



Decentralised hepatitis C testing and treatment in rural Cambodia: evaluation of a simplified service model integrated in an existing public health system

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Summary

Background Direct-acting antiviral treatment for hepatitis C virus (HCV) has provided the opportunity for simplified models of care delivered in decentralised settings by non-specialist clinical personnel. However, in low-income and middle-income countries, increasing overall access to HCV care remains an ongoing issue, particularly for populations outside of urban centres. We therefore aimed to implement a simplified model of HCV care via decentralised health services within a rural health operational district in Battambang province, Cambodia.

Methods The study cohort included adult residents (≥ 18 years) of the health operational district of Moug Russei who were voluntarily screened at 13 local health centres. Serology testing was done by a rapid diagnostic test using SD Bioline HCV (SD Bioline HCV, Standard Diagnostics, South Korea) with capillary blood. HCV viral load testing was done by GeneXpert (Cepheid, Sunnyvale, CA, USA). Viraemic patients (HCV viral load ≥ 10 IU/mL) received pretreatment assessment by a general physician and minimal treatment evaluation tests at the health operational district referral hospital. Viraemic patients who did not have additional complications received all HCV care follow-up at the local health centres, provided by nursing staff, and patients who had decompensated cirrhosis, previously treated with a direct-acting antiviral, HBV co-infection, or other comorbidities requiring observation continued receiving care at the referral hospital with a general physician. Patients deemed eligible for treatment were prescribed oral sofosbuvir (400 mg) and daclatasvir (60 mg) once a day for 12 weeks, or 24 weeks for patients with decompensated cirrhosis or those previously treated with a direct-acting antiviral. HCV cure was defined as sustained virological response at 12 weeks after treatment (HCV viral load < 10 IU/mL). Patients were assessed for serious and non-serious adverse events at any time between treatment initiation and 12 weeks post-treatment testing.

Findings Between March 12, 2018, and Jan 18, 2019, 10 425 residents (ie, 7.6% of the estimated 136 571 adults in the health operational district of Moug Russei) were screened. Of those patients screened, the median age was 44 years (IQR 31–55) and 778 (7.5%) were HCV-antibody positive. 761 (97.8%) of 778 antibody-positive patients received HCV viral load testing, and 540 (71.0%) of those tested were HCV viraemic. Among these 540 patients, linkage to treatment and follow-up care was high, with 533 (98.7%) attending a baseline consultation at the HCV clinic, of whom 530 (99.4%) initiated treatment. 485 (91.5%) of 530 patients who initiated treatment received follow-up at a health centre and 45 (8.5%) were followed up at the referral hospital. Of the 530 patients who initiated direct-acting antiviral therapy, 515 (97.2%) completed treatment. Subsequently, 466 (90.5%) of 515 patients completed follow-up, and 459 (98.5%) of 466 achieved a sustained virological response at 12 weeks after treatment. Two (0.4%) adverse events (fatigue [$n=1$] and stomach upset [$n=1$]) and five (0.9%) serious adverse events (infection [$n=2$], cardiovascular disease [$n=1$], and panic attack [$n=1$], with data missing for one of the causes of serious adverse events) were reported among patients who initiated treatment. All serious adverse events were deemed to be unrelated to therapy.

Interpretation This pilot project showed that a highly simplified, decentralised model of HCV care can be integrated within a rural public health system in a low-income or middle-income country, while maintaining high patient retention, treatment efficacy, and safety. The project delivered care via accessible, decentralised primary health centres, using non-specialist clinical staff, thereby enhancing the efficient use of limited resources and maximising the potential to test and treat individuals living with HCV infection.

