The epidemiology of hepatitis C virus in Pakistan: systematic review and meta-analyses

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To characterize hepatitis C virus (HCV) epidemiology in Pakistan and estimate the pooled mean HCV antibody prevalence in different risk populations, we systematically reviewed all available records of HCV incidence and/or prevalence from 1989 to 2016, as informed by the Cochrane Collaboration Handbook. This systematic review was reported following the PRISMA guidelines. Populations were classified into six categories based on the risk of exposure to HCV infection. Meta-analyses were performed using DerSimonian and Laird random-effects models with inverse variance weighting. The search identified one HCV incidence study and 341 prevalence measures/strata. Meta-analyses estimated the pooled mean HCV prevalence at 6.2% among the general population, 34.5% among high-risk clinical populations, 12.8% among populations at intermediate risk, 16.9% among special clinical populations, 55.9% among populations with liver-related conditions and 53.6% among people who inject drugs. Most reported risk factors in analytical epidemiologic studies related to healthcare procedures. Pakistan is enduring an HCV epidemic of historical proportions—one in every 20 Pakistanis is infected. HCV plays a major role in liver disease burden in this country, and HCV prevalence is high in all-risk populations. Most transmission appears to be driven by healthcare procedures. HCV treatment and prevention must become a national priority.

1. Introduction

Hepatitis C virus (HCV) is a blood-borne pathogen and a significant global health concern [1]. Following the acquisition
of the virus, acute HCV infection can progress to chronic infection [2], which is associated with several morbidities, such as liver cirrhosis and cancer [3–5]. HCV-related morbidity strains healthcare systems worldwide, with approximately 71 million people chronically infected globally [6]. Direct-acting antivirals (DAAs), a highly efficacious HCV treatment, can clear HCV infection and may substantially reduce HCV disease burden and onward transmission [7]. As such, global targets have been set by the World Health Organization (WHO) to eliminate HCV infection by 2030 [8,9].

The Middle East and North Africa (MENA) region is the most affected region by HCV infection, with approximately 15 million individuals chronically infected [6]. HCV is highly endemic in Pakistan, where a national survey, conducted in 2007–2008, estimated HCV prevalence at 4.8% [10]. Ongoing transmission appears to be widespread, occurring in both healthcare and community settings [10]. Understanding HCV epidemiology in Pakistan is critical in developing and targeting cost-effective prevention and treatment interventions against HCV, in order to meet the global target of HCV elimination.

The objective of this systematic review is to characterize HCV epidemiology in Pakistan by: (i) systematically reviewing and synthesizing available published data of HCV incidence and prevalence in six population categories defined according to risk of exposure and (ii) pooling available HCV prevalence measures in each of the six pre-defined risk population categories to estimate population-specific pooled mean HCV prevalence.

This work was conducted as part of the MENA HCV Epidemiology Synthesis Project, which aims to characterize HCV epidemiology in MENA to inform key public health research, policy, programming and resource allocation priorities [11–24].

2. Methods

The methodology used in this study follows that used in previous systematic reviews of the MENA HCV Epidemiology Synthesis Project [11–17]. The subsequent subsections summarize this methodology. Further details are available in previous publications [11–17].

2.1. Data sources and search strategy

All available records reporting HCV incidence and/or prevalence measures in Pakistan were systematically reviewed, as informed by the Cochrane Collaboration Handbook [25]. Results were reported using the Preferred Reporting Items for Systematic and Meta-analyses (PRISMA) guidelines (electronic supplementary material, table S1) [26]. Our main data sources included PubMed and Embase databases. Broad search criteria (electronic supplementary material, figure S1) were used to retrieve articles and abstracts on PubMed and Embase, from 1989 (the year in which HCV was first identified [27,28]) up to 19 April 2016, with no language restrictions.

2.2. Study selection

Similar to our previous systematic reviews [11–17], all records identified through our search were imported into the reference manager Endnote, where duplicate publications were identified and excluded. The remaining unique reports were subjected to a two-stage screening process, performed by Z.A.K. and S.P.K. In the first stage, titles and abstracts were screened for relevance. Records marked as relevant or potentially relevant proceeded to the second stage of screening, in which full-texts were obtained and assessed for eligibility based on predetermined inclusion/exclusion criteria. Eligible reports were included in this study, and ineligible reports were excluded with reasons specified in figure 1. Additional records were identified by screening references in full-text articles and the literature reviews, as well as a country-level report.

2.3. Inclusion and exclusion criteria

The inclusion and exclusion criteria used in this study were adapted from our previous systematic reviews [11–17]. Briefly, any article reporting HCV antibody incidence and/or antibody prevalence, based on primary data, qualified for inclusion in this review. An article was excluded if it was a case report, case series, editorial, letter to editor(s), commentary, review, referred to HCV as non-A non-B hepatitis, contained duplicate information, reported HCV prevalence based on self-reporting, and if the study population was Pakistani nationals residing outside Pakistan.
1375 citations identified through PubMed (n = 480) and Embase (n = 895)

436 duplicates removed

939 unique citations identified and titles/abstracts screened

422 excluded after abstract screening

517 unique reports retrieved for full-text searching

*286 reports excluded

231 eligible reports

1 additional report through screening references of full-text articles and reviews

1 report on the Pakistan national survey 2008

1 HCV incidence study and 248 HCV prevalence measures

*reasons for exclusion:
- duplicate data (n = 172)
- full-texts could not be retrieved and abstract does not have data on relevant outcomes (n = 61)
- eligibility criteria not met (n = 142)
- full-text did not include relevant indicators (n = 140)

**Figure 1.** Flowchart of article selection for the systematic review of hepatitis C virus (HCV) incidence and prevalence in Pakistan, adapted from the PRISMA 2009 guideline [26].

In this work, for clarity, a ‘report’ refers to a document (article, conference abstract, country-level report and others) including one or several outcome measures of those included in our systematic review, while a ‘study’ refers to any one specific single outcome measure. One report may contribute multiple studies (say several prevalence measures in different populations), and multiple reports of the same outcome measure (say same prevalence measure in the same specific sample) were identified as duplicates and deemed as one study.

2.4. Data extraction and data synthesis

Data from relevant reports were extracted by Z.A.K., of which 20% were double extracted by S.P.K. to ensure consistency. Nature of extracted data followed our previous systematic reviews [11–17]. HCV prevalence measures were extracted and reported as per original reports. These measures were
rounded to one decimal place except for measures below 0.1%, which were rounded to two decimal places.

Risk factors that were found to be significantly associated with HCV infection through multivariable regression analyses were extracted. HCV ribonucleic acid (RNA) prevalence among HCV antibody-positive individuals (that is HCV viraemic rate [20]) was extracted whenever available in reports including an HCV prevalence.

The extracted data were synthesized by risk population in six distinct categories defined according to the risk of exposure to HCV infection as follows:

1. General population (populations at low risk): these included blood donors, pregnant women, children, refugees, household-based survey participants and national army recruits, among others.
2. High-risk clinical populations: these included populations exposed to frequent medical injections and/or blood transfusions, such as haemodialysis, thalassaemia, haemophilia and multi-transfused patients, among others.
3. Populations at intermediate risk: these included populations whose risk of exposure is higher than the general population but lower than populations at high risk, such as healthcare workers (HCWs), household contacts of HCV-infected patients, patients with diabetes and prisoners, among others.
4. Special clinical populations: these included clinical populations whose risk of exposure to HCV infection is difficult to ascertain, such as patients with non-liver-related malignancies, dermatological manifestations and rheumatological disorders, among others.
5. Populations with liver-related conditions: these included patients with liver-related conditions of an epidemiological significance to HCV infection such as patients with chronic liver disease, acute viral hepatitis, hepatocellular carcinoma and liver cirrhosis, among others.
6. People who inject drugs (PWID).

2.5. Quantitative analysis

The quantitative analysis approach was similar to that in our previous HCV systematic reviews [11–17]. HCV prevalence measures were presented by risk population in reports with a sample size greater than or equal to 50 in tables 1–3; electronic supplementary material, S2–S4. If no explicit HCV prevalence measure was reported, it was calculated based on the sample size and number of events reported, if available. HCV prevalence for the total sample was replaced with stratified measures, whenever the sample size was greater than or equal to 25 participants for each stratum. Stratified data were included using a pre-defined order that prioritizes stratifications by population followed by sex, year, region and age. Meta-analyses were conducted for studies/strata with a minimum sample size of 25 participants. Only one final stratification per study was included in the meta-analyses.

The variance of the prevalence measures was stabilized using the Freeman–Tukey type arcsine square-root transformation [138]. Estimates for HCV prevalence were weighted by the inverse variance and pooled using a DerSimonian–Laird random-effects model. This model accounts for sampling variation (random chance) and expected heterogeneity in effect size across studies [139]. Heterogeneity was assessed and characterized using several statistical measures.

With a recently identified potential issue with the Freeman–Tukey type arcsine square-root transformation [140], we conducted sensitivity analyses by performing meta-analyses using the generalized linear mixed models (GLMM) method to confirm validity of our results.

Meta-analysis of RNA HCV prevalence measures among HCV antibody-positive individuals (that is HCV viraemic rate) was also conducted to estimate the pooled mean of this prevalence measure.

A sensitivity analysis was further performed to examine whether the advent of more specific and sensitive diagnostic tools (third or fourth generation assays) could have affected the prevalence estimates in the general population. Meta-analyses were performed on the general population prior to and after 2005, since after this year the vast majority of studies were likely to have been conducted using third of fourth generation assays. The results of the meta-analyses were assessed to determine whether the estimated pooled mean HCV prevalence was significantly different prior to 2005.

