondary care units include Tehsil hospitals, serving 0.5-1 million residents and District hospitals comprise largely of doctors, nurses, midwives and laboratory technicians and provide more in-depth services including radiology, general anesthesia, routine and emergency surgeries. Tertiary care centers serve 1-2 million residents and are teaching hospitals, specialized intensive care units, advanced diagnostic services and specialized care providing care to difficult cases via specialized doctors and nurses, located in urban settings. (7) In recent years, hepatitis screening has treatment been extended to rural primary and secondary rural "sentinel sites".

The informal health sector consists of uncertified GP's and complementary & alternative medicine (CAM) providers including homeopaths, hakeems, traditional healers, herbalists and bone setters. There are also unregulated medical stores and healthcare facilities (HCF). The informal sector is geographically and financially accessible to rural and urban groups.

Chapter 2: Problem Statement, Objectives, Methodology, Conceptual Framework.

"This is hepatitis..."

World Hepatitis Day subtheme (2012)

2.1 Problem statement

HCV, a viral hepatitis, is one of the leading causes of chronic hepatitis and chronic blood-borne disease (BBI). Globally, an estimated 130-170-million people are affected, accounting for 2.2%-3.0% of the global population, with large regional variation. The highest burden (85%) is in developing countries. Most people (75%) are unaware they are infected. It reduces productivity, incurs additional healthcare costs and drives poor families into poverty. (8)

It is a major cause of liver cirrhosis and hepatocellular cancer (HCC) in a significant proportion. In 2002 alone, an estimated 211,000 out of 446,000 global deaths from cirrhosis were attributed to HCV while in the case of HCC, it accounted for about 155,000 deaths from a 483,000 total. (9) HCV-related mortality has surpassed that of HBV and HIV/AIDS in many regions with a continual rising trend. Mathematical models expect HCV-related morbidity and mortality to rise in developed countries due to long periods of chronicity.

Studies surrounding contextual factors are lacking with policy formulated primarily on high-risk prevalence data and scarce community cross-sectional studies. In Pakistan, the estimated prevalence is among the highest in the world at (4.5%-5.3%). Regional variations exist, with high prevalence in both urban regions, e.g. Gujranwala (23.8%) and Lahore (19.9%), and rural regions, e.g. Darsano Channo (44%). It affects men and women of all ages and socioeconomic backgrounds driving many households into financial debt. Transmission through contaminated blood products is the main route of transmission which is linked to broad underlying determinants seen for other infectious diseases. (10). Thus it extends outside the realms of individual health and into education, the physical environment, health sector reform and politics. Additionally, broad sociopolitical issues similar to that of HIV come into play including equity, human rights, international tourism and security. The scope of this thesis is to provide an organized and logical order

of HCV burden, the risk factors and determinants in HCV transmission and spread and evidence based practices for possible applicability in Pakistan.

In conclusion, HCV remains an avoidable disease but without proper understanding of the determinants and evidence based strategies , HCV will continue to spread with the cost being borne by future generations.

2.2 Objective:

2.2.1 Overall Objective

To analyze the burden of HCV globally and in Pakistan, critically discuss specific determinants and reviewing current and potential strategies on the basis of applicability, effectiveness and feasibility.

2.2.2 Sub-objectives

- 1) describe and critically discuss the burden of HCV and it's trends, both globally and in Pakistan.
- 2) review the risk factors and broader determinants that influence the spread and transmission of HCV and it's sequelae.
- 3) present and discuss the evidence based control measures for HCV
- 4) review and critically discuss current strategies in Pakistan
- 5) Formulate recommendations for HCV control in Pakistan.

2.3 Methodology

2.3.1 Study Design

A literature review was conducted in the writing of this thesis.

2.3.2 Study Method

The author conducted literature reviews of quantitative and qualitative public health and biomedical articles. Various search engines and keywords were used, sometimes alone other times in combinations. Listed as follow;
Search engines: Pubmed, Cochrane, Medline, Scopus, Google Scholar, Google
Websites: WHO, Hepatitis Foundation, Department of Health, PakMediNet, Gomal Journal of Medical Science, World Hepatitis Alliance, CDC

Key words: hepatitis C, hepatitis B, viral hepatitis, HCV, HBV, HIV, AIDS, intervention strategies, prevention, needle injury, human resources, harm reduction, Australia, Pakistan, ethical considerations, infectious diseases.

2.3.3 Conceptual framework

The Lalonde model on social health determinants and health inequities was used as a conceptual framework. The model focuses on 4 key determinants in HCV transmission that will be discussed throughout the thesis.

Lalonde Framework

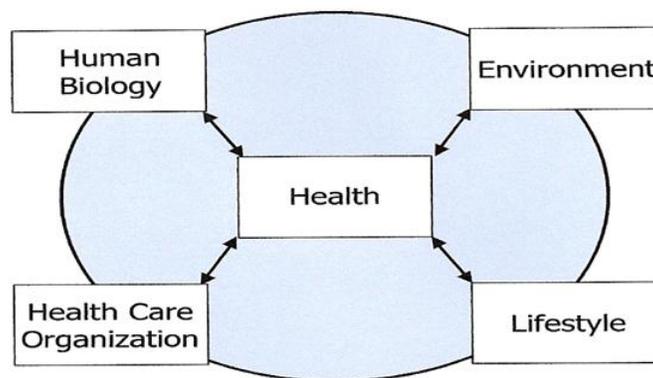


Figure 2: Source: The Lalonde Report (11)

2.3.4 Limitations

The limitations of this thesis are scarce contextual literature on HCV specific health determinants in Pakistan. Also details on previous and current national hepatitis programs in Pakistan are limited especially in Balochistan and NWFP. It is possible that this was published in the local language or not yet made electronically available. Furthermore, specific subcultures with their own traditions, custom, language and religious interpretations exist. However rational generalizations have been made. Additionally, most data found are sero-prevalence studies from high risk groups which may not be representative of the general population.

Chapter 3: Global Burden.

This chapter will attempt to address the burden of HCV in the global context and that of Pakistan. The focus will not be on a specific region and thus the data provided is by no means exhaustive. Significant variations between and within regions but evidence-based generalizations will provide a baseline comparison for Pakistan's context, and see her standing in the HCV burden.

3.1 Introduction:

Prior to 1989, groups requiring multiple transfusions developed post-transfusion "non-A non-B hepatitis". Following its diagnosis in April 1989 by the CDC, blood screening was initiated in 1990 through development of HCV serologic tests. It was discovered that HCV accounted for 95% of post-transfusion cases. By 1992, 3rd generation tests were developed, still in use today, with high sensitivity and specificity. By 1991, Interferon (INF) was approved by the FDA to treat HCV. By 1998, combination therapy of INF and ribavirin, initially developed for HIV, became FDA approved that led to dramatic cure rates, depending on HCV genotype, discussed later. By 2001, pegylated INF (pINF) came into the market with better cure rates and less frequent dosing intervals. By 2005, the National Institutes of Diabetes and Digestive and Kidney Diseases (NID-KID) replicated HCV in a test tube, gaining valuable insight into HCV life cycle and therapeutic opportunities. (13)

3.2 Clinics of HCV:

3.2.1 The HCV virus

HCV, a hepacivirus genus of the flavivirus family, causes viral hepatitis, developing chronicity in most cases. HCV survives for 16 hours on surfaces and up to 4 days in blood products and is 10 times more infectious than HIV. (16)

Six major genotypes have been identified each with subtypes. (17)

The predominant genotype varies between countries (type 1a and 1b accounting for 60% of global burden) and between provinces. Rate of chronicity does not change with genotype but treatment duration and cure rate do which has major health implications. (18) Developing immunity is termed as a mounting a sustained virological response (SVR), defined as the normalization of transaminase (ALT) levels and undetectable HCV-RNA which

can occur naturally in 25% or through treatment. (19) A SVR towards one genotype does not award immunity towards another. Hence re-infections with different strains can occur.

3.2.3 Regional variations in Genotype:

Genotype 1 is prevalent in Northern, Southern and Eastern Europe, Japan, Canada and USA, type 1a and 1b accounting for 60% of global prevalence. SVR is seen in 70% following 48 weeks of treatment. Genotype 2 and 3 have a SVR of 90% after a treatment duration of 24 weeks and seen in Sub-Saharan Africa and South-east Asia, respectively. Genotype 4 is seen in the Middle East, Egypt and central Africa with a cure rate of 65% after 48 weeks while genotype 5 is prevalent in South Africa and genotype 6 across eastern Asia with an 80% cure rate following treatment. (20)

3.3 Screening and diagnostics

Screening diagnoses new HCV cases, assess stage of liver damage and assess time to initiate treatment. With the exception of Blood banks, screening is not routinely done unless indicated, leading to under-detection of cases.

Diagnosis rests on 2 positive tests, each costing US\$78 each and take 3-4 laboratory days. (21)

The initial screening test, enzyme immunoassay (EIA), is a serologic test. When positive, referred to as anti-HCV positive in literature, it hints at current or previous exposure. The time taken between exposure and building a becoming anti-HCV positive is 30-90days. Testing during this window period will often lead to a false negative. Currently, third generation EIA are used, which confer high sensitivity (98.9%) and specificity (100%).

Confirmatory tests are either serologic recombinant immunoblot assay (RIBA), or the gold standard polymerase chain reaction (PCR) which detects serum HCV-RNA. Serologic tests do not distinguish between chronic and active infections while PCR does but is more costly and requires higher expertise.

(17), (22)

Confirmatory tests require a second visit and additional testing costs, which can be barriers. Additional tests include ELISA, viral genotyping, ultrasound, CT scan and liver biopsy. Liver biopsy until April 2012 was required to initiate treatment. (18)

The latest diagnostic, Surface plasmon resonance, is easy to use, cost less (US\$8), has high sensitivity and specificity and yields results in an hour, thus potentially removing geographical and fiscal barriers. (21) (23)

3.4 Clinical progression

A fundamental understanding of the natural course of any disease is vital to estimate probable burden, identify groups and factors favoring transmission and spread, which lead to informed policy design. The natural course of the disease, is depicted below. Worth mentioning, once a person acquires HCV, they remain infectious indefinitely unless the virus is cleared.

