Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.15827

SYSTEMATIC REVIEW

Seroprevalence and burden of hepatitis C virus infection in WHO South-East Asia Region: A systematic review

Amit Goel,* Bharat Bhushan Rewari,† Mukta Sharma,† Nabeel Mangadan Konath† and Rakesh Aggarwal‡

*Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, †World Health Organization, Regional Office for South-East Asia, New Delhi, ‡Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India

Key words
Hemodialysis, Hepatitis C virus, hepatocellular carcinoma, high risk behavior, disease burden, people living with HIV, people who inject drugs, prison inmates, South East Asia region, transfusion transmitted infections.

Accepted for publication 27 February 2022.

Correspondence
Dr Rakesh Aggarwal, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India.
Email: aggarwal.ra@gmail.com

Declaration of conflict of interest: Dr Rakesh Aggarwal is an Editorial Board member of JGH and a co-author of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication.
Author contribution: AG did the study research and selection, data extraction, analysis, and first draft. BBR did the concept, study research and selection, analysis, and critical editing. MS carried out the concept, analysis, and critical editing. NMK did the study research and selection, data extraction, and first draft. RA carried out the concept, study research and selection, analysis, and critical editing. All the authors had full access to all the data in the study and approves the final version of the manuscript.
Ethical approval: Not applicable.
Financial support: This work was supported by a financial grant from WHO South-East Asia Region (SEAR) Office, New Delhi, India (Ref No 202539149).
Guarantor of the article: Dr Rakesh Aggarwal and Dr Amit Goel.

Abstract

Background: This systematic review was aimed to estimate hepatitis C virus (HCV) seroprevalence and burden in disease in WHO South East Asia Region (SEAR).
Methods: Electronic databases (PubMed, Scopus, Embase, and Google Scholar) and websites of non-indexed national medical journals, government and international health agencies were searched to identify English language literature published between 1991 and June 2020. We selected the studies reporting HCV seroprevalence in asymptomatic general (low-risk) and high-risk adult populations, that is, persons living with HIV (PLHIV), persons who inject drugs (PWID), sex workers, persons on maintenance hemodialysis (MHD), people in prison, and men sex with men (MSM). Seroprevalence data were combined to estimate weighted pooled prevalence (95% confidence interval) in each group and in each country, using the random-effects model. Estimated pooled seroprevalences were multiplied with estimated populations at risk to estimate the overall HCV burden.
Results: The analysis included 538 studies (35 Bangladesh, 6 Bhutan, 2 DPR Korea, 323 India, 43 Indonesia, 2 Maldives, 18 Myanmar, 29 Nepal, 11 Sri Lanka, 67 Thailand, and 2 Timor-Leste). In SEAR, the weighted pooled anti-HCV seroprevalence was estimated as 0.84% (0.56–1.12) in low-risk population and 13.67% (10.95–16.40) in PLHIV, 51.44% (43.67–59.20) in PWID, 25.80% (20.34–32.09) in MHD, 8.39% (5.84–11.51) in prison inmates, 2.69% (1.43–4.13) in people with high-risk sex behavior, and 11.43% (8.61–14.74) in MSM. The total HCV burden in low-risk and high-risk populations in SEAR countries was estimated as 12.45 million and 1.65 million, respectively.
Conclusion: Our estimates of HCV seroprevalence and burden should help the respective countries in planning their HCV elimination strategies.

Introduction

According to Global Health Estimates (GHE) 2020, globally approximately 1.9 million people died of cirrhosis and liver cancers in the year 2019. Infection with hepatitis C virus (HCV), a common cause for these conditions, contributed about 521 000 of these deaths. Of these HCV-related deaths, approximately 129 000 occured in 11 countries included in the World Health Organization's (WHO) South-East Asia Region (SEAR).[1]