Meta-analyses were conducted in R v. 3.1.2. [141], using the package meta [142].
Table 1. Studies reporting hepatitis C virus (HCV) prevalence among the general population (populations at low risk) in Pakistan. Prev, prevalence; CC, case-control; CS, cross-sectional; Conv, convenience; MsRS, multi-stage random sampling, RCS, random cluster sampling; SRS, simple random sampling; SS-CS, single-stage cluster sampling; NWFP, North West Frontier Province; NHL, non-Hodgkin’s lymphoma.

| Author (citation) | Year(s) of data collection | Province or city | Study site | Study design | Study sampling procedure | Population | Sample size | HCV prev\(^a\) (%) |
|-------------------|----------------------------|-----------------|------------|--------------|--------------------------|------------|-------------|------------------|
| Agboatwalla [29]  | 1990–1991                  | —               | community  | CS           | Conv                     | Healthy children | 226         | 0.4              |
| Kakepoto [30]     | 1989–1994                  | Karachi and Hyderabad | Blood donation camps | CS           | Conv                     | Blood donors   | 16 705      | 1.2              |
| Luby [31]         | 1993                       | Hafizabad       | Community  | CS           | RCS                      | General population | 309         | 6.5              |
| Parker [32]       | —                          | Lahore          | Hospital   | CS           | Conv                     | Pregnant women | 417         | 6.7              |
| Parker [32]       | —                          | Lahore          | Hospital   | CS           | Conv                     | Children       | 538         | 1.3              |
| Majeed [33]       | 1996–1997                  | Karachi         | Medical centre | CS           | Conv                     | Blood donors from students’ community | 612         | 0.5              |
| Khan [34]         | 1995                       | Darsano Channo Karachi | General clinic | CS           | Conv                     | Outpatients from health clinics | 135         | 44.0             |
| Majeed [35]       | 1997–1998                  | Karachi         | Medical centre | CS           | Conv                     | Replacement blood donors | 7047        | 2.4              |
| Aslam [36]        | 2000                       | Lahore          | Community  | CS           | Conv                     | General population | 488         | 15.9             |
| Majeed [36]       | 2000                       | Gujranwala      | Community  | CS           | Conv                     | General population | 1922        | 23.8             |
| Khattak [37]      | 1996–2000                  | Rawalpindi      | Community  | CS           | Conv                     | Healthy blood donors | 103 858     | 4.1              |
| Qureshi [38]      | 1996–1999                  | Karachi         | Blood bank in a hospital | CS           | Conv                     | Blood donors | 401         | 4.5              |
| Mumtaz [39]       | 2001–2002                  | Rawalpindi      | Hospital   | CS           | Conv                     | Healthy blood donors | 563         | 6.2              |
| Asif [40]         | 2002–2003                  | Northern Pakistan | Blood transfusion unit | CS           | Conv                     | Replacement blood donors | 3187        | 5.1              |
| Asif [40]         | 2002–2003                  | Northern Pakistan | Blood transfusion unit | CS           | Conv                     | Voluntary blood donors | 243         | 2.5              |
| Khokhar [41]      | 2001–2002                  | Islamabad       | Hospital   | CS           | Conv                     | Pregnant women | 503         | 4.8              |
| Aslam [42]        | —                          | Lahore          | Community  | CS           | Conv                     | General population | 523         | 14.9             |
| Jaffrey [43]      | 2001–2002                  | Islamabad       | Hospital   | CC           | Conv                     | Pregnant women | 947         | 3.3              |
| Muhammad [44]     | 1998–2002                  | Buner, NWFP     | Hospital   | CS           | Conv                     | Outpatients     | 16 400      | 4.6              |
| Jafri [45]        | 2003–2004                  | Karachi         | Community  | CS           | Conv                     | Healthy children | 3533        | 1.6              |
| Majeed [46]       | 2000                       | Karachi         | Medical centre | CS           | Conv                     | First time replacement blood donors | 7325        | 3.6              |
| Rifat-uz [47]     | 2004                       | Bahawalpur      | Community  | CS           | Conv                     | General population | 6815        | 4.4              |

(Continued.)
| author (citation) | year(s) of data collection | province or city | study site | study design | study sampling procedure | population | sample size | HCV prev (%) |
|------------------|---------------------------|-----------------|------------|--------------|--------------------------|------------|------------|--------------|
| Ahmad [48]       | 2004                      | Faisalabad      | hospital   | CS           | SRS                      | blood donors and general population | 300        | 20.6        |
| Bhatti [49]      | 2003–2005                 | Rawalpindi      | blood transfusion unit | CS    | Conv                      | blood donors | 94 177     | 4.2          |
| Bhatti [49]      | 2004                      | Rawalpindi      | blood transfusion unit | CS    | Conv                      | blood donors | 966        | 3.8          |
| Sultan [50]      | 1996–2005                 | Lahore          | tertiary care centre | CS    | Conv                      | replacement blood donors | 41 498     | 3.7          |
| Abbas [51]       | —                         | Sukkar          | community   | CS           | SCS                      | general population | 873        | 33.7         |
| Butt [52]        | 2004–2005                 | —               | hospital    | CS           | Conv                      | army recruits | 57 07       | 1.7          |
| Hakim [53]       | 2002–2006                 | Karachi         | university  | CS           | Conv                      | female university students | 4 000      | 5.2          |
| Idrees [54]      | 1999–2007                 | Punjab          | community   | CS           | Conv                      | general population | 6 817      | 15.1         |
| Khattak [55]     | —                         | Peshawar        | blood banks in hospitals | CS    | Conv                      | general population | 1 131      | 4.1          |
| Mujeeb [56]      | 2004–2007                 | Sindh           | blood bank in a medical centre | CS    | Conv                      | blood donors | 5 345      | 7.5          |
| Abbas [57]       | 2005–2008                 | —               | liver clinic | CS           | Conv                      | blood donors | 804        | 14.0         |
| Ali [58]         | 2003–2005                 | Multan          | community   | CS           | SRS                      | general population | 116        | 6.7          |
| Bangash [59]     | 2007                      | Parachinar and Sadda | blood transfusion unit | CS    | Conv                      | blood donors | 1 300      | 1.6          |
| Bangash [60]     | 2007–2008                 | Parachinar      | blood bank in a hospital | CS    | Conv                      | blood donors | 10 343     | 0.4          |
| Gul [61]         | 2006–2007                 | Abbottabad      | hospital    | CS           | Conv                      | pregnant women | 500        | 8.9          |
| Jalbani [62]     | —                         | Khaipur Nathan Shah and Shahdadkot | community | CS    | Conv                      | general population | 406        | 30.3         |
| Junejo [63]      | 2007–2008                 | Hyderabad       | hospital    | CS           | Conv                      | outpatients | 931        | 17.2         |
| Hussain [64]     | 2008                      | Karachi         | blood bank  | CS           | Conv                      | blood donors | 98 012     | 6.0          |
| Sami [65]        | 2005                      | Karachi         | medical centre | CS    | Conv                      | pregnant women | 5 902      | 1.8          |
| Shaikh [66]      | 2006–2007                 | Larkana city    | general clinic | CS    | Conv                      | general population | 450        | 6.6          |
| Sheikh [67]      | 2006                      | Karachi         | Hospital    | CS           | Conv                      | pregnant women | 2 592      | 0.7          |
| Abbas [68]       | —                         | Karachi         | community   | CS           | SRS                      | general population | 504        | 3.2          |
| Ali [69]         | 2009–2010                 | Khyber Pakhtunkhwa | community | CS           | SRS                      | healthy inhabitants of District Mansehra | 400        | 7.0          |

(Continued.)
| author (citation) | year(s) of data collection | province or city | study site | study design | study sampling procedure | population | sample size (n) | HCV prev (％) |
|------------------|----------------------------|-----------------|------------|--------------|--------------------------|------------|----------------|--------------|
| Aziz [70]        | 2007–2008                  | Sindh           | community  | CS           | Conv                     | general population from peri-urban area | 129        | 3.9           |
| Aziz [70]        | 2007–2008                  | Sindh           | community  | CS           | Conv                     | general population from rural area     | 388        | 28.6         |
| Hashmi [71]      | 2006                       | Islamabad      | community  | CS           | MsRS                     | female inhabitants: 15–50 years old    | 252        | 24.6         |
| Hyder [72]       | 2007–2009                  | Punjab          | community  | CS           | Conv                     | healthy men: 16–59 years old           | 58 680     | 6.9           |
| Jadoon [73]      | 2008                       | —               | blood bank in a hospital | CS           | Conv                     | healthy blood donors                 | 550        | 8.2           |
| Jadoon [74]      | —                          | Multan          | hospital   | CC           | Conv                     | blood donors                          | 10 000     | 4.9           |
| Jamil [75]       | 2010                       | Tehsil Oghi     | community  | CS           | Conv                     | general population                    | 648        | 10.3          |
| Janjua [76]      | 2005                       | Karachi         | community  | CS           | SCS                      | general population                    | 1997       | 23.8          |
| Qureshi [10]     | 2007–2008                  | All regions of Pakistan | national | CS           | MsRS                     | household survey members              | 47 043     | 4.8           |
| Shah [77]        | 2007–2008                  | Karachi         | hospital   | CS           | Conv                     | blood donors                          | 32 042     | 1.6           |
| Taseer [78]      | 2006–2007                  | Multan          | hospital   | CS           | Conv                     | pregnant women                         | 500        | 7.0           |
| Aziz [79]        | 2005–2009                  | Karachi         | hospital   | CS           | Conv                     | pregnant women: 18–45 years old       | 18 000     | 5.8           |
| Bohany [80]      | 2007–2009                  | Karachi         | specialized clinic | CS           | Conv                     | blood donors                          | 577        | 1.9           |
| Iqbal [81]       | —                          | Gadap Town, Karachi | community  | CS           | Conv                     | previously unscreened adults: more than 10 years old | 600        | 5.0           |
| Khan [82]        | 2009                       | Khyber Pakhtunkhwa | blood bank | CS           | Conv                     | voluntary blood donors                 | 7 448      | 1.9           |
| Rauf [83]        | 2009                       | NWFP            | refugee camp | CS           | Conv                     | refugees in Baghicha Dheri camps       | 590        | 8.8           |
| Safi [84]        | 2008–2009                  | NWFP            | hospital   | CS           | Conv                     | blood donors                          | 62 251     | 2.6           |
| Saleem [85]      | 2008                       | Azad Kashmir    | hospital   | CS           | Conv                     | outpatients                           | 9564       | 6.4           |
| Yousaf [86]      | —                          | all regions of Pakistan | laboratory | CS           | SRS                      | general population                    | 120        | 29.2          |
| Ahmed [87]       | 2007–2009                  | Balochistan     | community  | CS           | MsRS                     | general population                    | 2000       | 5.5           |
| Ansari [88]      | 2010                       | Karachi         | specialized clinic | CS           | Conv                     | blood donors                          | 5517       | 1.9           |