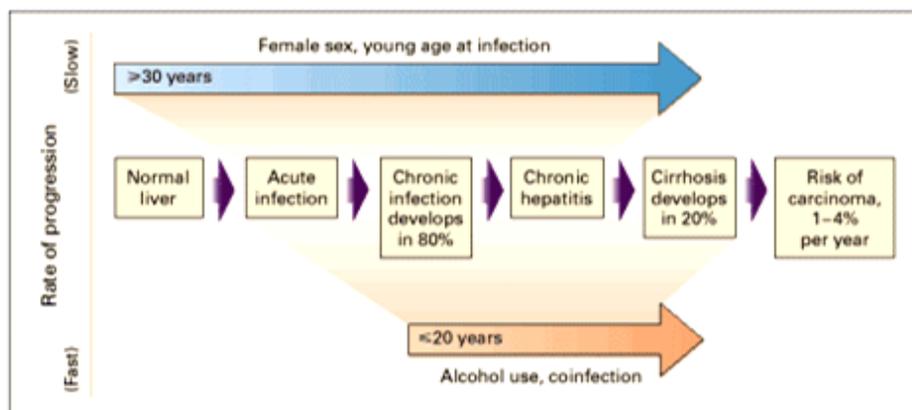
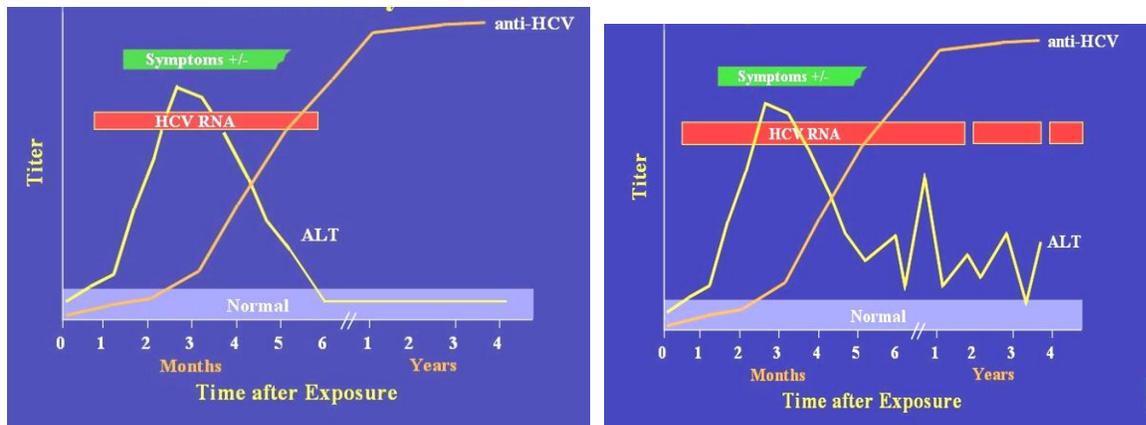


Figure 3: Natural HCV progression (24)

Acute Hepatitis: A quarter develop a mild or asymptomatic acute hepatitis with a 6-10 week incubation period with raised liver enzymes (ALT) and a positive seroconversion (anti-HCV positive). Viremia (rise in blood HCV-RNA) occurs, detected by PCR. Groups with higher viremia are more infectious. ALT normalization and HCV-RNA clearance indicates remission. Rarely, fulminant HCV infections cases occur, mostly in HBV or HIV co-infections. Cases that have mounted a SVR account for 20% of cases.



(a)

(b)

Graph 1: Serologic pattern of a) acute HCV with recovery b) acute hepatitis progressing to chronicity (25)

Chronic hepatitis and cirrhosis: Majority (60-95%) develop chronicity, marked by persistent HCV RNA levels and fluctuant ALT. About 85% of these are alive 10 years later and 10%-30% develop liver decompensation after 20-30 years from cirrhosis. Chronic alcohol consumption, males, late age of infection and detection and co-infections accelerate chronicity and sequelae. Younger age groups are less likely to develop chronicity. (24) Extra-hepatic manifestations, e.g. arthritis, kidney disease and cancer, can occur during any stage of chronicity.

Hepatocellular cancer (HCC): HCC develops in 1-4% cases, mostly following cirrhosis, with high mortality rate (mortality/ incidence ratio of 0.93). From an estimated 694,000 HCC-related deaths, 69% occurred in men. About 85% occur in developing countries, highest burden seen in Mongolia. (20) The mean age group varies tend to be older age groups. HCV attributable fraction (AF) varies between regions, from 15% in Taiwan to 23% EU countries. However, the AF for HCV is significant. (20)

3.5 Treatment

Currently no vaccine exists. Treatment rests on combination therapy with ribavirin and pegylated interferon (pINF). Cure rate and duration treatment vary between genotypes, cure rate is highest for genotype 3 (90%) following a 24 week course and lowest for genotype 1 (45%-65%) after 48 weeks. (26), (27) Additionally successful cure rate is highest among younger age groups and early stage of diagnosis and treatment.

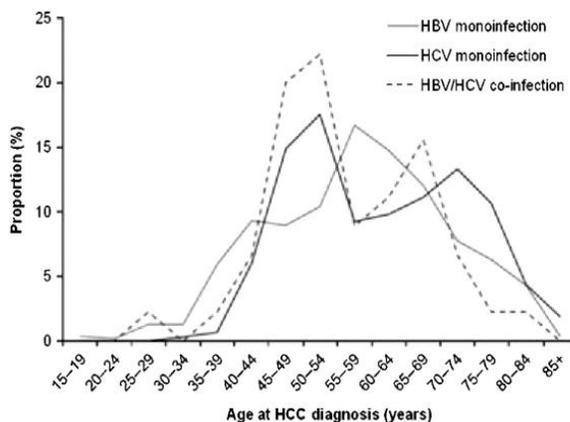
Pharmacological treatment is expensive and can have severe flue-like and psychological side-effects. This hampers productivity and quality of life and thus requires a strong social support group setting to reduce chances of dropout or poor compliance.

HCV related liver decompensation is the leading cause of liver transplantation in a growing number of regions including the USA. Re-infection following liver transplantation is inevitable, with an accelerated progression to cirrhosis, especially in HIV cases. (18) Additionally, liver transplantation requires highly specialized services which are geographically and financially inaccessible to rural groups. Direct costs for liver transplantation can reach USD\$50,000/- per transplant.

3.6 Co-infections

Co-infections accelerate the rate of liver damage and are thus important factors in HCV prevention programs. An approximate 30% of HIV and 15% of hepatitis B (HBV) co-infections are reported in HCV some groups. (13)

Graph shows the proportion of HCC attributable to HCV mono- and co-infections (with HBV) following age standardization. The co-infection curve shows a bimodal variation. Striking is the higher proportion of HCC death due to co-infection and reduced life expectancy compared to mono-infections.



Graph 2 . Age at HCC diagnosis attributable to HCV, HBV, HIB mono-infection proportion.

Following age standardization, HCV mono-infected cohorts show a bimodal variation, with a rise in proportion of HCV cases 30, peaking at 50-55 years age group (17% of HCC) and around 70 years (14%).

3.7 Global Epidemiology:

Globally, 130-170 million individuals are chronic carriers, an estimate 3.3 % of the global population, predominantly in developing countries as previously mentioned. Egypt (22%), Pakistan (4.8-5.4%), Thailand (4-5%) have some of the highest prevalence, but in absolute numbers, highest burden is in China and India (12 million). (30) Annual 3-4 million estimated new cases are seen globally, majority from unsafe injection practices. About 350,000 HCV-related deaths occur yearly. (28)

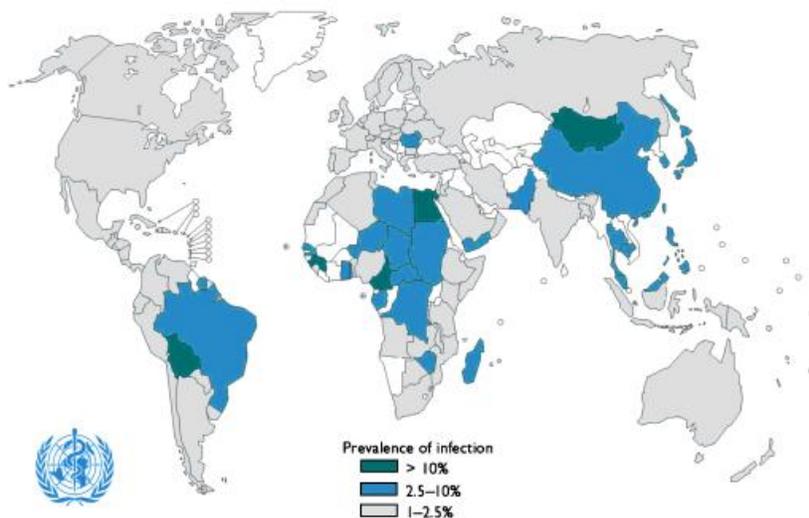


Figure 4. Global HCV prevalence (2004) (29)

WHO region	Total population (millions)	HCV 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	1.0	8.9
Southeast Asia	1500	2.0	32.3
Western Pacific	1600	3.9	62.2
Total	5811	3.1	169.7

Table 1. Global HCV estimates (by WHO region) (28)

Men and older age groups bear the brunt of HCV. Section C of this chapter will elaborate on high risk groups.