In recent years, several direct-acting antivirals agents (DAAs) against HCV have been developed.[2] The very high efficacy rates of DAA-based treatment regimens in clearing HCV infection,[3] their widespread availability at affordable prices, their oral route of administration, and an excellent safety record with need for minimal attention during treatment have led to a paradigm shift in the treatment of this infection.[4] Further, the success of DAA-based treatment has paved the way for the adoption by the WHO of a goal for elimination of HCV infection as a public health threat by the year 2030. Mathematical modeling has shown that this can be carried out if the following defined targets can be met: a 65% reduction in hepatitis-related deaths, a 90% reduction of new infections with HCV, 90% of those with HCV infection being diagnosed, and 80% of those diagnosed being treated.[5]

As of November 2017, 84 countries around the world have launched national programs for HCV treatment and a few of them are on the way to eliminate hepatitis C by 2030.[6] However, in WHO SEAR, despite most of the member states having access to generic versions of highly-potent DAAs at affordable prices, the progress in treatment of HCV has been slow. A major reason for this is the lack of adequate resources for HCV treatment. However, the problem is aggravated by a lack of data on the prevalence of and the disease burden associated with HCV infection, leading to weak advocacy for hepatitis elimination programs. It has been previously estimated that nearly 10 million of the 71 million HCV-viremic people live in SEAR countries.[7] However, estimates for individual countries in the region are lacking. Availability of reasonably-accurate estimates of country-specific data on burden of HCV infection would help convince the policy makers in these countries to allocate resources for HCV treatment and for the program managers to plan public-funded programs for this purpose.

We therefore decided to undertake independent systematic reviews for 11 member countries in WHO SEAR to estimate HCV seroprevalence in general population and in various high-risk subpopulations. Using these estimates, we further estimated the number of HCV-infected persons in each country.

Methods

Literature search. We searched several electronic medical literature databases (PubMed, Scopus, Embase, and Google Scholar) for English language articles published between 1991 and June 2020 from each of the 11 SEAR countries. In addition, for each country, we also searched non-indexed national medical journals, government websites for data from blood banks, HIV programs and national health statistics, websites of international agencies such as the WHO, WHO-SEAR, WHO country offices, Polaris Observatory; and Global Burden of Disease estimates 2017. The search strategies included various alternative terms used for HCV, the name of the country, and the major states/cities of the country.

Study selection. We included full-text articles published in English language, irrespective of article type, which reported original data on HCV seroprevalence in one or more of the asymptomatic adult population groups. The included population groups were categorized as either low-risk or high-risk. The high-risk population groups were selected as per WHO guidelines for HCV screening, which recommend HCV screening for people at higher risk of acquiring HCV.[8]

The different group of populations, as described in data sources, included in either low-risk or high-risk category are summarized in Data S1. Data from community prevalence studies, blood donors, pregnant women, health survey, or other representative population of the community were grouped as low-risk category. The data from people living with HIV (PLHIV), patients on maintenance hemodialysis (MHD), people who inject drugs (PWID), people with high-risk sexual behaviors, men who have sex with men (MSM), and people in prison were grouped in high-risk category. Studies on patients with liver disease or another disease (e.g. lichen planus, cryoglobulinemia, cholangiocarcinoma, retinopathy, etc.) were excluded to avoid bias. Studies carried out on health care workers (HCWs), transgenders, non-native or refugee population, children (<18 years), transfusion-dependent persons (such as those with thalassemia, hemophilia, etc.) were excluded.

Studies were included if they reported data on prevalence using one of the following tests: anti-HCV antibodies, HCV RNA, or HCV core antigen (HCVcAg). Studies that included short-term migrants or heterogenous groups or those in which the source population was unclear were excluded, whereas data from long-term migrant populations settled in another country were included. Reports in which data were available only as an abstract were also excluded.

For the identified records, titles and abstracts were screened to exclude duplicates and the studies that did not meet the above selection criteria. Thereafter, for the remaining studies, full-text papers were reviewed to determine eligibility for inclusion in the review. Following this preliminary screening, full-texts of each of the screened records were reviewed.

Additional data sources. The results of the aforementioned searches were supplemented through manual searches of cross-references in the identified documents and through personal communication with key medical professionals, researchers, program managers, and other stakeholders in the field in the respective country to identify additional data sources.