(Continued.)
Table 1. (Continued.)

| Author (citation) | Year(s) of data collection | Province or city | Study site | Study design | Study sampling procedure | Population | Sample sizea | HCV prevb (%) |
|------------------|---------------------------|-----------------|------------|--------------|--------------------------|------------|-------------|---------------|
| Attaullah [89]   | 2008–2011                 | Khyber Pakhtunkhwa | Blood bank in a hospital | CS | Conv | Blood donors | 127828 | 2.5          |
| Bhutta [90]      | 2010                      | Sargodha         | Hospital   | CS | Conv | Replacement blood donors | 100 | 12.0         |
| Haifez-ud [91]   | 2010                      | Punjab           | Community  | CS | Conv | Healthy adult males | 14027 | 3.1          |
| Ijaz [92]        | 2011–2012                 | Lahore           | Hospital   | CS | Conv | Blood donors | 3652 | 12.4         |
| Khan [93]        | 2008                      | Lakki Marwat     | Hospital   | CS | Conv | Outpatients | 1443 | 4.4          |
| Khan [94]        | 2009–2012                 | Peshawar         | Hospital   | CS | Conv | Blood donors | 6513 | 1.1          |
| Memon [95]       | 2007–2008                 | Karachi          | Private security company | CS | Conv | Security personnel | 457 | 9.0          |
| Muhammad [96]    | 2009–2010                 | Sindh            | Medical centre | CC | Conv | Family members of NHL patients (controls) | 584 | 7.7          |
| Nawaz [97]       | 2011                      | —               | Hospital   | CS | Conv | General population | 435 | 12.2         |
| Waheed [98]      | 2010                      | Islamabad       | Hospital   | CS | Conv | Blood donors | 10145 | 8.3          |
| Abbas [99]       | 2010                      | Balochistan      | Community  | CS | Conv | General population | 2800 | 7.0          |
| Butt [100]       | 2013                      | Lahore           | Blood bank in a hospital | CS | Conv | Male blood donors | 833 | 1.9          |
| Irfan [101]      | 2004–2010                 | Karachi          | Hospital   | CS | Conv | Blood donors | 108598 | 2.7         |
| Khan [102]       | 2011                      | Quetta, Balochistan | Hospital | CS | Conv | Male blood donors | 356 | 20.8         |
| Khan [103]       | 2010–2011                 | Karachi          | Community  | CS | SRS | Household survey members | 679 | 8.0          |
| Qadeer [104]     | 2007–2012                 | Punjab           | Community  | CS | Conv | Blood donors from students’ community | 5000 | 4.1          |
| Raff [105]       | 2011                      | Karachi          | Community  | CS | Conv | Male garbage scavengers | 117 | 8.5          |
| Seema [106]      | 2010                      | Hyderabad, Sindh | Hospital   | CS | Conv | Pregnant women | 3078 | 4.7          |
| Zafar [107]      | 2010                      | Mardan           | Hospitals and clinics | CS | Conv | General population | 1419 | 11.7         |
| Ali [108]        | 2013–2014                 | Peshawar         | Community  | CS | Conv | General population | 982 | 13.4         |
| Moiz [110]       | 2011–2012                 | Southern Pakistan | Hospital   | CS | Conv | Healthy noncommercial blood donors | 42830 | 1.7          |

(Continued.)
Table 1. (Continued.)

| author (citation) | year(s) of data collection | province or city | study site | study design | study sampling procedure | population | sample size<sup>a</sup> | HCV prev<sup>b</sup> (%) |
|-------------------|---------------------------|------------------|------------|--------------|--------------------------|------------|-------------------------|------------------------|
| Parveen [111]     | 2013                      | Multan           | hospital   | CS           | Conv                     | potential employees sent for HCV screening | 10 666                  | 2.9                    |
| Kumari [112]      | 2012                      | Karachi          | hospital   | CS           | Conv                     | pregnant women                             | 300                     | 13.3                   |
| Niazi [113]       | 2012–2013                 | Rawalpindi       | transfusion unit | CS           | Conv                     | blood donors                               | 56 772                  | 1.8                    |
| Sheikh [114]      | —                         | Gwadar Port      | disaster management camp | CS | Conv                     | blood donors in rural areas                 | 300                     | 4.3                    |
| Donchuk [115]     | 2015–2016                 | Karachi          | community  | CS           | Conv                     | outpatients                                 | 458 9                   | 27.0                   |
| Karim [116]       | 2015                      | Mardan           | hospitals  | CS           | Conv                     | blood donors                                | 5318                    | 1.1                    |

<sup>a</sup>The table reports only studies whose sample size is greater than or equal to 50 participants. For space considerations, the table shows the overall HCV measure of each study rather than stratifications within population subgroups.

<sup>b</sup>The decimal places of the prevalence figures are as reported in the original report, but prevalence figures with more than one decimal place were rounded to one decimal place, with the exception of those below 0.1%.
Table 2. Studies reporting hepatitis C virus (HCV) prevalence among high-risk clinical populations in Pakistan.

| Author (citation) | Year(s) of data collection | Province or city | Study site | Study design | Study sampling procedure | Population | Sample size | HCV prev<sup>b</sup> (%) |
|------------------|---------------------------|-----------------|------------|--------------|--------------------------|------------|-------------|------------------------|
| Mujeeb [117]     | —                         | Karachi         | medical centre | CS           | Conv                     | thalassaemia patients | 91          | 50.5                   |
| Gul [118]        | 1999                      | Lahore          | haemodialysis unit | CC           | Conv                     | haemodialysis patients | 50          | 68.0                   |
| Khokhar [119]    | 2002–2003                 | Islamabad      | hospital     | CS           | Conv                     | haemodialysis patients | 97          | 23.7                   |
| Mumtaz [120]     | 2008                      | Lahore          | hospital     | CS           | Conv                     | haemodialysis male patients | 50          | 28.0                   |
| Ullah [121]      | —                         | Karachi         | hospital     | CS           | Conv                     | thalassaemia patients | 79          | 43.0                   |
| Khan [122]       | 2010                      | Khyber Pakhtunkhwa | hospitals | CS           | SRS                      | haemodialysis patients | 384         | 29.2                   |
| Borhany [80]     | 2007–2009                 | Karachi         | specialized clinic | CS           | Conv                     | haemophilia patients | 173         | 51.4                   |
| Riaz [123]       | 2009                      | Karachi         | hospital     | CS           | Conv                     | thalassaemia patients (multi-transfused) | 79          | 45.5                   |
| Ansari [88]      | 2010                      | Karachi         | specialized clinic | CS           | Conv                     | thalassaemia patients | 160         | 13.1                   |
| Sadiq [124]      | 2008–2009                 | Lahore          | hospital     | CS           | Conv                     | transfusion dependent children | 120         | 54.2                   |
| Daud [125]       | 2008–2012                 | Islamabad      | HIV care centre | CS           | Conv                     | HIV patients who use drugs (non-intravenously) | 81          | 6.2                    |
| Din [126]        | 2013                      | Rawalpindi      | transfusion unit | CS           | Conv                     | thalassaemia patients | 95          | 49.5                   |
| Mahmud [127]     | 2012–2013                 | Karachi         | —            | CS           | Conv                     | haemodialysis patients | 189         | 16.4                   |
| Chishti [128]    | 2010–2011                 | Karachi         | medical centre | CS           | Conv                     | haemodialysis patients (multi-transfused) | 200         | 29.0                   |
| Khan [129]       | 2013–2014                 | Khyber Pakhtunkhwa | hospitals | CS           | Conv                     | thalassaemia patients | 180         | 7.8                    |
| Yasmeen [130]    | 2012–2013                 | —              | hospital     | CS           | Conv                     | thalassaemia patients | 300         | 47.3                   |

<sup>a</sup>The table reports only studies whose sample size is greater than or equal to 50 participants. For space considerations, the table shows the overall HCV measure of each study rather than stratifications within population subgroups.