A joint partnership initiative between the WHO and the World Hepatitis Alliance, called the "Viral Hepatitis Global Policy Survey" collected data from 135 countries that responded from the 193 Member States, and published

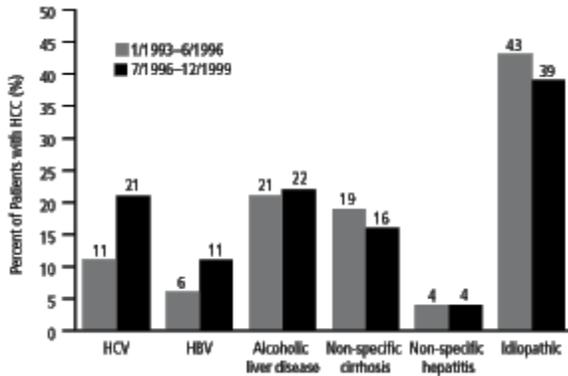
the "The Viral Hepatitis: Global Policy" that was initiated in 2009. It described the policies and interventions against HCV. About 33% had no hepatitis prevalence data to report and 80% said HCV was an emergency issue but they did not have the finances. Pakistan was one of the states that did not respond. (31)

3.7.1 Trends

Many issues exist around HCV trends. Ideally, community-based cross-sectional studies are used for prevalence studies, however most developing countries lack the capacity to carry out such studies. This makes it difficult to obtain incidence and prevalence data and monitor trends. Retrospective-based studies on HCV-related cirrhosis and HCC mortality provides a mean to monitor previous trends and thus predict future outcomes using mathematical models. However, premature deaths from other causes can cause under-reporting. (32)

Also these studies are conducted in industrialized countries so assumptions made may not be applicable. Similarly, data on viral genotype, rate and dose of alcohol consumption, previous HCV treatment and re-infection is not clearly mentioned in these studies. As previously mention, serology does not differentiate between active or resolved infections, a problem in prospective cohort studies. Also false negativity exists among HIV cases and chronic patients, a process called seroreversion, has been reported. Little is understood about this phenomenon. It is reported in 2-10% of post-transfusion cohorts, occurs in immuno-competent cases, and among certain age groups. (33), (34)

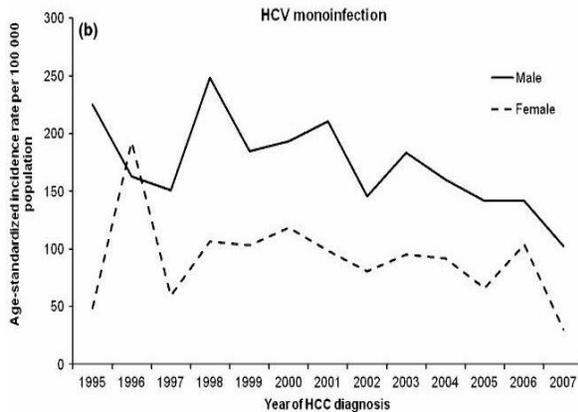
Trends reflect changes in transmission and onset of infection, e.g. declining trends in 90's in the US which resulted in lower HCV prevalence versus the decline in 2000's in Australia. Regardless, a drop in new reported cases and a rise in sequelae is common and pockets of endemic clusters pose a persistent threat. (35)



HCC: change in causal proportion among 2,548 patients during two 2-3 years time period.

Graph 3. In terms of HCC reported incidence cases, an American study showed the rise in HCV related-incidence following age-standardization in age groups 65 and older. The increase, from 14.2 per 100,000 in 1993 to 18.1 per 100,000 in 1999. Mentioned in the same study was the report from a multivariate analysis that reported a 126% and 67% increase risk for HCV related HCC and HBV-related HCC, respectively. This rising trend is similar to other developed countries. (36)

Australian population-based retrospective studies, with data obtained from national cancer registries, death records and "Bureau of Statistics", from Jan '92 to Dec '07, showed HCC age-standardized incidence to be 132.7 (95% CI 118.8, 147.6) persons-per-year among HCV cases. Graph 3, stratified by sex, shows the HCC-related incidence rate was almost 3-4 times higher in men with overall progressive decline in both sexes. Detection remains highest among men.



Graph 4. Age-standardized HCV incidence rate among HCC cases. (Australia)

HCC Age-standardized incidence rate by gender, showing twice the number of men affected, peaking in 1996 (195 / 100,000) ; for women and 1998 (250/ 100,000) for men, with fluctuating but progressive drop in trend in both sexes, a steep drop by 2006.

The drop in HCV-related HCC incidence rate among these cohorts, is due to improved therapeutic response to combination therapy and increased uptake via government subsidies thus increasing financial accessibility of these groups. (37) HCV related deaths are expected to continue for decades because of the chronic nature of the illness.

The shift in transmission route, from nosocomial to intravenous drug use (IDU) in developed countries, has also impacted the trend and prevalence. Post transfusion have become rare since 1991 to 0.004%-0.0004% per blood unit transfused. (38) Thus single horizontal strategy will unlikely eliminate HCV.

The in developing countries the main route is still nosocomial, but pockets of IDU are increasingly becoming infected.

3.8. Pakistan:

3.8.1 Epidemiology

In Pakistan, adult chronic-HCV prevalence is 4.8-5.4%, and approximately 14% are serologically positive, implying active or resolves disease. (39) Pediatric prevalence is surprisingly lower at than 2%.(40)

The highest burden is borne by thalassemia patients, men and marginalized groups, discussed later.

The predominant genotype is 3 (between 50-67% cases), highest proportion in Punjab (68%), which has greatest potential for cure with early combination-therapy. The regional distribution of prevalence according to genotype is in table below. (41)

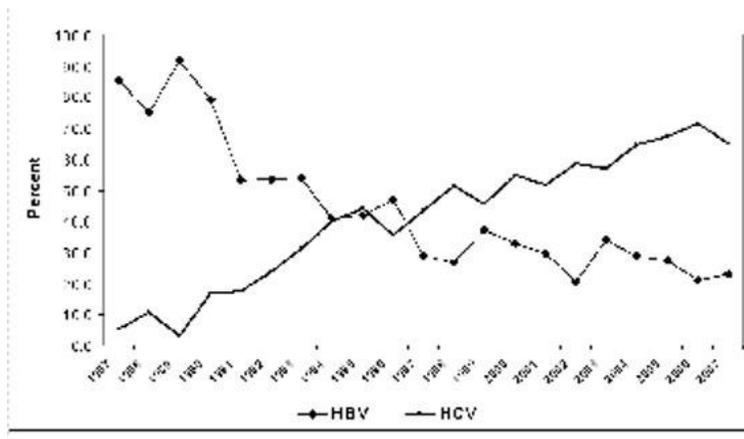
HCV genotype	NWFP	Punjab	Sindh	Balochistan	Total
1	2 (8%)	1 (4%)	3 (12%)	3 (12%)	9 (9%)
3	7 (28%)	17 (68%)	12 (48%)	14 (56%)	50 (50%)
4	1 (4%)	1 (4%)	3 (12%)	1 (4%)	6 (6%)
Not typed	15 (60%)	6 (24%)	7 (28%)	7 (28%)	35 (35%)
Total	25	25	25	25	100

Table 2: Proportion of HCV genotype in Provinces (41)

Population based surveys are lacking and seroprevalence data is used in HCV prevalence estimation. This is not necessarily representative of the population but provides a picture of burden.

3.8.1.1 Trend

There has been a rising trend of viral hepatitis cases. The prevalence of HCV as a proportion of total chronic viral hepatitis has slowly been rising and surpassed that of HBV, partly due to increased screening, improved HBV vaccine coverage and suboptimal HCV prevention strategies.



Graph 5: Changing trend of HCV and HBV in 21 years in Karachi, Sindh. (42)

3.8.2 Surveillance

Surveillance is the backbone in responding to any epidemic. In Pakistan, there is no national hepatitis surveillance system. There are 5 pilot hepatitis surveillance projects functioning and regional Disease Early Warning System (DEWS) but with limited capacity. First Level Care Facilities (FCLF) which are BHC, RHC and out-patient-departments (OPDs), collect data and report it to District level. However, data is not cross checked. Delay and incomplete reporting is endemic and often not standardized.

A study reported some of the underlying issues. Only 20% said they were able to detect epidemics. Employees expressed wanting incentives to report diseases timely, and only 25% were regularly sending reports. Only 10% were properly trained and 100% of FCLF workers required more training. (43) A weak surveillance system has profound impact on health response.

Chapter 4: Determinants of Health and Risk factors.

"It is much more important to know what sort of a patient has a disease, than what sort of disease a patient has."

William Osler (1849-1919)

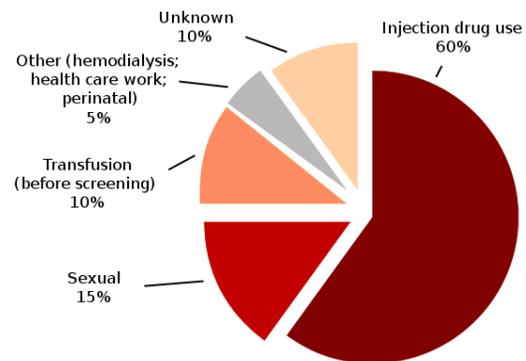
This section will examine the transmission pattern, intermediate and structural determinants and identify high risk groups within the context of Pakistan.

HCV is spread by blood contact (75%-85%) and, less commonly, by sexual contacts (15%). In developed countries, primary mode of transmission is through sharing of infected drug needles. In Pakistan, and other developing countries, transmission is primarily nosocomial.

A list of transmission routes has been listed below which will be explained further in the next section.

- Blood Transfusion (curative, routine)
- IDU
- therapeutic injections
 - formal service
 - CAM administered
- other blood-infected contacts
 - barbers
 - scarification rituals, e.g. circumcision
 - tattoo, piercings, acupuncture
 - waste scavengers
- occupational
 - HCW
 - barbers
- sex transmission
 - Commercial sex workers (CSW)
 - Men who have sex with men (MSM)
- perinatal transmission (rare)
- co-morbidities
 - chronic alcohol consumption
 - HIV
 - HBV

Breast feeding does not transmit HCV and for a 10% the transmission route



remains undetermined.