Data extraction. From each eligible record, the following data were extracted independently by two authors (A. G. and B. B. R.), and the discrepancies were resolved after discussion with third author (R. A.): the first author's name, year of publication, population group(s) studied, number of study participants, and number of participants who tested positive for HCV infection. Any discrepancies were resolved by mutual discussion. If a record contained data on more than one groups, the relevant data were extracted separately for each group. In studies where the specimens

had also been tested for infection with another marker (e.g. a serological marker for hepatitis B virus or HIV infection), the data were extracted irrespective of the result for the other marker. Besides the general (low-risk) population, data were separately extracted for the following high-risk subpopulations: PLHIV, PWID, people on MHD, MSM, high-risk sex behavior, and people in prison.

For general (low-risk) population, wherever available, data from community-based large studies were preferred for the estimation of pooled prevalence. Where high-quality data from community-based studies were not available, data from blood donors were used.

Data analysis for seroprevalence. For each country and population group studied, weighted pooled estimates were calculated from the available data, wherever adequate studies were available. In brief, the data on proportion of those seropositive and 95% confidence intervals (CI) from individual studies were combined to obtain a pooled proportion and its 95% CI. Heterogeneity in data was assessed using the I^2 method. Irrespective of the degree of heterogeneity, the random-effects model was used for pooling the data. All analyses were performed using STATA software, version 12 (StataCorp LLC, College Station, TX, USA).

Disease burden estimation. For each country, the estimated pooled seroprevalence in each population group/subgroup was multiplied with the estimated size of the corresponding subpopulation. In brief, first, the low-risk population at risk was calculated by subtracting the aggregate of estimated high-risk populations groups (MHD, PLHIV, PWID, sex workers, people in prison, and MSM groups) for which separate HCV seroprevalence data were available for the country from the total adult (age ≥15 years) population, and this was multiplied by the pooled seroprevalence for this group to obtain the number of seropositive people among low-risk population. The United Nations estimate on 1 July 2020 was accepted as the total adult (≥15 years) population of a country.[9] The age cut-off of 15 years was selected, assuming that the burden of chronic HCV would be quite low in children, to get a more pragmatic estimate of disease burden.

Thereafter, the number of HCV-seropositive persons in each high-risk group in the country was estimated. For this, data sources which were believed to be the most reliable and widely acceptable by the country experts were selected to estimate the population of people on MHD,[10] PLHIV,[11,12] PWID,[13–21] commercial sex workers,[22] prison inmates,[22,23] and MSM[22] for each country. Each of these was multiplied with the estimated pooled seroprevalence for the particular group. If the HCV prevalence data were not available for any of the high-risk populations in the country, the estimated seroprevalence of low-risk population was used to estimate the disease burden for those high-risk groups. Finally, the estimated number of HCV-seropositive persons in all groups were aggregated to obtain an estimate of the total number of such persons in the country.

The uncertainty interval of the estimated HCV burden in each subgroup was calculated by multiplying the lower-bound and upper-bound of 95% confidence intervals of the estimated prevalence with the estimated population at risk.

Assessment of study quality. We did not do a formal quality assessment of the selected data sources because it was difficult to apply the commonly used tools of quality assessment of prevalence studies on the selected data sources for several reasons. First, a large number of data sources were published >20 years ago when the criteria used for quality assessment tools were not as well known, and hence, information on these was often not included in the papers. Second, several large data sources, included in our analysis, had not been published as scientific papers but were instead available as reports, and hence, it was not feasible to apply quality assessment tools to such reports. Therefore, as an alternative, we individually scrutinized each of the included reports to assess the overall acceptability of their results based on the study population and coherence with other reports.

Results

Data points identified. In all, our analysis included data from 35 data sources for Bangladesh, 6 for Bhutan, 2 for DPR Korea, 323 for India, 43 for Indonesia, 2 for Maldives, 21 for Myanmar, 29 for Nepal, 11 for Sri Lanka, 67 for Thailand, and 2 for Timor-Leste (Table 1). These studies provided a total of 625 datasets for analysis. The major characteristics of the included reports and studies are summarized in Data S1. The results of literature searches, screening, and selection process of abstracts and full-text papers for each country are summarized as separate PRISMA flow diagrams (Data S2). The citations of the studies selected for inclusion from each country are tabulated in supplementary table (Data S2). Separate data for all the population subgroups were available for only three countries, namely, India, Thailand, and Indonesia.