<sup>b</sup>The decimal places of the prevalence figures are as reported in the original report, but prevalence figures with more than one decimal were rounded to one decimal place, with the exception of those below 0.1%. Prev, prevalence; CC, case-control; CS, cross-sectional; Conv, convenience; SRS, simple random sampling.
### Table 3. Studies reporting hepatitis C virus prevalence among people who inject drugs (PWID) in Pakistan.

| Author (citation) | Year(s) of data collection | Province or city | Study site | Study design | Study sampling procedure | Population | Sample size | Sample sizea | HCV prevb (%) |
|-------------------|---------------------------|-----------------|------------|--------------|--------------------------|------------|-------------|--------------|---------------|
| Kuo [131]         | 2003                      | Lahore and Quetta | outpatient centres | CS | Conv | PWID | 351 | 88.0 |
| Achakzai [132]    | 2004                      | Quetta           | community | CS | Conv | PWID | 50  | 60.0 |
| Altaf [133]       | 2003                      | Karachi          | rehabilitation centre | CS | Conv | PWID | 161 | 94.3 |
| Abbasi [134]      | 2003                      | Quetta           | community | CS | Conv | PWID | 300 | 44.7 |
| Platt [135]       | 2007                      | Rawalpindi       | community | CS | RDS | PWID | 302 | 17.3 |
| Platt [135]       | 2007                      | Abbottabad       | community | CS | RDS | PWID | 302 | 17.3 |
| Rehan [136]       | 2004                      | Karachi          | community | CS | SRS | PWID | 399 | 87.0 |
| Rehan [136]       | 2004                      | Lahore           | community | CS | SRS | PWID | 380 | 91.8 |
| Rehman [137]      | 2007–2008                 | Khyber Pakhtunkhwa | community | CS | Conv | PWID | 200 | 31.5 |
| Memon [95]        | 2007–2008                 | Karachi          | laboratory | CS | Conv | PWID | 407 | 68.3 |
| Daud [125]        | 2008–2012                 | Islamabad        | HIV care centre | CS | Conv | HIV patients who inject drugs | 81  | 77.8 |

a The table reports only studies whose sample size is greater than or equal to 50 participants. For space considerations, the table shows the overall HCV measure of each study rather than stratifications within population subgroups.

b The decimal places of the prevalence figures are as reported in the original report, but prevalence figures with more than one decimal were rounded to one decimal place, with the exception of those below 0.1%. Prev, prevalence; CS, cross-sectional; Conv, convenience; RDS, respondent-driven sampling; SRS, simple random sampling.
2.6. Quality assessment

The quality of HCV prevalence measures was assessed for each study as informed by the risk of bias (ROB) Cochrane approach [143], as well as by examining the precision of each reported measure. The ROB assessment was based on three domains: type of HCV ascertainment (biological assays versus unclear), the sampling methodology (probability-based versus convenience sampling) and the response rate (greater than or equal to 80% versus less than or equal to 80% of the target sample size).

Studies were considered as having high precision if the number of HCV tested individuals was at least 100 participants, as informed by previous studies [11–17].

3. Results

3.1. Search results

Figure 1 describes the process of study selection, adapted from the PRISMA flow diagram [26]. A total of 1375 citations were identified: 480 through PubMed and 895 through Embase. A total of 517 reports were identified as relevant or potentially relevant after removing duplicates and screening the titles and abstracts. Out of these, 285 reports were excluded for various reasons as summarized in figure 1. An additional report was identified through screening of articles’ references, and 11 HCV prevalence measures/strata were obtained from the Pakistan National Survey [10]. Finally, 233 eligible reports were included in this systematic review, yielding one incidence study and 248 prevalence measures. The 248 prevalence measures contributed 341 prevalence measures/strata. Though no language restrictions were imposed, all identified studies were in English.

3.2. HCV incidence overview

Our search identified one HCV incidence study, which reported seroconversion risk. This study included (as its baseline) HCV-negative HCWs who reported a needle stick injury from documented HCV-positive patients. After six weeks follow-up, investigators reported a seroconversion risk of 4.8% [144].

3.3. HCV prevalence overview

3.3.1. General population

Among the general population (table 1), our search identified 148 prevalence measures/strata, ranging from 0.4 to 44.0%, with a median of 5.3%. Among blood donors (number of studies: \( n = 57 \)), HCV prevalence ranged from 0.4 to 20.8%, with a median of 3.5%. Among pregnant women (\( n = 12 \)), HCV prevalence ranged from 0.7 to 20.7%, with a median of 6.0%. Among outpatients (\( n = 9 \)), HCV prevalence ranged from 4.4 to 51.0%, with a median of 9.0%. Among other general populations (\( n = 65 \)), HCV prevalence ranged from 0.4 to 35.9%, with a median of 6.8%.

3.3.2. High-risk clinical populations

Among high-risk clinical populations (table 2), our search identified 21 prevalence measures/strata, ranging from 7.8 to 68.0%, with a median of 34.5%. Among thalassaemia patients (\( n = 12 \)), HCV prevalence ranged from 7.7 to 60.0%, with a median of 42.2%. Among haemodialysis patients (\( n = 7 \)), HCV prevalence ranged from 16.4 to 68.0%, with a median of 28.0%. Only one study was conducted for each of haemophilia patients (prevalence of 51.4%) and multi-transfused patients (prevalence of 54.2%).

3.3.3. Intermediate risk populations

Among intermediate risk populations (electronic supplementary material, table S2), our search identified 64 prevalence measures/strata, ranging from 0.0 to 70.9%, with a median of 12.9%. Among hospitalized populations (\( n = 25 \)), HCV prevalence ranged from 2.5 to 71.0%, with a median of 13.2%. Among HCWs (\( n = 11 \)), HCV prevalence ranged from 0.0 to 5.6%, with a median of 3.2%. Among prisoners and/or volunteer prisoner blood donors (\( n = 9 \)), HCV prevalence ranged from 8.7 to 18.2%, with a median of 13.1%. Among diabetics (\( n = 6 \)), HCV prevalence ranged from 5.1 to 43.0%, with a median of 15.5%. Among household contacts of HCV index patients (\( n = 4 \)), HCV prevalence ranged from 4.4 to 38.0%, with a median of 18.3%. A study conducted in Karachi among men who use roadside barbers measured HCV prevalence at 38.0% [145].
3.3.4. Special clinical populations

Among special clinical populations (electronic supplementary material, table S3), our search identified 18 prevalence measures/strata, ranging from 1.0 to 81.0%, with a median of 15.5%. Among patients with skin disorders ($n = 4$), HCV prevalence ranged from 3.0 to 23.4%, with a median of 7.7%. Among patients with urological conditions ($n = 4$), HCV prevalence ranged from 1.0 to 25.9%, with a median of 9.6%.

3.3.5. Populations with liver-related conditions

Among populations with liver-related conditions (electronic supplementary material, table S4), our search identified 73 prevalence measures/strata, ranging from 3.0 to 100.0%, with a median of 63.5%. Among chronic liver disease patients ($n = 20$), HCV prevalence ranged from 4.9 to 78.4%, with a median of 41.1%. Among cirrhosis patients ($n = 21$), HCV prevalence ranged from 28.0 to 100.0%, with a median of 68.0%. Among hepatocellular carcinoma patients ($n = 18$), HCV prevalence ranged from 33.3 to 92.0%, with a median of 70.1%. Among acute viral hepatitis patients ($n = 6$), HCV prevalence ranged from 6.4 to 57.1%, with a median of 20.9%.

3.3.6. People who inject drugs

Among PWID (table 3), our search identified 15 prevalence measures/strata, ranging from 8.0 to 94.3%, with a median of 44.7%.

3.4. Overview of HCV RNA prevalence among HCV antibody-positive individuals

Our search identified a total of 12 HCV RNA prevalence measures among HCV antibody-positive individuals (HCV viraemic rate). The details of these measures can be found in the electronic supplementary material, table S6. HCV viraemic rate ranged from 44.4 to 98.0%, with a median of 74.2%.

3.5. Pooled mean HCV prevalence estimates

Pooled mean estimates for HCV prevalence for the six risk populations are summarized in table 4. The pooled mean prevalence for the general population (populations at low risk) was estimated at 6.2% (95% CI: 5.7–6.7%). Meanwhile, the pooled mean HCV prevalence was estimated at 34.5% (95% CI: 27.0–42.3%) for high-risk clinical populations, 12.8% (95% CI: 10.8–15.1%) for intermediate risk populations, 16.9% (95% CI: 6.2–31.3%) for special clinical populations, 55.9% (95% CI: 49.2–62.5%) for populations with liver-related conditions and 53.6% (95% CI: 36.2–70.6) for PWID.

Of note, the GLMM meta-analyses produced similar pooled mean estimates for all risk populations. For example, the pooled mean HCV prevalence for special clinical populations, that showed the largest difference between the fixed effects result and the random-effects result, was 13.1% (95% CI: 6.9–31.3) using the GLMM method versus 16.9% (95% CI: 6.2–31.3) using the Freeman–Tukey type arcsine square-root transformation method.

Statistically significant heterogeneity in effect size (that is HCV prevalence) was observed in all meta-analyses (Cochrane’s Q-statistic’s $p$-value was always less than 0.0001; table 4). Most of the variation across pooled studies was due to true difference in effect size rather than chance ($I^2 > 93.7$%). The prediction intervals were generally very wide. The totality of these heterogeneity measures indicates high heterogeneity in HCV prevalence measures in each risk population category.

The pooled mean HCV RNA prevalence among HCV antibody-positive individuals (HCV viraemic rate) was estimated at 74.1% (95% CI: 59.5–86.5%).

The meta-analyses performed prior to and after 2005 among the general population, as part of our sensitivity analysis, estimated a pooled mean HCV prevalence of 5.0% (95% CI: 4.0–6.0%), and 6.5% (95% CI: 5.9–7.0%), respectively.

3.6. Risk factors for HCV infection

Risk factors for HCV seropositivity were assessed in 11 studies using multivariable regression analyses. Healthcare-related risk factors were most commonly reported, including history of blood transfusions [54,71,146], dental work [51,71,147], surgery [54,71,146], medical injections [42,51,147] and being a HCW [87].