Figure 6. HCV proportion distribution among groups

4. Determinants of Health

In 2009, the World Health Assembly (WHA) called for a reduction in health inequity by passing a resolution based on the report of the Commission on Social Determinants of Health, 2005-2008. These determinants play an integral role in disease transmission and spread. They have considerable overlap, and at times difficult to separate. The determinants are listed below and categorized according to the conceptual framework in Chapter 2.

4. 1 Sociocultural and Physical Environment

4.1.1. SocioCulture & Socioeconomic:

4.1.1.1. Excessive use of injections

Injection overuse is a common practice in Pakistan, accounting for the highest global annual injection per person use, at 13.6, almost always for curative purposes (96%). (72) About 84% of HCV cases are from unsafe injection practices. It is performed by trained and untrained care givers. It is perceived to provide rapid relief which is the case for manual laborers who seek immediate relief out of fear of job security. Also, people are unaware of alternative oral medication. (61) The HCW performed excessive injections for financial incentives. Additionally, use of injections (more than 4 a year) has a 11 times higher chance of infecting other household members. (73)

Pakistan has a black market of repackaging used syringes that leaks into the patients hands which are cheaper through unregulated dispensaries. (72) Thus low income and poor regulation are a problem.

4.1.1.2 Ritual practices

Circumcision is a common practice among muslim boys due to religious obligation. In poor groups, male (and possibly female) circumcision is performed by barbers. These barbers charge little money, are trusted members in the community and are within geographical reach. They also perform toe nail removals and abscess drains at cheap prices. This provides immediate relief to the client.

Beautification rituals among women are common, e.g. multiple nose and ear piercings. These rituals are promoted by peers and family members from a young age. It is considered traditional and feminine.

4.1.1.3 Home-delivery

In Pakistan, a woman's reproductive role is highly valued in society. The average Pakistani woman has 4-5 children in her lifetime and 65% are delivered at home by midwives. Main reasons for home delivery are family tradition (72%) and poor socioeconomic income (68.6%) were main reasons for home delivery. (74). Midwives are trusted members of the community and perform these deliveries. They have no or little formal training and might not follow new double glove wearing guidelines. They run the risk of HCV transmission and spread. Additionally, transporting a woman during bleeding-related complications can potentially infect family members and HCW staff. Home deliveries also reported due to lack of women's autonomy. Husbands, and mother-in-laws, are decision makers and control fiscal resources. Also she is not allowed to leave the house unaccompanied due to social norms. This hampers mobility and access to HCV testing. (75)

4.1.1.4 Sex & sexuality

Sex and sexuality are taboo in Pakistan. Stigmatized groups engage in risky sexual practices with multiple partners and report less frequently to HCF. Red light districts and CSW, both male and female, are tolerated but rarely talked about. Multiple sex partners increase the risk of contracting HCV. They are concentrated at strategic locations, urban and truck route settings, have poor safe sex knowledge and practices. Condom usage is low among both male and female CSW, less than 50% of Lahori female CSW used a condom with their last client and lacked sex negotiating power out of financial desperation. CSW are less likely to seek treatment and thus remain reservoirs for HCV. They have a wide clientele, from all socioeconomic classes and sectors of society. (72)

MSM are marginalized communities. Many offer sex for money, have multiple sex partners and have higher levels of STI e.g. HIV (2%-4%). (72) The recent increase in traumatic anal sex practices has contributed to rising

cases of HCV and HIV in some countries. Data on specific sexual behavior patterns in Pakistan are invisible.

4.1.1.5 Support networks & Stigma

The supportive network in Pakistan is family, which offer mental support and motivation to seek care. However, disclosure to spouse has caused physically or sexually distance between serodiscordant HCV couples. This causes psychological stress for both partners and 33% HCV cases expressed regret over disclosure. (76) This can prevent future disclosure and cause psychological ailments.

Work environment plays a negative role. HCV sero-disclosure has resulted in stigma, loss of job security and prolonged unemployment. Discrimination by HCW has also been reported. This prevents serodisclosure, puts others at risk and reduces access to HCF. All these factors impact health negatively. (76)

4.1.2. Physical environment:

4.1.2.1 Regional variations & Urbanization

HCV prevalence shows regional variation, highest for Punjab (4.3%) followed by NWFP (2.2%) Sindh (1.8%), then Balochistan (1.9%). Districts also differ between in prevalence, e.g. Punjab's 2 districts Darsano Channo (44%), (51) and Faisalabad (20.6%), (50). Variations in HCV genotype variation has also been noted.

Urban groups report higher injection prevalence (75%) than rural groups (53%). Tribal areas remain out of reach due to militants, leaving potential pockets of HCV. (52) Pakistan has an urban slum population of 26 million people where there are concentrated pockets of infectious diseases, most notably TB. Ranked at 141 (of 182) on the "United Nation's Human Poverty Index", poor urban planning and lack of prioritization in Public Sector Housing Schemes have resulted on poor living conditions and health outcomes. Children and adults are in arms reach from open commune waste sites. (53)

4.1.2.2 Homelessness

Housing is an indicator of poverty. Homeless groups lack shelter, diminished personal cleanliness and physical health. Following the 2010 floods, 20 million became homeless. (54)

About a quarter of homeless population have HCV . Additionally they have frequent contact with sex workers, have drug dependency (36%-64%). (55)

4.1.2.3 Household

In poor Pakistani households, overcrowded is common with 7-9 people in a 2-3 bedroom house, with extended families cohabiting the same house, for both financial reasons and tradition. These groups share utensils and come into frequent contact with infected razors, clippers or knives. A study in Hafizabad, showed 16.2% HCV seroprevalence among household members, twice as high than the general public (OR 2.8; p=0.01). The rate was high among confined conditions where a family member received regular injection use, household with thalassemia major relatives or hemodialysis patients. (57) Married couples have a higher HCV seroprevalence than never married individuals, 87.7% versus 12.5% respectively. (58) If the husband acquires HCV outside the marriage, e.g. extra marital affair or before marriage, he can transmit it to his wife, and vice versa.

Age group (years)	Anti-HCV prevalence	
	Family members (n = 74)	General population (n = 309)*
0-19	7.1% (2/28)	2.7% (4/149)
20-39	14.8% (4/27)	5% (5/101)
40-59	25% (4/16)	12.2% (5/41)
> 60	66.7% (2/3)	35.5% (6/17)

Table 3: Comparison in HCV seropositivity rate between family members and general public in Hafizabad between 1993-1994. (44), (45)

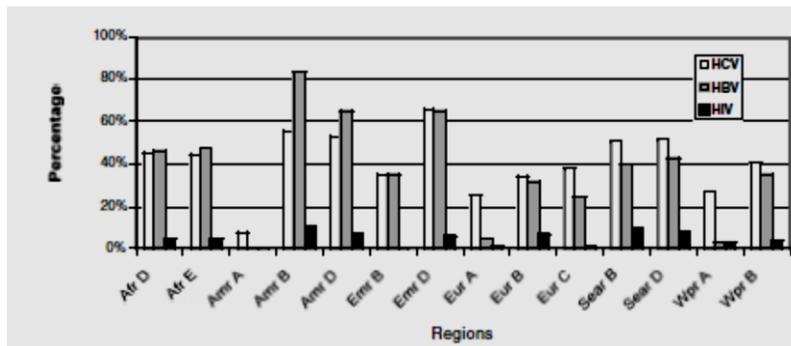
4.1.2.4 Waste

Used syringes are found in open communal waste sites where waste scavenger boys look for needles which are sold on the black market, discussed later. Open waste sites are a source for contaminated products, especially in urban slums where children (and adults) frequently cross waste areas to go to school or work , and also play out of curiosity and because homes are overcrowded with few, but far, urban park plans for children to plan. During episodes of heavy rain, poor sewage results in increased environmental exposure.

4.2 Occupation:

4.2.1 HCW

The highest risk of HCV transmission is seen in dentists. Doctors have a 52% chance of getting a needle stick injuries (NSI) in their life but prevalence of HCV remains low due to precautionary measures put in place. (59) Seroprevalence among Pakistani HCW is higher (>4.5%) than other countries, e.g. India (0.87%). (60) This is partly because by the very nature of their work but also from NSI from excessive injection practices.



Graph 6: Attributable fraction of HCV , HBV and HIV among HCW per region. (101)

HCV, HBV and HIV attributable fraction in HCW between ages 20-65 years, due to injuries with contaminated sharps. HCV accounted for 50% of the proportion of BBI and STI's in South Asian region.

Regions:
Afr= Africa, Amr= America, Emr= Eastern Mediterranean region, Eur= Europe, Sear = South Asian Region, Wpr= Western Pacific region.

Many patients request IV medication over oral drugs or are given one as proxy by HCW, a proposed reason is greater financial profitability. A report showed 77% of staff throw needles in communal waste bins. Poor staff attitude towards waste disposal, in the absence of a infection control team, prolongs contact with infected products and contaminates hospital infrastructure. (61) NSI themselves do not transmit HCV, contaminated needles do.

4.2.2 Healthcare waste management (HCWM)

Majority of HCF lack a HCWM team. Many lack infection control programs, waste management plan and incinerators. Adhering to "Hospital Waste Management Rules 2005" guidelines is not a priority issue for overworked and unregulated HCF. Most laboratories and blood banks are privately owned. Strongly linked to HCV spread is HCW behavior discussed later (63)

It is seen as the duty of HCW and janitors. HCW, however they are overburdened or leave early to attend private clinics to earn additional income. Janitors, minimum wage earners, sell used needles to waste dealers for additional income. The remaining needles are picked up by boy waste

scavengers, aged 15-18 from poor backgrounds, that spend mornings and afternoons looking through communal waste areas for needles to sell to dealers who sell at reduced prices to unregulated dispensaries (and patients), who resell them to patients. Both janitors and sweepers have daily NSI of 0-5 NSI weekly and 0-3NSI weekly, respectively.(59) (62)
Thus poor HCWM trickles into the public, especially the poor and young.