Hepatitis C virus seroprevalence and its burden in low-risk population. For six countries (Bangladesh, Bhutan, DPR Korea, Indonesia, Myanmar, and Thailand), all of the identified community-based studies except two were found suitable for inclusion in the estimation of pooled seroprevalence (Table 2). One of these two excluded studies was from Thailand[24] which reported 15.5% anti-HCV seroprevalence, that is, many-fold higher than the other studies from Thai population. The other excluded study was from Myanmar,[25] and included people residing in four border cities; population in these border cities was deemed to have a higher proportion of those with high-risk behaviors such as drug use, and HIV positivity, and hence as unlikely to be representative of the general low-risk population in Myanmar.

For India, Maldives, Nepal, and Timor-Leste, a large proportion of the studies reported as population-based data were deemed unlikely to be representative of the general population, due either to their small sample size or poor quality leading to a high risk of bias; hence, for these countries, pooled estimates were calculated from blood donor data, which were also much larger. For instance, for India, there was no country-wide representative population survey; and 11 community-based studies were from only eight of the 35 administrative territories; a disproportionately large number of studies were from two states—Punjab and Haryana—which are known to have higher prevalence of HCV infection; and, mostly

Table 1 Number of datasets identified in systematic review for various study populations in each country

Study population		Bangladesh	Bhutan	DPRK	India	Indonesia	Maldives	Myanmar	Nepal	Sri Lanka	Thailand	Timor-Leste
Low-risk populations	Community based studies	8	2	1	11	5	-	2	3	1	10	-
	Blood donors	10	7	3	184	11	3	7	16	15	20	3
	Other low-risk population	6	-	-	26	1	-	2	4	1	10	-
High-risk populations	PLHIV	2	-	-	42	12	-	5	8	-	16	-
	PWID	9	-	-	36	4	-	4	8	1	14	-
	MHD	2	-	-	41	8	-	1	-	1	3	-
	Prison inmates	-	-	-	1	4	-	-	-	1	1	-
	High-risk behavior	4	-	-	13	1	-	-	-		5	-
	MSM	1	-	-	2	1	-	-	-		2	-
Total number of datasets (625)		42	9	4	356	47	3	21	39	20	81	3
Total number of studies (538)		35	6	2	323	43	2	18	29	11	67	2

The numbers in parentheses indicate the number of studies.
DPRK, Democratic People's Republic of Korea; MHD, people on maintenance hemodialysis; MSM, men who have sex with men; PLHIV, people living with HIV; PWID, people who inject drugs.

Table 2 Estimation of HCV seroprevalence and disease burden in low-risk population

Country	Number of datasets included	Number of study participants	Weighted pooled estimate of HCV seroprevalence as % (95% confidence interval)		Population at risk (x1000)	Estimated burden of HCV	Uncertainty estimates	
							Lower limit	Upper limit
Bangladesh	8	9677	0.72	(0.47–0.97)	120 253	865 822	565 189	1 166 454
Bhutan	2	1761	0.47	(0.15–0.79)	580	2726	870	4582
DPR Korea	1	44 510	0.34	(0.28–0.39)	20 664	70 258	57 859	80 590
India	185	68 164 245	0.49	(0.47–0.51)[†]	1 014 762	4 972 334	4 769 381	5 175 286
Indonesia	5	83 561	2.03	(0.52–3.54)	200 641	4 073 012	1 043 333	7 102 691
Maldives	3	24 224	0.41	(0.14–0.69)[†]	435[‡]	1784	609	3002
Myanmar	1[§]	5547	2.65	(2.26–3.11)	39 776	1 054 064	898 938	1 237 034
Nepal	16	1 844 188	0.38	(0.32–0.44)[†]	20 682.1	78 592	66 183	91 001
Sri Lanka	15	5 158 489	0.23	(0.21–0.25)[†]	16 341	37 584	34 316	40 853
Thailand	8[¶]	18 096	2.28	(1.48–3.07)	56 614	1 290 799	837 887	1 738 050
Timor-Leste	3	6973	0.29	(0.01–0.57)[†]	832	2413	83	4742
South-East Asia Region			0.84	(0.56–1.12)	1 491 580.1	12 449 387	8 274 649	16 644 284