Injecting drug-use-related risk factors were also commonly reported, including history of injecting drug use [54,87,95,146,148], duration of injecting drug use [131], sharing of needles or syringes [54],
### Table 4. Pooled mean estimates for hepatitis C virus (HCV) prevalence for each of the six risk population categories in Pakistan.

| risk population                              | studies | samples | HCV prevalence | pooled HCV prevalence | heterogeneity measures |
|-----------------------------------------------|---------|---------|----------------|-----------------------|------------------------|
|                                               | total n | total N | range (%)      | median (%)            | mean (%) 95% CI        |
| general population (populations at low risk)   | 148     | 1352 080| 0.4–50.6       | 5.3                   | 6.2 5.7–6.7            |
| Q (p-value)<sup>a</sup>                       | 17 552 0 (<0.0001) | 99.2% (99.1–99.2%) | 17.5–13.0          |
| I² (confidence limits)<sup>b</sup>            | 99.2% (99.1–99.2%) | 1.7–13.0 |
| high-risk clinical populations                | 21      | 2377    | 7.8–68.0       | 33.3                   | 34.5 27.0–42.3        |
| Q (p-value)<sup>a</sup>                       | 294.3 (<0.0001) | 93.2% (90.9–94.9%) | 5.5–72.0               |
| I² (confidence limits)<sup>b</sup>            | 93.2% (90.9–94.9%) | 5.5–72.0 |
| populations at intermediate risk               | 64      | 156 623 | 0.0–70.9       | 12.9                   | 12.8 10.8–15.1        |
| Q (p-value)<sup>a</sup>                       | 8680.5 (<0.0001) | 99.3% (99.2–99.3%) | 1.2–33.7               |
| I² (confidence limits)<sup>b</sup>            | 99.3% (99.2–99.3%) | 1.2–33.7 |
| special clinical populations                  | 20      | 11 940  | 1.1–80.8       | 15.5                   | 16.9 6.2–31.3         |
| Q (p-value)<sup>a</sup>                       | 5666.9 (<0.0001) | 99.7% (99.6–99.7%) | 0.0–90.2               |
| I² (confidence limits)<sup>b</sup>            | 99.7% (99.6–99.7%) | 0.0–90.2 |
| populations with liver-related conditions      | 73      | 23 132  | 3.1–100.0      | 63.5                   | 55.9 49.2–62.5        |
| Q (p-value)<sup>a</sup>                       | 7028.9 (<0.0001) | 99.0% (98.9–99.1%) | 6.7–98.2               |
| I² (confidence limits)<sup>b</sup>            | 99.0% (98.9–99.1%) | 6.7–98.2 |
| PWID                                           | 15      | 2815    | 7.8–93.8       | 44.7                   | 53.6 36.2–70.6        |
| Q (p-value)<sup>a</sup>                       | 1181.9 (<0.0001) | 98.8% (98.6–99.0%) | 0.0–100                |
| I² (confidence limits)<sup>b</sup>            | 98.8% (98.6–99.0%) | 0.0–100 |

<sup>a</sup>: Q: the Cochran’s Q-statistic, a measure assessing the existence of heterogeneity in effect size.

<sup>b</sup>: I²: a measure assessing the magnitude of between-study variation that is due to differences in effect size across studies rather than chance.

<sup>c</sup>: Prediction interval: estimates the 95% interval in which the true effect size in a new HCV study will lie.
source of needles or syringes [135] and ‘jerking’ (drawing blood into a syringe while injecting) [131]. Sexual risk factors were also reported, including sex work (females and males), and sex for drugs [146].

3.7. Quality assessment of HCV incidence and prevalence measures

Findings of the quality assessment are summarized in the electronic supplementary material, table S5. Only one study was identified for HCV incidence [144] (not shown in the electronic supplementary material, table S5), in which there were greater than or equal to 100 participants, and was therefore classified as having high precision. As it was based on convenience sampling, it had high ROB for this domain. Meanwhile, it had low ROB in HCV ascertainment and in the response rate domains.

The majority of HCV prevalence studies (86.7%) was based on samples with greater than or equal to 100 participants, and were therefore classified as having high precision. Most studies (67.7%) reported specific details about HCV ascertainment, but nearly 70% did not report the assay generation. When information was provided, 94.2% of studies reported use of third or fourth generation assays.

A sensitivity analysis was performed to assess whether HCV prevalence in the general population differed prior to and after 2005, because the vast majority of studies after this year were likely to have been conducted using third or fourth generation assays. The confidence intervals of the estimated pooled mean HCV prevalence prior to and after 2010 overlapped, indicating HCV prevalence was not significantly different between these two time durations.

The majority of HCV prevalence studies (92.3%) used convenience, non-probability-based sampling approach. Nearly half of studies had low ROB in the response rate domain and 48.8% had missing information—only 1.6% of studies had high ROB in this domain.

To summarize, 78.6% of studies had low ROB based on at least one domain, and 41.1% had low ROB based on at least two domains. Furthermore, 1.2% of studies had high ROB based on two domains, and no study had high ROB based on three domains. The totality of the quality assessment measures indicates reasonable study quality.

4. Discussion

We presented a systematic review and synthesis of HCV incidence and prevalence in Pakistan. Our results affirm that Pakistan has one of the highest HCV infection levels in both MENA [11–17] and worldwide [149–151]. HCV prevalence in the population at large is at about 5%—one in every 20 Pakistanis has been already exposed to HCV infection. HCV prevalence was also found to be high in all risk populations, testifying to the scale of the epidemic in this country. Our results further supported a major role for HCV infection in liver disease burden in Pakistan—over half of the populations with liver-related conditions were found HCV antibody-positive.

Our results collectively indicate a major role for healthcare in HCV transmission. High HCV prevalence was observed in the populations exposed to healthcare in one form or another. In high-risk clinical populations, the pooled mean HCV prevalence was high at 34.5% (95% CI: 27.0–42.3%) (table 4), with HCV prevalence ranging across studies from 7.8 to 68.0% (table 2)—much higher than that found in the general population. In special clinical populations, the pooled mean HCV prevalence was also high at 16.9% (95% CI: 6.2–31.3%) (table 4), with HCV prevalence ranging across studies from 1.0 to 81.0% (electronic supplementary material, table S3). In all identified reports on hospitalized populations, HCV prevalence ranged from 2.5 to 71.0%, with a median of 13.2% (electronic supplementary material, table S2).

Our assessment of HCV risk factors further indicates that HCV transmission appears to be primarily driven by healthcare-related exposures, such as therapeutic injections, intravenous infusions and poor sterilization of medical equipment [42,51,54,71,87]. Injecting drug use and other community-based exposures appear also to play a role, but their relative (as opposed to absolute) role is probably small compared with healthcare procedures [152]. These findings demonstrate the urgency of addressing the HCV epidemic in Pakistan, one of the world’s largest, and where 10% of the global number of chronically infected people are living [6,21].

The apparent major role for healthcare in HCV transmission distinguishes Pakistan from most other countries. Though healthcare plays a role in both developing and developed countries [11–17,153–155], healthcare practices appear to have driven HCV prevalence to atypically high levels in this country, a pattern seen only in a limited number of countries globally, such as Egypt [13,22,23] and former Soviet republics [156]. This role for healthcare is not only manifested in the high HCV prevalence in the different clinical populations (table 4) and in the reported risk factors in analytical epidemiologic studies
A population-based survey was conducted in this country [10]. Despite the large epidemic, only one (now outdated) nationally representative and probability-based survey has been performed in Pakistan [18]. Pakistan has one of the highest rates of therapeutic injections worldwide [159,160]—with widespread perception that injectable medications are more expensive than oral medications [161–163]. Financial incentives appear also to sustain this preference for injectable medications, as healthcare providers can charge more for medications when they are administered by injections [163]. Though Pakistan has attempted to enhance provision and use of disposable injections and passed regulations for the management of disposable medical devices [164], implementation has been challenging in a country where the private sector accounts for 70% of healthcare services [157,162,165]. It bears notice that despite a possible key role for therapeutic injections, the totality of the evidence synthesized in the present study suggests that HCV healthcare exposures occur through multiple and diverse healthcare procedures.

The regional context of Pakistan and drug trafficking routes [166] support a conducive environment for injecting drug use. Our results indicated a high HCV prevalence among PWID (table 4), and evidence for injecting drug use as a mode of HCV exposure [54,87,131,157]. However, with an estimate of only 104,804 active PWID in Pakistan [167–169], the relative contribution of injecting drug use to HCV incidence is probably substantially smaller than that of healthcare, although the exact quantitative contribution remains uncertain.

Our results highlight the urgent and immediate need for expansion of HCV treatment and prevention programmes in Pakistan. High HCV prevalence was observed among all risk populations (table 4), with about one in every 20 Pakistanis being infected. Furthermore, three-quarters of all HCV antibody-positive individuals in Pakistan, per the meta-analysis of HCV viraemic rate (Section: Pooled mean HCV prevalence estimates), are chronically infected with HCV and can transmit the infection further. In spite of heavily discounted prices for DAAs in Pakistan [170], treatment scale-up has been limited, with only 311,000 chronic infections treated since 2013 [171]. To reach the WHO global target of reducing incidence by 80% by 2030, a recent modelling study indicated that the annual number of treatments must reach 490,000 and be sustained at this level for at least a decade [24]. To address the alarmingly high burden of HCV and achieve WHO global targets by 2030, Pakistan has recently developed the first National Hepatitis Strategic Framework, emphasizing the scale-up of interventions in healthcare settings and of HCV screening and treatment as well as harm reduction services [172].

Our study has identified key gaps and weaknesses in HCV epidemiological evidence in Pakistan. Despite the large epidemic, only one (now outdated) nationally representative and probability-based population-based survey was conducted in this country [10]. Repeating and enhancing this survey is critical to assess trends in prevalence and risk factors, as well as potential changes in the epidemiology. Such surveys have played an instrumental role in elucidating our knowledge of HCV transmission and in informing HCV response in other countries, such as in Egypt [173–179] and the USA [180].