4.2.3 Barbers

Barbers provide haircuts, facial and armpit shaves and minor surgical services. The high probability of HCV transmission following daily face (aOR 5.1, 95% CI: 1.5±17.0) and armpit shavings (adjusted OR . 2.9, 95% CI: 1.3±6.5) from reuse of razors is common due to financial constraints. (66)
Barbers recruit relatives and friends as employees, who come from villages and slums and earn a meager income. They work into the evening, sleep in the barbershop with 2-3 people in a narrow room, next to the parlor and live close to infected razors, clippers, etc. (64)

HCV knowledge among barbers is low. Barbers in Gujrat (Punjab), 67% of young barbers (15-25) have some formal education and better knowledge of infectious disease than 23.5% of illiterate barbers. Also these barbers had less work experience and still susceptible to health messages. (65)

4.3. Behavioral practices:

Lifestyle choices play a proximal role in HCV transmission and spread in IDU, CSW, MSM and HCW are the main groups prisoners. CSW and MSM were discussed previously.

4.3.1 IDU

IDU are not a large community per se but have a 94% of HCV prevalence. Most are unaware about HCV and only worry where their next "fix" will come from. They share needles among one another and inject in open streets and parks. They are often polydrug users including alcohol. (59)
Result from a cross-sectional study conducted by the Marie Adelaide Rehabilitation Center Needle Exchange Program in Karachi, showed that 81.3% IDU spent an average of 7.9 years on the streets. About 64.5% never used a condom, 58.3% sold sex for drugs or money. Only 72% were aware of HIV and its mode of spread and 28% had ever sold their blood to blood banks. Half expressed willingness to quit but found rehabilitation treatment to be financially out of reach. (86)

Furthermore, unemployment following rehabilitation leads to high relapse rates. And thus any strategy targeting IDU must also take into consideration into their planning and logistics former IDU who are potential HCV reservoirs for their household and public, plus vulnerable to relapse at a later time.

4.3.2 HCW

Poor behavioral practices have also seen a rise in HCV among HCW. About 4.5% of HCW use gloves when handling infectious material, 16% of the facilities used a disinfectant on waste, 29% used needle cutting equipment, 70% of syringes were discarded in community waste areas, and 9% reported selling syringes to waste dealers. The underlying factors are inattentiveness, lack of equipments and poor regulation. (63)

4.3.3 Alcohol

Alcohol accelerates the process of chronicity and thus shortening window for pharmacological intervention. Islamic law, has criminalized alcohol consumption. However, 10 million and 1 million chronic drinkers have been estimated. Alcohol is served behind closed doors to ministers at social events e.g. federal functions and weddings. Culture of hospitality propagates alcohol consumption. Private rehabilitation centers treat alcohol addictions discreetly, but costs prevent access to most (85 pounds a night). The poor resort to home-made brewery, utilizing impure products e.g. antifreeze, leading to cases of liver damage and blindness. (70) Breweries have so far been tolerated and are a booming industry, with smuggling between borders. (71)

4.3.4 Prisons

Incarcerates come from poor educational and financial backgrounds. Many have a history of IDU and multiple sexual partners before prison. This places other prisoners and staff at risk. Within prisons, inmates also engage in IDU, tattoo rituals out of clan loyalty and rebellion, and MSM, out of sexual frustration. Additionally, they live in crowded, poor hygiene conditions and no means for prisoners to discard infected needles. Prisoners also receive little to no healthcare services and can spend exceedingly long times in prison due to sluggish court procedures. These measures place the public at risk, where inmates eventually return to. In Sindh, 12.8% of inmates were HCV positive, higher in prisons in northern Sindh. (56)

4.3.5 Refugees and Migration

An estimated 97% of refugees come from Afghanistan. Eastern groups in Afghanistan have a 20-30% IV opium-user prevalence, from easily available and affordable opium (\$0.50-\$1.00/- per dose) and as a means of escapism from reality. (78) They are a marginalized community that have a high pattern of transmigration for job opportunity and family visits. This makes treatment difficult and may lead to HCV spread and erroneous regional reporting.

Refugees have lower STI awareness and live in crowded conditions. Reports show increased risk of IDU and unsafe sex practices. Two newspapers release cited a study stating approximately 2% of Afghani refugees have HIV, 30% have HCV and 5% HBV, however the source was unclear. (79),(80) Studies on Pakistani expats and military officials are lacking.

4.3.6 Tattooing and beautification

The American Association for the Study of Liver Diseases confirm tattoos as a causal factor in HCV transmission through infected or poorly sterilized needle reuse. (68) Tattoo's are becoming an increasingly popular trend among Pakistan's rich youth despite the high cost (averaged at USD\$165). Many get tattoos for cosmetic or religious reasons, as an act of defiance and for covering scars and birth mark. Subjective reporting reveals these groups are Sikhs and muslims and over 70% of clientele are women. (69) High cost, parent's disapproval and conservative nature of society is potentially protective in discouraging tattoos. Beautification was discussed previously.

4.4 Healthcare system:

4.4.1 Organization and delivery of services

Healthcare can itself become a barrier on 3 fronts, namely geographical access, financial access and quality of services.

Weak referrals systems in rural regions prevent HCV cases from accessing necessary healthcare. Specialized services are located in urban regions. Geographical access to these centers can take up to several hours especially in Balochistan and NWFP, followed by long waiting queue at hospitals. Thus people resort to CAM and more nearby options.

Financial constraints deter patients and encourage poor groups to utilize easily accessible and affordable CAM, self medicate or delay treatment altogether and present once sequelae have set in driving them into catastrophic health expenditure. Health insurance coverage is extended to

only 27% of the population through employer-employee contracts. And according to the Pakistan Integrated Household survey 2001, less than a quarter go to a public HCF.

The private sector is perceived to provide higher quality services which prompts poor groups to pay out of pocket for formal private services, instead of opting to use the public HCF with long waiting queues, stock ruptures, and under the table bribes. The resulting underutilization of BHU, and poor coordination between public-private sector, leads to reduced HCV reporting.

Furthermore, there are no public drug substitution programmes and detoxification centers. Main providers are NGOs making sustainability a concern. Private services are too costly for poor groups. (81)

Barriers in communication with HCW was also noted, with HCV patients complaining of inability to communicate with specialists, feeling stigmatized and abandoned thus potentially damaging rapport and hamper compliance. Thus training of specialists in communication skills should also be considered during planning. (82)

4.4.2 Blood transfusion services

Anemia is common in Pakistan , thus frequently urging the need for blood transfusions (1.2-1.5 million transfusions annually) for obstetric cases, thalassemia and chronic renal patients. The blood used is attained from privately owned blood banks that are not thoroughly regulated. About 50% of them recruit blood donors through financial incentives and large portion are family members who donate blood at times of emergency. About 29% HCF did not stored blood according to WHO recommended guidelines and only 23% were screened for HCV. (63)

In addition, infrastructural limitations, electrical shortages and poor staff training have been reported.

Poor adherence to hygiene measures and poor waste management practices similar to HCF settings are seen here too. (63)

4.4.3 Healthcare and HCV Governance

Poor governance has shown to drive the HIV epidemic in SubSaharan Africa. Similarly poor stewardship and transparency has led gross underfunding of viral hepatitis programs and misappropriation of funds. The National Alliance of State & Territorial AIDS Directors, NASTAD, reported gross underfunding of the Viral Hepatitis Funding Needs for the fiscal year 2012. (84)Other

reports showed HIV/AIDS programs usurped hepatitis funds which created conflict.

Poor political support and criminalization of controversial interventions, discussed later, to appease to voters led to NGO working underground and being arrested to provide services to IDU. BBI and STI were perceived to be a "gay" disease that did not apply to them. Thus information asymmetry is also a factor in governance. Poor stewardship, commitment and corruption are driving forces of the BBI and STI epidemics.

4.5 Biology & Genetics:

An estimated 20% of individuals mount a SVR and significant proportions do not develop sequelae. There remains a knowledge gap. What is known is that infections in older age groups and diagnosis at a later stage are associated with increased chronicity. Waning immunity has been theorized. Poor income quintiles on average have a poor general status and more psychological ailments in addition to higher rates of infectious diseases due to poverty. They also have poor nutritional status. This hampers the body to mount a SVR.

4.5.1 Age & Sex

Infections at a younger age is related to lower risk of developing chronicity. The causes remain unclear but waning immunity with age is theorized. Community-based survey in Punjab, Hafizabad, showed a high prevalence of HCV positive cases (6.5%) , lower in younger age groups, 0-19 (35.3%) and highest over 59 years (35.3%). (63)

Men are at higher risk. Univariate regression analysis of HCV cases from 5,989 laboratory reports from rural Sindh, showed higher propensity for +30 age groups (58.3%) compared to younger age groups (41.7%), and highest in among men (62.0%), $p=0.05\%$, OR =1.3, 95% CI = 1.00-1.57. **(44)**, **(45)** The reason is not clear.

4.5.2 Co-infection

Lifelong medication associated with HBV and HIV have toxic effects on the liver which accelerates chronicity and sequelae. Additionally, HCV, HBV and HIV have common transmission routes and thus seen in similar groups who have similar risky behaviors e.g. IDU and risky sexual behavioral patterns and IDU.

An average prevalence of 15.5% HBV (compared to 12.3% HCV prevalence) was noted among CSW with variations in regions, e.g. 12% in Lahore, and 3.4% in Karachi. Similarly, dialysis patients have a HBV prevalence of 12.4% (compared to 20% HCV prevalence). Further comparison is shown in table 4. Data on HIV in these groups is scarce and primarily limited to IDU and commercial sex workers. (77)

High Risk Groups	HBV prevalence (%)	HCV prevalence (%)
General population	2.6	5.3
Children	2.3	2.5
Pregnant women	2.5	5.2
Military recruits	3.5	3.2
Blood donors	2.4	>3.6
HCW	6.0	5.4
Chronic liver disease	25.7	54

Table 4. Estimated prevalence of HBV and HCV among different high risk groups in Pakistan. (77)

4.6. High Risk groups

From the determinants, the high risk groups can be summed up as thalassemia major patients (47.2%), chronic dialysis patients (38.8%), Spouses and household contacts (19%), HCW (5.5%), pregnant women (5.3%), prisoners, barbers, sex workers, HCF janitors, scavenger boys, IDU, MSM, men, older age groups and Punjabis. For many, data is still lacking. Worth noting is the importance of hygiene standard, waste management and sterile needle usage.