[†]Weighted pooled estimate of HCV seroprevalence among blood donors.
[‡]There were no country-specific data on HCV seroprevalence in any high-risk population for the country, and hence, the high-risk population was not subtracted to estimate the low-risk population.
[§]Data from only one of the two community serosurveys were included.
[¶]Only eight of the 10 identified datasets were included.

included participants who were not sampled using a random technique.

The pooled anti-HCV seroprevalence and disease burden in low-risk population groups in the SEAR countries are shown in Table 2; the seroprevalence ranged from as low as 0.23% (95% CI 0.21–0.25) in Sri Lanka to as high as 2.65% (95% CI 2.26–3.11) in Myanmar. Total HCV burden in low-risk population in SEAR countries was estimated as 12 449 387 (uncertainty estimates 8 274 649 to 16 644 284).

Hepatitis C virus seroprevalence and its burden in high-risk populations. For the key high-risk population subgroups, the available data for Bhutan, DPR Korea, Maldives, and Timor-Leste were very limited (Table 3). All the available studies were included in analysis, except for some studies among PWID in Myanmar. Of the four studies in PWID from Myanmar (with a total of 7057 subjects), one study (n = 6061) was a well-designed, representative national serosurvey,[17] whereas the other three were deemed to be of low quality; the latter were excluded for this reason and the fact that their overall size was small. The estimated pooled HCV seropositivity in various high-risk population groups in the SEAR countries are listed in Table 3.

Estimation of hepatitis C virus burden in South-East Asia Region. The weighted pooled HCV seroprevalence among low-risk group populations in the region was

Table 3 Estimation of HCV seroprevalence and disease burden in high-risk population

	Bangladesh	Bhutan	DPR Korea	India	Indonesia	Maldives	Myanmar	Nepal	Sri Lanka	Thailand	Timor-Leste
People living with HIV (PLHIV)											
Number of datasets included	2	None	None	42	12	None	5	8	None	16	None
Number of study participants	218	-	-	18 995	6290	-	40 185	2814	-	8388	-
Weighted pooled estimate (%) of HCV seroprevalence (95% CI)	1.29 (−0.21–2.78)	-	-	3.81 (3.06–4.55)	48.2 (40.5–56.0)	-	9.43 (6.70–12.16)	26.17 (9.77–42.57)	-	13.45 (9.41–17.50)	-
Population at risk	14 000	Not known	Not known	2 140 000	640 000	Not known	240 000	30 000	3 600	480 000	1500
Estimated burden of HCV	181	-	-	81 534	308 480	-	22 632	7 851	-	64 560	-
Uncertainty estimates											
Lower limit	0	-	-	65 484	259 200	-	16 080	2931	-	45 168	-
Upper limit	389	-	-	97 370	358 400	-	29 184	12 771	-	84 000	-
People who inject drugs (PWID)											
Number of datasets included	9	None	None	36	4	None	1[#]	8	1	14	None
Number of study participants	11 859	-	-	52 861	835	-	6061	3002	305	8052	-
Weighted pooled estimate (%) of HCV seroprevalence (95% CI)	40.89 (29.44–52.33)	-	-	51.48 (44.88–58.07)	63.5 (38.7–88.3)	-	56.00 (54.74–57.25)	27.48 (17.28–37.68)	5.57 (3.51–8.74)	58.86 (39.30–78.42)	-
Population at risk	29 626	Not known	Not known	854 296	33 492	793	93 215	41 521	900	71 000	53
Estimated burden of HCV	12 144	-	-	439 792	21 267	-	52 200	11 410	50	41 791	-
Uncertainty estimates											
Lower limit	8722	-	-	383 408	12 961	-	51 026	7175	32	27 903	-
Upper limit	15 503	-	-	496 090	29 573	-	53 366	15 645	79	55 678	-
People on maintenance hemodialysis (MHD)											
Number of datasets included	2	None	None	41	8	None	1	None	1	3	None
Number of study participants	93	-	-	9321	1457	-	111	-	179	5073	-
Weighted pooled estimate (%) of HCV seroprevalence (95% CI)	37.28 (30.11–44.46)	0.47 (0.15–0.79) *	0.34 (0.28–0.39) *	20.08 (16.62–23.54)	60.5 (45.6–75.3)	-	15.3 (9.18–23.38)	-	5.59 (3.06–9.98)	13.13 (2.-23.86)	-
Population at risk	50 385	312	10 050	517 815	122 548	186	23 662	9784	12 353	43 023	421
Estimated burden of HCV	18 784	1	34	103 977	74 142	-	3620	-	691	5649	-
Uncertainty estimates											
Lower limit	15 171	1	28	86 061	55 882	-	2172	-	378	1033	-
Upper limit	22 401	2	39	121 894	92 279	-	5532	-	1233	10 265	-
Prison inmates											
Number of datasets included	None	None	None	1	4	None	None	None	1	1	None
Number of study participants	-	-	-	1611	2042	-	-	-	393	1648	-
Weighted pooled estimate (%) of HCV seroprevalence (95% CI)	0.72* (0.47–0.97)	0.47 (0.15–0.79) *	-	10.43 (9.03–12.02)	17.5 (6.8–28.2	-	-	-	6.87 (4.76–9.81)	5.22 (4.25–6.40)	-
Population at risk	73 400	1119	Not known	433 000	224 522	1852	92 000	23 775	122 000	373 169	695
Estimated burden of HCV	528	5	-	45 162	39 291	-	-	-	8381	19 480	-