Despite the major role for healthcare, a relatively small number of studies have been conducted among clinical populations, or investigated healthcare-related exposures. This is to be contrasted, for example, with Iran where a large number of studies investigated the role of healthcare—despite the relatively small role of this mode of exposure in this country [16]. Hardly any analytical cohort studies have been conducted in Pakistan despite the large epidemic, in contrast to Egypt [13,22], another MENA country with a large HCV epidemic [23]. Despite some suggestive evidence for community-based exposures [152], such as visiting roadside barbers [161], this mode of exposures remains to be clarified with concrete analytical studies. Though HCV vertical transmission appears to account for a quarter of HCV infections among children under 5 years of age in Pakistan [181], only one study appears to have investigated this mode of exposure in this country [32].

Our study is limited by the quantity and quality of reviewed studies, as well as their representativeness of the different risk populations—most studies used convenience sampling as opposed to probability-based population-based sampling. Only PubMed and Embase databases were searched, but other HCV data may exist in unpublished (grey literature) form, or are published in non-indexed journals. There was extensive heterogeneity in HCV prevalence measures in each risk population—possibly because of variability within the specific studied subpopulation, geographical location, sex and age-group representation in the sample, sampling technique and participant recruitment, year of study and study quality.
Despite these limitations, the main strength of our study is that we identified a large number of studies that covered different risk populations, and that facilitated a comprehensive synthesis of evidence and identification of gaps and weaknesses that preclude a satisfactory understanding of HCV epidemiology in Pakistan.

5. Conclusion

Pakistan is enduring an HCV epidemic of historical proportions—one in every 20 Pakistanis has been already infected with this infection playing a major role in liver disease burden in this country. HCV prevalence is high in all risk populations with most transmission apparently driven by healthcare procedures. Though our knowledge of the specific modes of exposure that drive transmission is improving, our understanding is still hampered by key gaps and weaknesses in available evidence. Conduct of repeated and comprehensive nationally representative and probability-based population-based surveys is critical to assess HCV prevalence and trends, identify risk factors and modes of exposure, examine the spatial variability in prevalence, and assess HCV knowledge and attitudes.

HCV treatment and prevention must become a national priority in Pakistan. Although Pakistan has made efforts to increase coverage of safe injection and blood screening and to improve injection control [164,182–184], commitment to prevention in all segments of the healthcare system, including the private sector, should be secured for this country to accomplish the HCV elimination target by 2030. Major expansion of infection control in healthcare facilities, and of harm reduction services for PWID, are warranted, as well as adoption of the WHO guidelines for the use of safety-engineered syringes [185,186].

Data accessibility. The datasets supporting this article have been uploaded as part of the manuscript and electronic supplementary material.

Competing interests. The authors have no competing interests to declare.

Authors’ contributions. Z.A.K. conducted the systematic review of the literature, data retrieval, extraction, analyses and wrote the first draft of the article. S.M. conducted analyses and drafting of the article. S.P.K. contributed to the systematic review of the literature, data retrieval and extraction. L.J.A. conceived and led the design of the study, analyses and drafting of the article. All authors have read and approved the final manuscript.

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References

1. Stanaway JD et al. 2016 The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet 388, 1081–1088. (doi:10.1016/S0140-6736(13)60579-7)

2. Chen SL, Morgan TR. 2006 The natural history of hepatitis C virus (HCV) infection. Int. J. Med. Sci. 3, 47. (doi:10.7150/ijms.3.47)

3. Rosen HR, Martin P. 2000 Viral hepatitis in the liver transplant recipient. Infect. Dis. Clin. 14, 761–784.

4. Lauer GM, Walker BD. 2001 Hepatitis C virus infection. N. Engl. J. Med. 345, 41–52. (doi:10.1056/NEJM200107123450301)

5. Bouvard V et al. 2009 A review of human carcinogens—part B: biological agents. World Health Organization (WHO), Amsterdam, The Netherlands: Elsevier.

6. World Health Organization (WHO). 2017 Global hepatitis report. See http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/.

7. Wedemeyer H, Dore G, Ward J. 2015 Estimates on HCV disease burden worldwide—filling the gaps. J. Viral. Hepat. 22, 1–5. (doi:10.1111/jh.12371)

8. World Health Organization (WHO). Combating hepatitis B and C to reach elimination by 2030: advocacy brief. 2016. (http://apps.who.int/iris/handle/10665/206453)

9. World Health Organization (WHO). Global health sector strategy on viral hepatitis 2016–2021. 2016. (http://www.who.int/hepatitis/strategy2016-2021/ghs-hep/en/)

10. Qureshi H, Bile KM, Jooma R, Alam SE, Afzal HUR. 2010 Prevalence of hepatitis B and C viral infections in Pakistan: findings of a national survey appealing for effective prevention and control measures. East Mediterr. Health J. 16, 515–523.

11. Mohamoud YA, Riome S, Abu-Raddad LJ. 2016 Epidemiology of hepatitis C virus in the Arabian Gulf countries: systematic review and meta-analysis of prevalence. Int. J. Infect. Dis. 46, 116–125. (doi:10.1016/j.ijid.2016.03.012)

12. Chemaitelly H, Chaabna K, Abu-Raddad LJ. 2015 The epidemiology of hepatitis C virus in the fertile crescent: systematic review and meta-analysis. PLoS ONE 10, e0135281. (doi:10.1371/journal.pone.0135281)

13. Mohamoud YA, Mumtaz GR, Riome S, Miller D, Abu-Raddad LJ. 2013 The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. BMC Infect. Dis. 13, 288. (doi:10.1186/1471-2334-13-288)

14. Fadlalla FA, Mohamoud YA, Mumtaz GR, Abu-Raddad LJ. 2015 The epidemiology of hepatitis C virus in the Maghreb region: systematic review and meta-analyses. PLoS ONE 10, e0121873. (doi:10.1371/journal.pone.0121873)

15. Chemaitelly H, Mahmoud S, Rahman AM, Abu-Raddad LJ. 2015 The epidemiology of hepatitis C virus in Afghanistan: systematic review and meta-analysis. Int. J. Infect. Dis. 40, 54–63. (doi:10.1016/j.ijid.2015.09.011)

16. Mahmoud S, Akbarzadeh V, Abu-Raddad LJ. 2018 The epidemiology of hepatitis C virus in Iran: systematic review and meta-analyses. Sci. Rep. 8, 150. (doi:10.1038/s41598-017-18296-9)

17. Chaabna K, Kouroumian SP, Abu-Raddad LJ. 2016 Hepatitis C virus epidemiology in Djibouti, Somalia, Sudan, and Yemen: systematic review and meta-analysis. PLoS ONE 11, e0149966. (doi:10.1371/journal.pone.0149966)

18. Mahmoud S, Al-Kanaani Z, Chemaitelly H, Chaabna K, Kouroumian SP, Abu-Raddad LJ. 2018 Hepatitis C virus genotypes in the Middle East and North Africa. rsos.royalsocietypublishing.org
Parker SP, Khan HI, Cubrit WD. 1999 Detection of antibodies to hepatitis C virus in dried blood spot samples from mothers and their offspring in Lahore, Pakistan. J. Clin. Microbiol. 37, 2061–2063.

60. Sultán F, Mehmoood T, Mahmood MT. 2007 Infectious pathogens in volunteer and replacement blood donors in Pakistan: a ten-year experience. Int. J. Transf. Dis. 11, 407–412. (doi:10.1016/j.iijtd.2006.10.004)

58. Abbaz Z, Jafri WA, Kakepoto GN, Islam M, Mehdi K, Jafri W. 2008 Prevalence and mode of spread of hepatitis B and C in rural Sindh, Pakistan. Trop. Gastroenterol. 29, 210–216.

57. Butt T, Amin MS. 2008 Seroprevalence of hepatitis B and C infections among young adult males in Pakistan. East Mediterr. Health J. 14, 791–797.

56. Hameed S, Kazmi S, Bagaro O. 2008 Seroprevalence of hepatitis B and C genotypes among young apparently healthy females of Karachi-Pakistan. Libyan J. Med. 3, 66–70. (doi:10.3402/ljm.v3i2.4360)

55. Idrees M, Lal A, Naseem M, Khalid M. 2008 High prevalence of hepatitis C virus infection in the largest province of Pakistan. J. Dig. Dis. 9, 95–103. (doi:10.3112/jdd.20080628.00329x)

54. Khattak MN, Akhtar S, Mahmod S, Roshan TM. 2008 Factors influencing hepatitis C virus sero-prevalence among blood donors in north west Pakistan. J. Public Health Policy 29, 207–225. (doi:10.1057/pjhp.2008.7)

53. Jafri WA, Pearce MS. 2008 Temporal trends in hepatitis B and C in family blood donors from interior Sindh, Pakistan. BMC Infect. Dis. 8, 43. (doi:10.1186/1471-2334-8-43)

52. Abbaz Z, Ali M, Muhammad AH, Shaw S, Abbas SO. 2009 Frequency of hepatitis B virus infection and its genotypes among patients attending a liver clinic and voluntary blood donors in a rural area of Pakistan. Pak. J. Med. Sci. 25, 579–582.

51. Ali M, Kanwal K, Tassadique K, Iqbal R. 2009 Prevalence of hepatitis C virus (HCV) in relation to its promotive factors among human urban population of Multan, Pakistan. Eur. J. Gen. Med. 6, 41–45. (doi:10.20931/egm.01647)

50. Bangash MH, Bangash TH, Alam S. 2009 Prevalence of hepatitis B and hepatitis C among healthy blood donors at Kurnam Agency. J. Postgrad. Med. 23, 140–145.

49. Bangash MH, Bangash TH, Ali J. 2009 Frequency of hepatitis B and C in healthy subjects in parachinar. J. Postgrad. Med. 23, 347–351.