Interventions aimed at these groups holds promise for curbing the HCV epidemic, as is evident by the progress made in developing countries. The impact of interventions on groups will undoubtedly vary and determine the trend as mentioned before. Thalassemia patients have highest HCV prevalence but the impact of interventions on the overall prevalence may be negligible. This has economic and stakeholder confidence implications.

Chapter 5: Interventions.

"... Know it. Confront it. Get tested".

Sub-theme World Hepatitis Day (2012)

Chapter 3 showed the wide range of interactions between HCV and various determinants at play. It is evident that there is a large potential for improvement of the situation both in terms and long term infection control and possibility to include many actors. The aim of this chapter is to provide an overview of the intervention strategies adopted by various countries in controlling the spread and transmission of HCV.

Primary focus of global efforts have been on education and harm reduction strategies, a range of public health responses that reduce impact of harmful behavioral practices and have broad social implications, addressing issues around drug criminalization and prostitution. They require a system in place to monitor and evaluate (M&E) the progress made, identify gaps in meeting the objectives, to report back to stakeholders and share data with the public and media and build momentum.

5.1 Primary Prevention:

5.1.1 Education

Program activities are focused on providing viral hepatitis education to public and private sectors. The Viral Hepatitis Provider Education Supplement, launched by the Department of Health and Human Services, USA, disseminates educational and training materials to HCW, with the aim to build capacity for detection and case management of high risk groups. (85)

Educational services can be extended through mass media and promotion campaigns e.g. street plays or during annual events, e.g. World Hepatitis Day . The Media people use is important. In Pakistan, 75% of barbers own a television, hence relaying message through media news outlets, dramas, influential actor involvement and broadcasting on both cable and private movie channels can be an effective strategy.

5.1.2 Behavioral Change Strategies

These strategies focus on 4 key areas: (86)

- Design, execution and evaluation of "Behavioral change communication" (BCC) strategies.
- Staff training to implement BCC
- Focus on information, awareness and skills to promote safe injection and sex practices. and remove misconceptions.
- Encourage access to services VCT and STI treatment, in particular the IDU groups and their family, since they require higher levels of motivation.

5.1.3 Provision of condoms and their use

Implementation requires following main steps:

- procuring availability and access of condoms to client, through dispensary outlets and community outreach programs to slums, rural areas and IDU and sex workers on the street, parks and shooting galleries.
- training on condom usage and safe disposal practice.
- training about what to do in the event condoms break and where to go.
- providing vouchers to unemployed and destitute groups who can get free condoms and remove financial barriers.
- timely renewal of contracts and expenditure to prevent stock out.

5.1.4 HBV vaccination:

- Extending existing HBV coverage to high risk groups and academic schools
- Mainstreaming HBV into national EPI program in all districts
- Arrange for cold chain in HCF where emergency generators are available, monthly audit to prevent stock out and regular reporting
- Training CHW to administer vaccines in timely fashion
- Raise awareness through mass media and annual world hepatitis day seminars for HCW and the public

5.1.5 Strengthening capacity of HCF and Sentinel Nodes

5.1.5.1 Infection Control Programs (ICP)

In Egypt, certain HCF changes were introduced. These included:

- Setting up infectious disease program, adherence to protocol and regular supervision were measures taken

- Focus on hygiene measures during surgical techniques, waste disposal, transport and patient interaction were part of the protocol.
- HBV vaccine coverage was extended to HCW.
- Setting up District Infection control committees and customary surveillance team and system were setup.

Preliminary results in 2008 showed reduction in HCV infections from 37% (2004) to 4.2% (2007) in hemodialysis units.

Difficulties in implementations were time constraints among HCW and supply issues.

5.1.5.2 Routine blood screening

Blood, routinely screened for HCV, HBV and HIV, is collected by HCW in majority of private blood banks. Has led to remarkable halt in spread of HCV globally. The National Blood Transfusion Center (NBTC) in Egypt collaborated with international and local NGO, with blood specimen referral for PCR confirmation to District hospitals. This halted the epidemic in the Delta Nile region. High risk groups, e.g. IDU were disqualified from selling their blood and those diagnosed, received return call and counseling. (97)

5.1.5.3 Access to Basic healthcare, STI treatment and specialized services

- Ensuring culturally acceptable and accessible of health care services for the public and marginalized groups
- Promotion of quality and gender sensitive STI and liver specialized services
- Training workshops and eHealth learning sessions for HCW on STI and viral hepatitis.

5.1.5.4 Access to Voluntary Counseling services (VCT)

Similar models from HIV programmes have focused on providing VCT services to provide guidance and increase chances of follow up.

- Staff training in VCT both pre-and post-screening to improve follow up and management
- Plan, implement and regular M&E of VCT quality.

5.1.5.5 Surveillance

Developed countries adopted the following goals in health systems information system (HMIS) strengthening

- Update current HMIS and standardize for all provinces

In addition to conventional approaches of demand-supply reduction measures, harm reduction focuses on education, reducing drug criminalization and provide IDU a safe environment for drug use, leading to less needle sharing and drug intoxication related deaths. This requires relentless advocacy and evidence based information dissemination and cooperation with drug and policing authorities. Additionally, oral alternatives have shown measures of success . Changing public perception, and federal funding have been barriers. The perception of promoting "drug paraphernalia" is a common concern among conservatives groups, however this claim has no proof. Additionally, IDU are a very mobile groups, thus targeting them is difficult.

5.2.1.1 Needle exchange programmes (NEP)

NEP started as an illegal underground program for IDU by former addicts. It provides clean needles and materials through outlets and by workers via outreach programs. This has yielded success in UK and USA. In Pakistan, independent NGOs such Nai Zindagi ("New Life") and The Marie Adelaide Rehabilitation Center have extended services to disenfranchised IDU with the aim of reintegrating them back into society. They focused on:

- Provision of clean needles, cloths, water, cooker, bandages to IDU in exchange for used ones.
- Encouraging uptake of services by removing financial barriers and geographical inaccessibility
- Providing a safe atmosphere (shooting gallery) free of fear of police, in a drug controlled setting, reduced drug impurity related events, reduce contact with CSW and provide health services.
- Increasing access through dispensary outlets and vendors.

5.2.1.2 Drug maintenance programmes

Two programmes, methadone and heroin maintenance therapy, MMT and HMT respectively, have been adopted by developing countries with significant levels of success.

Switzerland has integrated it's HMT program into the national health scheme and achieved measurable success in minimizing drug harm and usage. The 2008 national referendum had a majority (68%) favoring the continuation of the program. The impact is more clear for HIV. Medical prescription of for addicts has positive social and individual implications. People have been gone back to being employed and start a family life. (98) In addition, cost reductions of law enforcement time and resources, and fees on litigation and

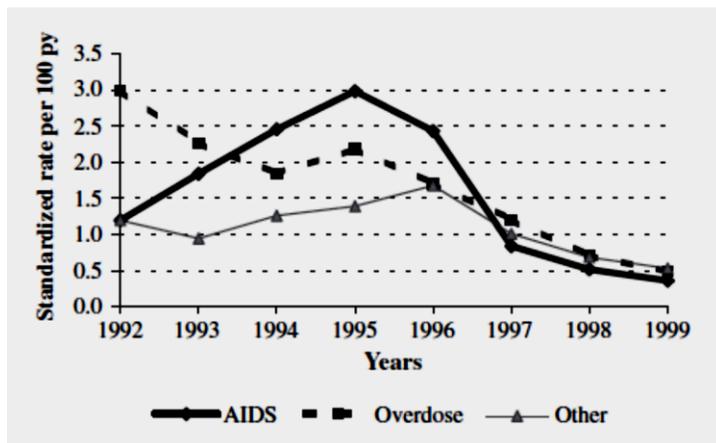
incarceration is seen. However, government corruption is a common problem. Lahore-based NGO's receiving international funding have faced governmental interference. Freezing of funds has prevented harm reduction programs from extending services to IDU and their families. (95)

Drug and alcohol rehabilitation HCF must be provided as an integral program in harm reduction strategies. Separate clinic have been constructed in discreet locations to provide anonymity in Islamabad, however these facilities are private and cost. Contracting to these services and providing subsidy can reduce the barriers.

5.2.2 Impacts of Interventions: A Case study of MTT

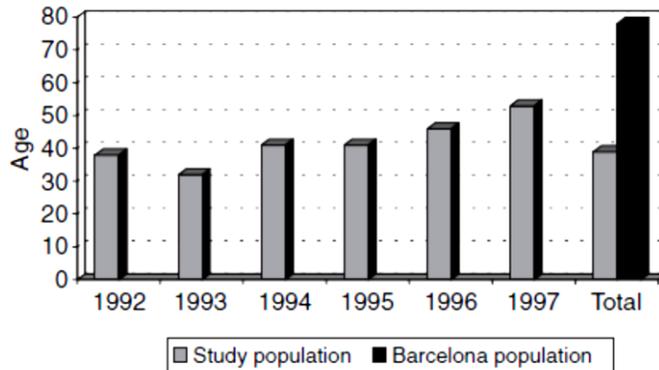
The impact of individual intervention strategies on HCV prevalence is not well studied, as most of them were designed for HIV/AIDS. One way is to look at case reports and mortality trends however, they have the potential for confounders. In Australia, the drop in new case detections from 14,000 (from 2001) to 10,000 (2010) can be attributed to HCV measures.