(Continues)

Table 3 (Continued)

	Bangladesh	Bhutan	DPR Korea	India	Indonesia	Maldives	Myanmar	Nepal	Sri Lanka	Thailand	Timor-Leste
Uncertainty estimates											
Lower limit	345	2	-	39 100	15 267	-	-	-	5807	15 860	-
Upper limit	712	9	-	52 047	63 315	-	-	-	11 968	23 883	-
High-risk sex behavior											
Number of datasets included	4	None	None	13	1	None	None	None	None	5	None
Number of study participants	914	-	-	12 438	200	-	-	-	-	1150	-
Weighted pooled estimate (%) of HCV seroprevalence (95% CI)	0.99 (0.34–1.64)	-	-	3.78 (2.41–5.16)	0.5 (0.09–2.78)	-	-	-	-	2.00 (0.55–7.00)	-
Population at risk	140 000	Not known	Not known	657 800	226 800	-	66 000	67 300	30 000	144 000	1700
Estimated burden of HCV	1386	-	-	24 865	1134	-	-	-	-	2880	-
Uncertainty estimates											
Lower limit	476	-	-	15 853	204	-	-	-	-	792	-
Upper limit	2296	-	-	33 942	6305	-	-	-	-	10 080	-
Men having sex with men (MSM)											
Number of datasets included	1	None	None	2	1	None	None	None	None	2	None
Number of study participants	290	-	-	5083	143	-	-	-	-	1111	-
Weighted pooled estimate (%) of HCV seroprevalence (95% CI)	0.69 (0.19–2.48)	-	-	1.28 (0.97–1.58)	28 (21.3–35.8)	-	-	-	-	1.62 (0.88–2.36)	-
Population at risk	101 700	Not known	Not known	238 200	754 300	-	252 000	60 300	73 800	527 900	8700
Estimated burden of HCV	702	-	-	3049	211 204	-	-	-	-	8552	-
Uncertainty estimates											
Lower limit	193	-	-	2311	160 666	-	-	-	-	4646	-
Upper limit	2522	-	-	3764	270 039	-	-	-	-	12 458	-

†There were no data on HCV seroprevalence in this population, hence the country specific HCV seroprevalence in low-risk population was used to estimate the burden estimation.
#Included data from only one among the four studies.