48. Bal N, Sarwar I, Idris M, Farrar J, Razvi F, Suleman M, Shah SH. 2009 Seroprevalence of hepatitis C in pregnant females of hazara division. J. Ayub Med. Coll. Abbottabad 21, 83–86.

47. Jalbani A, Ansari IA, Shah AH, MajGulRakshashani K, Chutto M, Jalbani MA. 2009 Prevalence of hepatitis C-virus infection in Kairpurnannah Shah and Shahdadot a city based screening program. Med. Forum Mon. 20, 15–17.

46. Junojo SA, Khan NA, Lodhi AA. 2009 Prevalence of hepatitis B and C infection in patients attending at tertiary eye care centre: a hospital based study. Pak. J. Med. Sci. 25, 397–400.

45. Mukhtar Hussain Sani E. 2009 Prevalence of blood screening markers in blood donor population of Pakistan at Hazarai Haematology and Oncology Trust. Khi. Pak. Vox Sang. 97, 148.

44. Sami K, Korejo R, Bhutta SZ. 2009 Prevalence of hepatitis B and C in a Jimnagh postgraduate medical centre experience. J. Obstet. Gynaecol. Res. 35, 533–538. (doi:10.1017/S095026880600991X)
80. Borhany M, Ali Abim H, Ali Chuhutto M, Abbasi PK, Shaikh AI, Ali Burro S. 2009 Hepatitis C: frequency and risk factors associated with sero-reactivity among adults in Larkana City. J. Ayub Med. Coll. Abbottabad 21, 107–109.
81. Iqbal A, Akram M, Ali H, Akhtar N, Nazir SUR, Ahmad I, Awan A, Asif HM. 2011 Prevalence of hepatitis C virus (HCV) in gadap town Karachi, Pakistan. J. Med. Plant. Res. 5, 602–604.
82. Khan NU et al. 2011 Prevalence of active HCV infection among the blood donors of Khyber Pakhtunkhwa and FATA region of Pakistan and evaluation of the screening tests for anti-HCV. Viral. J. 8, 154. (doi:10.4274/vj.2011.407-415)
83. Rauf A, Nadeem MS, Ali A, Iqbal M, Mustafa M, Latif MM, Ahmed NZ, Shaiq AR. 2011 Prevalence of Hepatitis B and C in internally displaced persons of war against terrorism in Swat, Pakistan. Eur. J. Public Health 21, 638–642. (doi:10.1093/eurpub/dqp894)
84. Sahz S, Afzal MS, Wahab Y, Butt U, Fatima K, Parvez Y, Qadir I. 2011 Seroprevalence of hepatitis C and human immunodeficiency viruses in blood donors of northwestern Pakistan. Asian Biomed. 5, 389–392.
85. Saleem M, Ahmad W, Sarwar J, Jamshed F, Gul N, Iqrae M. 2011 Frequency of hepatitis C in asymptomatic patients in district headquarters hospital Kotli, Azad Kashmir. J. Ayub Med. Coll. Abbottabad 23, 59–63.
86. Yousaf NZ, Iqrae M, Saleem Z, Rehman IU, Ali M. 2011 Expression of core antigen of HCV genotype 3a and its evaluation as screening agent for HCV infection in Pakistan. J. Viral. 8, 364. (doi:10.4274/vj.2011.407-364)
87. Ahmed F, Irving WL, Ammar M, Myles P, Neal KR. 2012 Prevalence and risk factors for hepatitis C virus infection in Kech District, Balochistan, Pakistan: most infections remain unexplained. A cross-sectional study. Epidemiol. Infect. 140, 716–722. (doi:10.1017/S0950268811001807)
88. Ansari SH, Shamis TS, Khan MT, Perveen K, Farzana T, Eum S, Ansari S. 2012 Seropositivity of hepatitis C, hepatitis B and HIV in chronically transfused beta-thalassaemia major patients. J. Coll. Physicians Surg. Pak. 22, 609–611.
89. Attaula S, Khan S, Khan J. 2012 Trend of transfusion transmitted infections frequency in blood donors: provide a road map for its prevention and control. J. Transl. Med. 10, 20. (doi:10.1186/1479-5876-10-20)
90. Bhutta AZ, Tahir Z, Ayub S, Mushqat S. 2012 Seroprevalence of anti-HCV in non-professional blood donors. Pak. J. Med. Health Sci. 6, 175–178.
91. Hafeez u d, Siddiqui TS, Lahrasib W, Sharif MA. 2012 Prevalence of hepatitis B and C in healthy adult males of paramilitary personnel in Karachi. J. Ayub Med. Coll. Abbottabad 24, 138–140.
92. Riaz R, Bhatti S, Ullah S. 2012 Prevalence of hepatitis B and C in healthy blood donors in a peripheral hospital: Ghurki trust hospital, Lahore. Pak. J. Med. Health Sci. 6, 368–369.
93. Khan MI, Muhammad M. 2012 Frequency of hepatitis B and C in patients visiting outpatient department of district head quarters hospital Lakho. J. Postgrad. Med. Inst. 26, 55–60.
94. Khan S. 2012 Improving the safety of blood products through stringent donor selection, pre and post donation screening of blood. Vox Sang. 103, 98–99.
95. Memon AR, Shaikhe F, Memon A, Draz AU, Rauf MUA, Afrat S. 2012 Hepatitis B and C prevalence among the high risk groups of Pakistan population. A cross sectional study. Arch. Public Health 70, 9. (doi:10.7758/7136-70-9)
96. Muhammad SK, Chandio MA, Soomro MA, Shaikh BA. 2012 Hepatitis C virus infection in non-Hodgkin’s lymphoma: a case-control study. Hepatit. Mon. 12, 16–22. (doi:10.1155/2012/91258)
97. Niaz W, Chaudhry A, Nazar W, Mirza A, Ali R, Riaz M, Yousaf S. 2012 Risk factors for development of chronic hepatitis in the developing world: risk factors and attitudes. Am. J. Gastroenterol. 107, S167. (doi:10.1038/ajg.2011.410)
98. Waheed U, Zahirer HA, Astori S. 2012 Transfusion transmitted infections among blood donors of a teaching hospital in Islamabad, Pakistan. Vox Sang. 103, 157.
99. Abbasi F, Mengal MA, Hamil M, Ali M, Pirzai GS. 2013 Seroprevalence of hepatitis C virus in general population of Balochistan, Pakistan. Pak. J. Med. Health Sci. 7, 190–194.
100. Butt KN, Shafig F, Yousaf MA. 2013 Prevalence of HIV, Anti-HCV, HBsAg and VDRL positive cases in blood donors of bhatti international Trust Hospital, Karaur. Pak. J. Med. Health Sci. 7, 662–663.
101. Irfan SM, Uddin J, Zahirer HA, Sultan S, Baig A. 2013 Trends in transfusion transmitted infections among replacement blood donors in Karachi, Pakistan. Turk. J. Hematol. 30, 163–167. (doi:10.4274/tjh.2012.0132)
102. Khan A, Tareen AM, Iqram A, Rahman H, Wadood A, Qasim M, Khan K. 2013 Prevalence of HCV among the young male blood donors of Quetta region of Balochistan, Pakistan. Viral. J. 10, 83. (doi:10.4274/vj.2011.407-83)
103. Khan FS et al. 2013 The burden of non-communable disease in transfusion community in an Asian megacity: baseline findings from a cohort study in karachi, Pakistan. PLoS ONE 8, e56008. (doi:10.1371/journal. pone.0056008)
104. Qadeer MI, Hasnain S, Yaseen HM. 2013 Sero-prevalence of sexually transmitted disease (HIV, syphilis, hepatitis-b and hepatitis-c) in volunteer donors of gaul inmates and student community in Punjab province of pakistan. Sex. Transm. Infect. Conf. STI AIDS World Congr. 89, A264.1–A264.2. (doi:10.1186/externalevent-2013-05184-0820)
105. Rauf M, Saleem MD, Anwer MO, Ahmed G, Aziz S, Memon MA. 2013 HIV, hepatitis B and hepatitis C in garbage scavengers of karachi. J. Pak. Med. Assoc. 63, 798–802.
106. Seema B. 2013 Seropositivity and risk factors for hepatitis C virus (HCV) infection in pregnant women attending public sector tertiary care hospital in Hyderabad sindh. Int. J. Obstet. Gynaecol. 120, 172.
107. Zaffar G, Ali R, Ayub M, Ahmed A, Ali A et al. 2013 Frequency and trends of infectious pathogen in blood donors at a tertiary care hospital in Pakistan. Hepatit. Int. 7, S346.
108. Ali S et al. 2014 Genotyping of HCV RNA reveals that 3a is the most prevalent genotype in Mandarin, Pakistan. Adv. Viril. 2014, 1–5. (doi:10.1155/2014/065201)
109. Ilyas M, Ahmad I. 2014 Chemiluminescent microparticle immunoassay based detection and prevalence of HCV infection in district Peshawar
Daud MY, Qazi RA, Bashir N. 2014. Anti-retroviral drug abuse. J. Ayub Med. Coll. Abbottabad 26, 437–440.

Dasti JJ, Uddin SG, Malik MS. 2014. Prevalence of HCV infection among thalassemia patients: a perspective from a multi-ethnic population of Islamabad region. FEBs J. 281, 154.

Mahmud HM, Siddiqui M, Bashir B, Ali SF, Baloch AA, Masroor M. 2014. Hemodialysis patients profile at Dow University of Health Sciences, Karachi, Pakistan. Pak. J. Med. Sci. 30, 1237–1239. (doi:10.12669/pjms.30.5364)

Chishti SM, Khan AM, Bazir F. 2015. Serological monitoring of HCV marker in hemodialysis patients from tertiary care hospitals of Karachi. Med. Forum. 26, 6–11.

Khan MS, Ahmed M, Khan RA, Mustaqui N, Shah MWU. 2015 Consanguinity ratio in β-thalassemia major patients in District Bannu. J. Pak. Med. Assoc. 65, 1161–1163.