MMT has reduced number of IDU addicted, reintegrated users back into society, improved social and family life. (98) High risk sexual and criminal behavior has been reported to be reduced within the first year of MTT programs. (87)



Graph 9. Age standardized mortality rate per 100 person per year in relation to time and MMT program initiation (1992). (88)

Furthermore, studies on MTT programmes on users in Barcelona showed a reduction in AIDS and "other" related mortality among enrolled cases. The 1997 drop in AIDS related mortality coincided with advent of ARV provision in Barcelona, producing a synergistic effect in mortality reduction. Concurrently, drug overdose mortality dropped continuously, from 3.1 per 100 person-years (1992) to 0.6 per 100 person-years (1999). By the end "other" related causes became leading cause of mortality among. Additionally, life expectancy of the cohort at birth increased from 32 (1993) to 53 (1997). Thus the impact on mortality reduction and increased life expectancy is incontrovertible.



Graph 10. Life expectancy. Comparison between ISDU addicts and general population, Barcelona (1992-1997).
(88)

Studies among patients undergoing methadone-therapy and combination-therapy, compliance was significantly better and subsequent higher cure rate. The incidence of depression was also lower compared to the general public, possibly because of psychiatric and psychological support provided during the program. (89)

5.3 Progress in Pakistan so far

5.3.1 Prime Minister Program for Prevention and Control of Hepatitis

Little data is available on the program. The program was launched on 29 August 2005 to reduce the prevalence of HCV by 50% by 2010. It focused on providing comprehensive health coverage from the existing health infrastructure. It focused on surveillance strengthening, drug and vaccination procurement, proper waste disposal and safe blood screening. In NWFP, it provided services to sentinel sites, District Hospitals and prisons, however the impact was far from 50%. Also IDU were not mentioned, nor were NEPs. Major constraints were poor HMIS, human resource constraints, issues of decentralization, poor management, long bureaucratic blocks and no reimbursements. The progress till today remains obscure. (90)

In Punjab, the Planning Commission formulated a development project, PC-1, with focus on social issues including health, which became the roadmap for PCHP from 2009-2012. A budget of Rs. 2286.23 million was allocated to the program, with the aim of adopting a systematic approach for evidence based practice in controlling the prevalence of viral hepatitis. Awareness campaigns, PCR diagnostics, drug procurement and strengthening capacity of the sentinel points were priorities. However, the project fell short. Coverage of free treatment was not extensive enough, and fiscal constraints in getting tested existed. Treatment without a confirmatory test was not

possible. Lahore alone has 488,000 HCV cases awaiting. Other issues were mismanagement of fund and lack of transparency led to additional inadequacy of the program and loss public confidence. (91), (92)

In NWFP and Balochistan, due to militancy and terrorism, the Prime Minister's Plan was unsuccessful in implementing hepatitis control and prevention. Less than 50% of the targets were met with no data from some projects. Contractors refused to go in volatile regions. Thus only 11 out of 24 incinerators were planted and 22 sentinel centers established providing screening and free treatment. (99)

5.3.2 Chief Minister's Initiative for "Hepatitis Free Sindh".

In Sindh, the program was launched in the wake of a freshly structured framework, with focus on 5 objectives: (93)

1. Prevention of new infections
2. Addressing the issue of long-term injections
3. Broadening public awareness
4. Environment policy changes
5. HCF Capacity strengthening

Currently, all objectives of the PC-1 (2009-2011) have been met through expanded services to sentinel sites and high risk areas including prisons, allocating beds in all teaching hospitals for HCV and HVB, extending free screening and treatment, antiviral procurement, vaccination coverage, strengthening capacity of infection control policies and waste management, providing 15 million auto-destructible syringes and creating hepatitis awareness campaigns and training workshops. An estimated 1.4 million HBV and HCV cases have been treated in total. (93)

A list of sentinel sites can be seen in the annex and HBV vaccination coverage achieved to date. (94)

The program has also treated 2000 Balochi's and Punjabi's thus the impact felt beyond the provincial borders. (100)

5.3.3 Surveillance strengthening:

The Pakistan FELTP, launched in Islamabad in 2006, operates in the framework of the National Strategic Framework on Disease Surveillance (2005-2015) aimed at strengthening surveillance capacity and readiness. It provides training and technical assistance to 5 sentinel sites, drafting of legal framework for stakeholders, reports on laboratory quality systems, working on 5 pilots on electronic hepatitis surveillance system.

Records, are primarily from tertiary hospitals, are not standardized nor electronic. This adds to nurse work load who are already understaffed. Quality control is also lacking in such cases. Midwives are not a part of the health system and are illiterate, unable to report by writing. Geographical distance from tribal conflict areas and frequent power cuts hamper efficiency of reporting. The private HCF poorly communicate with Health Departments.

Chapter 6 Discussion and Conclusions.

This chapter will aim at formulating a discussion based on the data from previous chapters that were built around the conceptual framework in order to answer the objectives in Chapter 2.

The focus of this thesis has been on 3 key issues; the global burden and position of Pakistan in the bigger picture, the determinants and high risk groups, and comment on HCV strategies with special attention of applicability to Pakistan.

6.1 Chronic HCV burden:

Literature remains scarce and primarily from developed nations which have a predefined set of assumptions not necessarily applicable to developing countries. Additionally, estimates are on sero-prevalence studies done in high risk groups and not necessarily applicable to the general population. Additionally measuring incidence directly is not possible in developing countries where most cases are located which hampers assessment. Nevertheless HCV is a global threat, with 3.3% of the global population at risk of HCV-related death. Following Egypt, Pakistan has the second highest reported HCV prevalence and has seen a continual rise in cases. Punjab has the highest burden of HCV. Furthermore, the measurable impact of determinants and strategies remains undetermined. The disease is asymptomatic and chronic. Thus people present when sequelae have set in and health cost too high.

6.2 Determinants

Spread of HCV is primarily through blood contact. In Pakistan nosocomial and IDU routes are strongly driving the epidemic. The impact of determinants on HCV epidemic is unclear. They are as follows.

Socio-cultural determinants , e.g. excessive injection practices ritual scarification practices and sex are a driving force, the latter especially for marginalized groups. Home delivery practices is a potential factor.

Occupational factors, e.g. lack of an infection disease control program in HCF, poor waste disposal and poor knowledge and practices has caused a high prevalence among HCW, barbers and CSW.

Physical environment , e.g. homelessness, waste disposal and close contact between large family units has provided clusters for HCV. Waste management is severely neglected exposing HCW, janitors, waste scavengers and slum inhabitants. Human resource issues , e.g.

overburdened staff, poor knowledge and practice, lack of needles, are all major constraints. Logistics e.g. geographical distance from sentinel sites and specialized facilities reduces access for the rural communities. Worth noting is IDU users who congregate at specific sites where they share needles and spread HCV in the absence of shooting galleries. Poverty is thus a strong factor.

Risky *behavioral practices* among marginalized groups e.g. inmates also affects prison staff and the public as a whole. Migration of refugees and internally displaced populations causes spread to other regions and difficulty in disease control and prevention. Poor hygiene practices at beauty parlors, tattoo salons and barber shops, e.g. reusing razors to save money, places additional risk.

Healthcare services and systems remain out of reach for the poor, underfunded, poorly regulated, and mismanagement of HCV funding towards HIV programs has led to a hampered response. BHU are underutilized and preference for private informal, cheaper option, and formal care, for quality services, is common. Regarding genetics not much is known. Higher age groups and men are more affected. Co-infections , e.g. HIV and HBV speed chronicity and lead to premature deaths.

6.3 Strategies:

The strategies are similar to those of HIV. Awareness and education are effective to promote screening and early detection, providing early treatment before sequelae set in. They promote behavioral change which has an immediate impact on nearby family and has a chain-reaction effect. Provision of condoms among CSW, MSM and IDU is good practice, as it also prevents HIV and HBV transmission. ICP, routine blood screening, HBV vaccination and increased access to special services have been successful in their countries. Extending VCT services, strengthening surveillance, harm reduction strategies implementation (including NEP and MMT), IEC and National procurement committees and Provincial Task force are integral components.

Stewardship and commitment is lacking in many settings and all determinants have a strong link with more structural causes , e.g. poverty and literacy. Behavioral determinants seem to be proximal causes which can yield immediate HCV reduction if addressed on a broad level through primary prevention programs. However, the overall impact this will have on the epidemic immediately and in the long run will probably be low unless underlying distal determinants are addressed. Also, the determinants are strongly inter-related thus provided sterile needles without a infection

control program and waste disposal program might not impact HCV in addition to being inefficient. Hence, a cocktail of high risk intervention approaches must be combined with wider population based approach.

Since significant high risk intervention approaches are NGO initiatives, without governmental support these projects will not be sustainable, especially in unstable economic and geopolitical environment with programs being shut-down pre-maturely.

Important to remember is successful implementation of strategies will still be met with increased burden from HCV-sequelae including HCC. because of chronic infection. Thus impact of measures in chronic patients might be low. Additionally, side effect from combination therapy may be too severe for elderly patients to endure, thus motivation becomes a factor.

6.3.1 Harm Reduction programmes

Harm reduction programmes encourage safe practices among high risk groups, prevent disease spread to others and try to re-integrated these groups into society. Needle exchange has had a profound positive impact on HIV and possibly HCV, however data on HCV is lacking. Outreach to prisons has not yielded negative results. MMT programmes yield encouraging short term results, integrating groups back among family and society, and making them productive members of society. Studies show increased life expectancy among these cohorts and psychosocial improvements.

Harm reduction is associated with false perceptions, e.g. encouraging drug addiction and is relatively costly to maintain.

6.3.2 HCV & HIV, the potential and the conflict

HCV strategies are usually a part of HIV/AIDS national responses. In the wake of increased HIV mortality due to HCV, the gaze of the HIV community is now shifting to HCV. The potential of a concerted and more holistic approach can prove to be beneficial. However usurping of fund from HCV to HIV programs has caused conflict between the two programs. Furthermore some HCV patients do not benefit from HIV strategies e.g. thalassemia patients, creating inequity. Nevertheless, a holistic approach by combining STI and BBI is efficient and is a good entry point for HCV programs.