Table 4 The HCV seroprevalence and burden among different subgroups of population in South-East Asia Region

Risk group	Study population	Estimated weighted pooled seroprevalence (95% confidence intervals) of hepatitis C antibody (%)	Estimated population at risk (%)	Estimated burden of HCV infection with uncertainty estimates (%)
Low-risk	General population ≥ 15 years of age	0.84 (0.56–1.12)	1 491 580 100 (99.32)	12 449 387 (8 274 649– 16 644 284) (88.32)
High-risk	People on MHD	25.80 (20.34–32.09)	790 539	203 959 (160 796–253 684)
	PLHIV	13.67 (10.95–16.40)	3 549 100	485 162 (388 626–582 052)
	PWID	51.44 (43.67–59.20)	1 124 896	578 647 (491 242–665 938)
	High-risk sex behavior	2.69 (1.43–4.13)	1 333 600	35 874 (19 070–55 078)
	MSM	11.43 (8.61–14.74)	2 016 900	230 532 (173 655–297 291)
	Prison inmates	8.39 (5.84–11.51)	1 345 532	112 890 (78 579–154 871)
Total high-risk groups			10 160 567 (0.68)	1 647 064 (1 311 968–2 008 914) (11.68)
Total burden of HCV infection in SEAR countries (100%)			1 501 740 667	14 096 451

MHD, people on maintenance hemodialysis; MSM, men who have sex with men; PLHIV, people living with HIV; PWID, people who inject drugs.

estimated as 0.84% (95% CI 0.56–1.12). The data revealed that the anti-HCV seroprevalence varied more than 20-fold among different countries in the region. About 80% of the eligible population (≥15 years of age) in the SEA region resides in countries with an HCV seroprevalence below 1%. Although prevalence is low in these countries, the total number of HCV-seropositive persons is large, because of the large population size of these countries. The data for various subgroups of the population in the region are summarized in Table 4. The total HCV burden in low-risk population in SEAR countries was estimated as 12.45 million (uncertainty estimates 8.27–16.64 million). The estimated HCV burden among the high-risk populations in the region was 1.65 million (1.31–2.01 million).

The natural history of HCV infection suggests that about 80% of the anti-HCV positive persons are viremic (positive for HCV RNA or with active HCV infection) and need treatment.[26] Accordingly, the estimated number of people who would need HCV treatment in the region is close to 11.27 million.

The HCV-seropositive persons in the low-risk general population accounted for more than 88% of the total HCV-seropositive population. The high-risk subgroups contributed only about 12% of the total HCV-seropositive burden in the SEA region. Nearly two-thirds of the HCV burden in high-risk subgroups was among PWID and PLHIV.

Discussion

In this analysis, we estimated the HCV seroprevalence and the burden of HCV infection for each of the 11 member countries in the WHO SEAR. For each country, the HCV burden was classified into that in low-risk general population and that in key high-risk subpopulations. The seroprevalence in low-risk population ranged from 0.23% in Sri Lanka to 2.65% in Myanmar and the weighted pooled HCV seroprevalence for the entire SEA region was estimated as 0.84%. The total HCV burden in SEAR countries was estimated to be 14.1 million, with nearly 11.27 million of them being actively viremic and requiring treatment. The high-risk subpopulations contributed ~12% (1.65 million) of the total HCV burden in the region, with a large majority being among PWID and PLHIV.

There have been several efforts to estimate the number of HCV seropositive and HCV viremic persons at the country, regional and the global level.[26–28] Our group had recently estimated HCV seroprevalence in India but similar data are lacking for other countries in the region.[29] Over time, the global estimate of persons with HCV-seropositive status has been revised downwards from 184 million in 2005[28] to 115 million in 2014.[27] Similarly, the global estimate for HCV-viremic persons has also been lowered form 80 million in 2014[26] to 71 million in 2017.[26] The current estimates are somewhat lower than those previous estimates. This is partly because the quality of data on HCV infection have gradually improved over time. The studies in early years were more likely to suffer from selection bias and were often carried out using tests with limited specificity, and hence tended to overestimate the HCV burden.