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Introduction

In 2016, WHO declared hepatitis C infection as a public health problem and subsequently set strategic targets for global elimination of hepatitis C virus (HCV), which

included diagnosing 90% of those with chronic HCV infection and treating 80% of patients with a confirmed infection by 2030.¹ Recent developments in direct-acting antiviral treatment for HCV have shown

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Research in context

Evidence before this study

Cambodia has an estimated population prevalence for chronic hepatitis C virus (HCV) of 1.6%. However, with 76% of the population living in rural areas, access to HCV care is often poor outside of major cities. In rural Cambodia, a district-based health system exists providing rudimentary health care via small, primary care health centres, with tertiary care support provided by referral hospitals. At the health centres, most care is provided by nursing staff. From 2016 to 2018, Médecins Sans Frontières (MSF) implemented a simplified model of HCV care via a governmental hospital in Phnom Penh, Cambodia. The model uses rapid, point-of-care diagnostics, greatly reduced pretreatment assessment and follow-up visits, and shifted many clinical tasks from doctors to nurses and pharmacists. The project achieved high linkage to care, retention, and cure rate. However, to increase the accessibility of HCV care for Cambodia's rural population, a decentralised model, responsive to the scarce resources of the rural context, is required. We have examined the care models of national HCV programmes from Georgia, Mongolia, and Egypt. Although decentralised HCV care was applied, it was implemented with a vertical strategy tackling high disease burden (>5% infected population). Between Dec 1, 2019, and Sept 28, 2020, we searched for studies done in low-income and middle-income countries among the general population on PubMed using the following search combinations: ("HCV" or "Hep C" or "hepatitis C") and ("treatment" or DAA) and ("decentralized" or "community" or "primary health care"). We did not limit the research type, language, or date of the studies. Four studies were identified, including two implemented at village level with decentralised HCV care

centres in Egypt, and two implemented at primary health-care centres in Pakistan and India. From all the studies, medical doctors were the main care providers, and at least laboratory or imagery examination of liver fibrosis were required. All of them have achieved good outcomes.

Added value of this study

This pilot project showed a highly simplified, decentralised model of HCV care, integrated within a public health system in a low-income or middle-income country. The project greatly enhanced accessibility to HCV care among a rural population while maintaining high patient retention, treatment efficacy, and safety. By further simplifying the Phnom Penh model, this project showed the effectiveness of HCV care provided via rudimentary health facilities, without extensive pretreatment assessment, largely by nursing staff. The project maximised the potential of existing health infrastructure and resources to test and treat individuals living with chronic HCV infection.

Implications of all the available evidence

The simplified, decentralised model of HCV care described in this study was integrated into an existing public health system and provides an example that can be replicated in other locations to scale-up HCV care accessibility within similar, resource-limited contexts. Particularly, this model can help achieve international HCV elimination targets. Since completion, this project has been highlighted within the Cambodian Government's National Strategic plan on Viral Hepatitis C Infection Control (December, 2019), and has been replicated in two other health operational districts. Further model simplification (eg, treatment initiation by nursing staff) is currently being explored to reduce additional barriers to HCV care.

high pan-genotypic efficacy and safety, providing opportunities for simplified models of HCV testing and treatment, delivered in decentralised settings by non-specialist clinical personnel.²⁻⁴ These improvements are particularly beneficial for low-income and middle-income countries, where scant resources need to be distributed efficiently. National HCV treatment programmes using vertical strategies have also been implemented in multiple low-income and middle-income countries (eg, Georgia, Egypt, and Mongolia).⁵⁻⁷ However, current efforts to address existing HCV epidemics in many of these countries are inadequate, as is clinical evidence from HCV programmes in low-income and middle-income countries.^{8,9}

Cambodia has a modelled national HCV viraemic prevalence of 1.6%, or an estimated 257 000 individuals.¹⁰ About 76% of Cambodia's population live in rural areas of the country.¹¹ Although population-level HCV prevalence estimates do not exist for this rural population, a previous sample-specific study reported a 1.9% prevalence of chronic HCV infection.¹² Because the majority of Cambodia's population live in rural areas, and a