6.3.3 HBV

HBV vaccine has been extended to over 52% of the population, with remarkable progress in Sindh. However, data does not elaborate if these vaccinations were complete or partial. Also common misconceptions and

some religious ruling against vaccinations can be problematic. Extending coverage to tribal areas poses security and cultural sensitive issues that may take additional efforts. However, the declining in HBV proportion is encouraging.

6.3.4 Cost-effectiveness and efficiency

Although in absolute terms, health spending has improved, the drop in %GDP allocation signifies low federal prioritization of health.

It is uncertain which interventions would yield the greatest benefit in terms of health gains and what impact this gain would have on the HCS as a whole. HIV studies, show primary prevention programs, e.g. behavior change strategies have had positive impacts, however these are short lived and prolonged behavioral change requires high level of motivation and repetition. It is uncertain the impact this strategy has in reducing spread in Pakistan as contextual factors differ. Also HCV and HIV are different infections.

Screening is a barrier both geographically and financially. Furthermore, free and subsidized treatment in Lahore public hospitals is not provided without 2 confirmatory tests costing a total of Rs. 10,000/- (approximately USD \$156/-) per person. In terms of treatment, one needs to consider the total costs, both direct and indirect, and whether this is affordable to the average Pakistani. Such studies are not available for Pakistan. Given over 20% of Pakistan lives under the poverty line, one can assume the cost of treatment to be far out of reach for the majority of the population.

6.4 Issues of Equity

Despite the higher prevalence in men, women are at risk due to frequent surgical and beautification techniques. Women have less access to healthcare services from cultural restraints and poor autonomy. Furthermore, the woman herself must be informed and motivated to seek care, which is difficult due to family responsibilities, fiscal and geographic limitations. Women GP are in shortage and most prevention and control programs are male-centric, creating gender inequity.

Additionally, population-based interventions are problematic as the richest section of society usually show greatest benefit while the most affected poorer communities cannot access services and thus benefit less, thus increases the gap and creates further inequity. This holds true for arid and impoverished provinces NWFP and Balochistan, and the largest benefit for Sindh and Punjab.

.5 Surveillance

Strengthening surveillance capacity is critical. This must start at municipal level with training and supervision. Providing performance based incentives might encourage better performance. A standardized and electronic system that communicates directly to the District level will allow disease monitoring, M&E of interventions and provide data for cost-effectiveness studies for policy makers.

6.6 Continual Health sector reform & growth

Health sector reform. Up scaling and mainstreaming of public HCF can be achieved, however this will require stewardship, political commitment, and regional based needs assessment. Multisectoral collaboration is essential to improve education, housing and waste management and prevent spread of HCV.

In conclusion, HCV is a highly prevalent epidemic that has plagued all sectors of Pakistani society. Studies are lacking in many regions and on many issues. It is driven by proximal and distal factors that require a more innovate approach to increase screening and awareness. The conventional wisdom of medical-interventions is too narrow a scope. Broader distal determinants must be addressed for HCV strategies to have any sort of lasting impact.

Chapter 7: Recommendations.

Based on the above discussion, the following recommendations have been formulated.

1. Perform contextual research on determinants, impact of interventions and their impact on health gain, and comparison studies between districts. Translated into local languages and English and made electronically available for locals and communities.

2.Primary Prevention:

- Advocacy and raise alertness of HCV and HBV to reduce transmission and spread in Districts. Developing pictorial mobile applications for children and adults to educate them about HCV can prove beneficial. Annual school and work-place seminars and skits to raise awareness about HCV and to get tested. Utilization of mass media, e.g. radio and tv skills to promote disease understanding and remove misconceptions.
- Continue vaccination efforts and broaden coverage. Incorporation of HBV into the national EPI program and including vaccination for hepatitis A as a priority to prevent liver damage. Strengthen cold chain storage for vaccine incase of electrical shortage.
- Strengthen safe blood screening, collection and storage strategies, including voluntary blood donation via community blood drives, extend blood screening, stronger regulation of protocols
- Establishing infection control programs at local level and a District or Provincial supervisory body.
- Provide sterile needles at HCF, encourage safe infection practices among HCW through training workshops
- Encourage safe sex, including sex education, awareness of dangers of multiple partner sexual behavior, distribution of free or subsidized condoms.
- Harm reduction interventions for IDU alongside free rehabilitation services. Employment opportunity for those going through the program.
- Work-safety interventions to reduce transmission and spread.
- Strengthening surveillance capacity to prevent reporting delays and informed policy formulation. See the Annex for Progress Indicators used to monitor progress of projects. Utilization of ICT for LHW to provide eLearning. Also design user-friendly mobile

application for LHW to report cases directly from point of service delivery to BHU.

3. Secondary & Tertiary Prevention:

- expanding free screening and treatment at sentinel points, hospitals and prison HCF, Provision of PCR and genotype screening equipment at a centralized District level initially with strong referral system, expanding with time.
- strengthen referral system and diagnostic capacity.
- extend pre- and post- VCT services to all HCV cases and their family.
- allocation of beds at major hospitals for HCV cases.
- procure anti-viral drugs for HCV , HBV and HIV at sentinel sites in timely fashion to prevent stock-out.
- Extending screening services to pregnant women for a more holistic approach.

4. Developing revised provincial HCV guidelines.

5.Regulation of tattoo shops and beauty-salons. Providing certifications for "excellence standards" for public to identify quality shops.

6. Strengthening partnerships with the private sector. Extending technical assistance to NGO and include them as stakeholders during annual reports and meetings.

7. Establish multilateral partnerships with other Asian hepatitis agencies and International actors and mobilize resources.

'This is hepatitis. It's closer than you think. Know it. Confront it. Get tested'.

-World hepatitis theme (2012)

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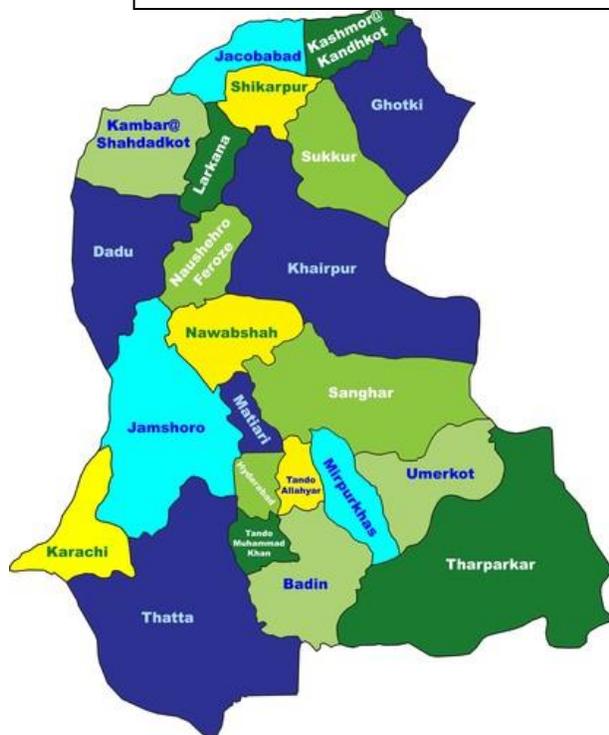
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ANNEX:

HCV progress indicators (Cited from Third National Hepatitis C Strategy 2010-2013)

Overall Objective	Objective	Indicators
Reduction in HCV transmission	Reducing HCV incidence	Incidence of HCV
	Increased access to NSP	Needle distribution to healthcare outlets annually.
		Proportion of IDU that reuse syringes in last 30 days.
Reduce HCV morbidity and mortality	Reduce burden attributable to HCV	Number of HCV cases in all stages of cirrhosis.
		Self reported health status by HCV cases
	Increased access to HCV services	Proportion of HCV using pINF and ribavirin in last 12 months.
Minimize social and social HCV impact	Reduce healthcare HCV stigma and discrimination	Proportion of HCV cases reporting discrimination

Sindh : Districts and Hepatitis Sentinel List



Kashmor Kandhkot- DHQ Hospital Kandhkot Kashmore
 Ghotki-Civil Hospital Mirpur Mathelo, Taluka Hospital Ghotki
 Sukkur-Civil Hospital Sukkur
 Shikarpur- RBUT Hospital Shikarpur
 Jacobabad-Civil Hospital Jacobabad
 Khairpur-Civil Hospital Khairpur, Taluka Hospital Thari Mirwah
 Larkana-CMC Hospital Larkana
 Kambar Shahdadkot-DHQ Hospital Kamber
 Dadu-Civil Hospital Dadu
 Naushehro Feroze-Civil Hospital Nausheroferoze
 Nawabshah-PMC Hospital Shaheed
 Sanghar-Civil Hospital Sanghar, Institute of Medical Science Shahdadpur
 Matiari- Taluka Head Quarter Hospital Hala
 Jamshoro- Taluka Hospital Kotri
 Karachi- Civil Hospital Karachi, Hospital New Karachi, Hospital Liaquatabad, Hospital Saudabad, Layari General Hospital, Abbasi Shaheed Hospital Karachi
 Thatta-Civil Hospital Thatta
 Badin-Civil Hospital Badin
 Tharparkar-Civil Hospital Mithi
 Umerkot-Civil Hospital Umerkot
 Mirpurkhas- Civil Hospital MirpurKhas
 Thando Allahyar-Taluka Hospital Tando Allahyar
 Hyderabad-Sindh Government Shah Bhitai Hospital, Sindh Government Hospital Paretabad, Sindh Government Hospital Qasimabad, Civil Hospital Hyderabad
 Tando Muhammad Khan-District Head Quarter Hospital Tando Mohammad Khan

Chief Minister's Hepatitis Control and Prevention, Sindh. Achievements (2009-2012)

HBV vaccine	
Groups vaccinated	Immunization coverage
General population	1,844,483
High risk population	1,485,471
School children	888,720
Newborns	792,050
Flood disaster victims	234,046
Inmates (prisoners)	26,860