Of the seven WHO regions, SEAR is the one with the largest population, accounting for 25% of the world's population. Further, the region is characterized by a high population density, a relatively younger population, marked resource constraint, low government expenditure on health care, in particular on preventive services, and a high burden of infectious disease, including bloodborne infections such as HCV. Hence, it has been believed that 30% of global disease burden of HCV in the 11 SEAR member countries, namely, Bangladesh, Bhutan, DPR Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste.[30]

Our estimated burden of HCV-viremic population in the SEAR is about 14% higher as compared to previous estimates. As compared to previous estimates, our estimates seem to be more realistic as we have specifically included data for high-risk populations, and the population at risk was restricted to those with age more than 15, and calculated the burden in general population after subtracting the high-risk population from the total population.[26] However, our estimates may still be somewhat of an underestimate for countries where seroprevalence data for the high-risk subgroups were not available, because we had to use the seroprevalence for low-risk population in such situations. In addition, we estimated the disease burden only among people older than 15 years of age and, hence, our estimates would have missed the disease burden in children. However, we believe that the error on this account is likely to be small because most of the HCV infections occur after this age, and the risk of infection through unsafe

injection, a major route of infection in children, has declined in most countries over the last one to two decades.

Furthermore, the previous exercise on estimation of HCV burden had several limitations which are particularly relevant in context of SEAR countries.[26] First, these excluded the data from blood donors and high-risk population and had relied primarily on population-based seroprevalence studies. Second, it primarily included studies with sample size exceeding 1000. For the SEAR member countries, the study used a modeling approach to obtain the disease burden. Further, it used seroprevalence estimates for only three (India, Indonesia, and Thailand) of the 11 SEAR member states. For these three countries too, the estimates for India and Indonesia were based on input from country experts and those for Thailand on a single population-based study. We thus believe that our estimates, being more broad-based, are more likely to be closer to the truth.

Our analysis shows that the seroprevalence and disease burden of HCV infection in SEAR countries are lower than those in other WHO regions. What are the implications of this finding? A low burden of HCV infection means that the public health programs in the region would need to work harder to detect each case. Further, our data show that only a small proportion of HCV-infected cases in the region are in the high-risk subpopulations. This implies that focused testing efforts to these specific groups would detect and hence link to treatment a smaller proportion of the total HCV cases in these countries. Thus, the countries in the region will need to go beyond testing of high-risk groups, and, in addition, either undertake general population-based testing or undertake studies to identify risk-factors for positivity so that the testing strategy can be based on those risk factors.

The other implication of a higher proportion of HCV infected cases being in the low-risk general population is that such cases are much simpler to handle in a public health context. This is because such cases, as compared to the HCV-infected cases in high-risk groups, are less likely to have cirrhosis or advanced liver disease, and a lower rate of comorbid conditions, and thus are less likely to need specialist care during and after DAA treatment for HCV infection. Also, such cases have somewhat better cure rates and a much lower risk of reinfection, and thus may require a less rigorous follow-up following treatment.

The proportion of HCV burden contributed by the high-risk populations varied across countries, being relatively larger in larger countries (India, Indonesia, Nepal, and Sri Lanka) than in smaller countries. This could be the result of a bias in our estimation, that is, (i) absence of data either on the number of people or on anti-HCV seroprevalence in high-risk subgroups in some of the countries. For instance, the seroprevalence data for all the high-risk subgroups were available for only three countries, namely, India, Thailand, and Indonesia. For some countries (Timor-Leste, Maldives, DPR Korea, and Bhutan), the data for these subgroups were extremely limited. This points to the need for obtaining better data for high-risk population subgroups in the countries where those data are lacking. Availability of such data should allow a better estimation of HCV burden in such countries and allow for better delineation of screening and treatment strategies for them.

In summary, data from our systematic reviews of data from each of the eleven member states in the WHO SEAR provide a granular estimate of HCV burden in the general population and selected high-risk groups for these countries and for this region. This information should help the member states in better planning the strategies for control of HCV infection, in particular those for diagnosis and treatment of HCV-infected persons in their populations, and move towards the WHO's global goal of elimination of HCV infection as a public health threat by the year 2030, in all countries and populations.

Data availability statement. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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