Yasmeen H, Hasnain S. 2015. Prevalence of transfusion transmitted infections in individuals with thalassemia in Pakistani population. Haematologica 100, 794–775.

Koo I, ul-Hasan S, Galal N, Thomas DL, Zafar T, Ahmed MA, Strathdee SA. 2006. High HCV seroprevalence and HIV drug use risk behaviors among injection drug users in Pakistan. Harm Reduct. J. 3, 26. (doi:10.1186/1747-7577-3-26)

Ashakzai M, Kassi M, Kasi PM. 2007. Seroprevalence and co-infections of HIV, hepatitis C virus and hepatitis B virus in injecting drug users in Quetta, Pakistan. Trop. Doct. 37, 43–45. (doi:10.1258/0049475077795198)

Alaf A, Shah SA, Zaidi NA, Memoon A, Nadeem ur R, Wray N. 2007. High risk behaviors of injection drug users registered with harm reduction programme in Karachi, Pakistan. Harm Reduct. J. 4, 7. (doi:10.1186/1747-7577-4-7)

Abbasi S, Faqir F, Khan S, Zaidi SK, Ahmed SQ, Sattar A, Satti M. 2009. A serological study of hepatitis C and human immunodeficiency virus in a cohort of intravenous drug users in Quetta, Balochistan, Pakistan. J. Postgrad. Med. Inst. 23, 3–6.

Platt L, Vickerman P, Collumbien M, Hasan S, Lalji N, Mayhew S, Muzaffar R. 2009. Prevalence of HIV, HCV and sexually transmitted infections among injecting drug users in Rawalpindi and Abbottabad, Pakistan: evidence for an emerging injection-related HIV epidemic. Sex. Transm. Infect. 85, 817–822. (doi:10.1136/sti.2008.034900)

Rehan N, Bokhari A, Nazimani NM, Jackson D, Naqi HR, Qayyum K, Mansoor S, Muzaffar R. 2009. National study of reproductive tract infections among high risk groups of Lahore and Karachi. J. Coll. Physicians Surg. Pak. 19, 228–231.

Ur Rehanman L et al. 2011. Active hepatitis C infection and HCV genotypes prevalent among the IDUs of Khyber Pakhtunkhwa. Vide. J. 8, 327. (doi:10.1786/j.1473-4228.2011.0048)

Al Cassimi FM, Mumtaz A, Ansari GM. 2010. A sero-prevalence study of viral hepatitis B, C and HIV in multi-transfused thalassemia major patients in Institute of Blood Transfusion, Karachi, Pakistan. J. Pak. Med. Assoc. 60, 327–330.

Prasad PV, Tripathi SK, Deka D, Deka S, Alloond L, Tilak AV, Madhukar S. 2011. A cross-sectional study of seroprevalence of hepatitis C virus infection in thalassemia patients in district Barpeta, Assam state, India. Trop. Doct. 41, 29–32. (doi:10.1186/1746-6185-41-29)

Sriram M, Rital MV, Subash Rao BV, Prasad PV, Padmanabhan PM, Nair P, Joglekar M. 2010. Prevalence of HCV infection among thalassemia major patients in district Bannu, Pakistan. J. Ayub Med. Coll. Abbottabad 22, 4–7.

Sriram M, Prasad PV, Nair P, Joglekar M. 2010. Prevalence of hepatitis C and HCV genotypes among thalassemia major patients in district Barpeta, Assam state, India. Trop. Doct. 41, 29–32. (doi:10.1186/1746-6185-41-29)

Sriram M, Prasad PV, Nair P, Joglekar M. 2010. Prevalence of hepatitis C and HCV genotypes among thalassemia major patients in district Barpeta, Assam state, India. Trop. Doct. 40, 21–23. (doi:10.1186/1746-6185-40-19)

Sriram M, Prasad PV, Nair P, Joglekar M. 2010. Prevalence of hepatitis C and HCV genotypes among thalassemia major patients in district Barpeta, Assam state, India. Trop. Doct. 40, 21–23. (doi:10.1186/1746-6185-40-19)

Sriram M, Prasad PV, Nair P, Joglekar M. 2010. Prevalence of hepatitis C and HCV genotypes among thalassemia major patients in district Barpeta, Assam state, India. Trop. Doct. 40, 21–23. (doi:10.1186/1746-6185-40-19)
virus in Central Asia: Systematic review and meta-analyses.

157. Centers for Disease Control Prevention (CDC). 2011 Establishment of a viral hepatitis surveillance system—Pakistan, 2009–2011. Morb. Mortal. Wkly. Rep. 60, 1385–1390. 1545-861X/1545-8619.

158. Ashraf A, Ashfaq UA. 2017 Epidemiology of hepatitis C infection in Pakistan: current estimate and major risk factors. Crit. Rev. Eukaryot. Gene Expr. 27, 63–77. (doi:10.1615/CritRevEukaryotGeneExpr.2017018953)

159. Simonsen L, Kane A, Lloyd J, Zaffran M, Kane M. 1999 Unsafe injections in the developing world and transmission of bloodborne pathogens: a review. Bull. World Health Organ. 77, 769–800.

160. Qureshi H. 2015 Pakistan: prevention & control of viral hepatitis. PMRC.

161. Centers for Disease Control. 2011 Prevention establishment of a viral hepatitis surveillance system—Pakistan, 2009–2011. Morb. Mortal. Wkly. Rep. 60, 1385.

162. Ahmad K. 2004 Pakistan: an cirrhotic state? Lancet 364, 1843–1844. (doi:10.1016/S0140-6736(04)17468-8)

163. Janjua NZ, Hussain YJ, Akhtar S, Ahmad K. 2006 Population beliefs about the efficacy of injections in Pakistan’s Sindh province. Public Health 120, 824–833. (doi:10.1016/j.puhe.2006.05.004)

164. Government of Pakistan, Ministry of Environment. 2005 Hospital waste management rules.

165. Ejaz I, Shaikh BT, Rizvi N. 2011 NGOs and government partnership for health systems strengthening: a qualitative study presenting viewpoints of government, NGOs and donors in Pakistan. BMC Health Serv. Res. 11, 122. (doi:10.1186/1472-6963-11-122)

166. United Nations Office on Drugs and Crime (UNODC). 2017 World Drug Report 2017. (https://www.unodc.org/wdr2017/index.html)

167. Mumtaz GR, Awad SF, Feizzadeh A, Weiss HA, Abu-Raddad LJ. 2017 HIV incidence among people who inject drugs in the Middle East and North Africa: mathematical modeling analysis. J. Int. AIDS Soc. 21, e25102. (doi:10.1002/1751-3198.e25102)

168. Mumtaz GR et al. 2014 HIV among people who inject drugs in the Middle East and North Africa: systematic review and data synthesis. PLoS Med. 11, e1000163. (doi:10.1371/journal.pmed.1001663)

169. Pakistan Global AIDS Response Progress Report (GARPR) 2015 National AIDS Control Program. Ministry of National Health Services, Regulation and Coordination. See http://www.aidsdatahub.org/pakistan-globals-aid-response-progress-report-2015-national-aids-control-program-2015.

170. The News International. 2016 Price of hepatitis C drug fixed at Rs 5,868. See https://www.thenews.com.pk/print/97674-Price-of-Hepatitis-C-drug-fixed-at-Rs5868.

171. Polaris Observatory. See http://cdafound.org/polans-hepc-dashboard/ (accessed 2017).

172. Ministry of National Health Services, Regulations and Coordination (NHSRC). 2017 National Hepatitis and Transfusion System—Pakistan, 2009–2011. Establishing of a Viral Hepatitis Surveillance System in Pakistan, 2009–2011. Ministry of National Health Services, Regulation and Coordination, Islamabad (NHSRC). 2017 National Hepatitis and Transfusion System—Pakistan, 2009–2011. Establishing of a Viral Hepatitis Surveillance System in Pakistan, 2009–2011. Medicine. 11, 834–842. (doi:10.1002/hep.27596)

173. Guerra J, Garenne M, Mohamed M, Fontanet A. 2012 HCV burden of infection in Egypt: results from a nationwide survey. J. Viral Hepat. 19, 560–567. (doi:10.1111/j.1365-2893.2011.01576.x)

174. Ahmad K. 2004 Pakistan: an cirrhotic state? Lancet 364, 1843–1844. (doi:10.1016/S0140-6736(04)17468-8)

175. Miller FD, Abu-Raddad LJ. 2010 Evidence of vertical transmission of hepatitis C virus in Pakistan in 2007 and 2012 birth cohorts. J. Viral Hepat. 17, 1177–1183. (doi:10.1111/j.1365-2893.2010.01274.x)

176. Zaheer HA, Waheed U. 2014 Blood safety system reforms in Pakistan. Blood Transfus. 12, 452.

177. Zafer A, Habib F, Hadwani R, Ejaz M, Khwaja K, Khwaja R, Irfan S. 2009 Impact of infection control activities on the rate of needle stick injuries at a tertiary care hospital of Pakistan over a period of six years: an observational study. BMC Infect. Dis. 9, 78. (doi:10.1186/1471-2334-9-78)

178. Ikram A, Shah SH, Naseem S, Aabas SF, Ullah S, Ambreen T, Sabeeh SM, Niazi SK. 2010 Status of hospital infection control measures at seven major tertiary care hospitals of northern Punjab. J. Coll. Physic. Physicians Surg. Pak. 20, 266–270.

179. World Health Organization. 2015 Making all injections safe. Ginebra, OMS.

180. World Health Organization. 2015 WHO guideline on the use of safety-engineered syringes for intramuscular, intradermal and subcutaneous injections in health-care settings. WHO/HIS/SDS/2015.5.