HCV prevalence potentially comparable to that found in urban areas, it is fair to presume Cambodia's rural population bears a considerable proportion of the overall HCV burden. Despite this burden, access to HCV care is inadequate in rural areas. Most HCV screening and treatment services are available only in major cities, provided by specialists at national hospitals or private clinics at a cost to the patient, representing highly centralised provision of care.¹³ The time and cost of travelling to major cities also represent a substantial barrier to receiving HCV care among people living outside urban centres.¹⁴

Cambodia's health system is structured as health operational districts, each covering approximately 100 000–200 000 individuals in the population.¹⁵ Inhabitants in rural areas can access rudimentary clinical care at primary health-care centres, provided mainly by nursing staff.¹⁶ The health centres are positioned below district referral hospitals generally situated in semi-urbanised areas of the health operational district. Referral hospitals can provide limited services, often without advanced laboratories or specialist health staff,

such as hepatologists.^{17,18} With these limited resources, implementation of models of HCV care in Cambodia's rural areas is needed to maximise available resources while also reaching as many people with HCV infection as possible.

In 2018, Médecins Sans Frontières (MSF), collaborating with the Cambodian Ministry of Health, implemented a pilot HCV screening and treatment programme in the health operational district of Moug Russei—a rural district in Battambang province, which is 230 km from Phnom Penh. Following implementation of an MSF-developed simplified HCV care model in a national hospital in Phnom Penh during 2016–18, the Moug Russei project represented a more simplified care model, suitable to the rural context.¹⁹ The project was implemented via Moug Russei's primary health-care centres and referral hospital, with care largely integrated within daily activities. The project was intended to explore the effectiveness of decentralised HCV care within a very resource-limited context.

Consequently, we aimed to describe the demographic and disease prevalence characteristics of a patient cohort presenting for voluntary HCV testing at rural health centres and those subsequently accessing HCV treatment, and to evaluate the efficacy and patient retention of a decentralised and simplified HCV care model implemented in a rural health operational district in Cambodia.

Methods

Study design and participants

The health operational district of Moug Russei has a total population of 213 392 individuals. Of this population, 136 571 (64.0%) comprises the adult population (≥ 18 years) from 175 villages.²⁰ The catchment area of this health operational district includes 13 health centres, each covering a catchment area with a median of 11 villages (IQR 9–13) and a median adult population of 10 001 individuals per catchment area (IQR 7961–12 258) and supported by a district referral hospital in Moug Russei's urban centre. The median distance from any village to its corresponding catchment health centre is

8 km (IQR 4–14), and from any health centre to the referral hospital is 10 km (7–25).

The MSF pilot HCV testing and treatment project was implemented in March 12, 2018. It was integrated in Moug Russei's 13 rural health centres and via a specially established HCV care clinic at the referral hospital. MSF provided tailored training on HCV diagnosis, treatment, and patient management for clinical staff identified as responsible for HCV care from existing staff at the health centres and referral hospital. Voluntary HCV screening, with some restrictions, was initiated for all patients presenting at the health centres. Simple pretreatment evaluation was done at the HCV clinic, and differentiated follow-up was done at either the health centres or the HCV clinic depending on the complexity of the patient's treatment requirements. The health centres and referral hospital imposed a service fee for patients: 5000 Riels (US\$1.25) for screening and 25 000 Riels (US\$6.25) for consultation. Fees were waived for patients holding a Cambodian Government identification card for low-wage individuals. MSF hired four nurse supervisors to coordinate patient management along the care continuum, logistics for the health centres, and some patient data collection.

This study cohort includes residents of Moug Russei's health operational district who were voluntarily screened at any of the 13 health centres. No data were recorded for patients who presented at the health centres but refused HCV screening (therefore not a part of the study). Although non-residents were also screened and treated in the project, they were not included in the study. People aged 18 years or more were eligible for screening, regardless of previous HCV treatment experience. Patients living with HIV were referred to the National Center for HIV/AIDS of Cambodia that also provided HCV screening and treatment. Women who were pregnant or breastfeeding and patients with tuberculosis were also ineligible for screening but were encouraged to return once eligible.

The National Ethics Committee for Health Research (NECHR) of Cambodia ethically approved the evaluation

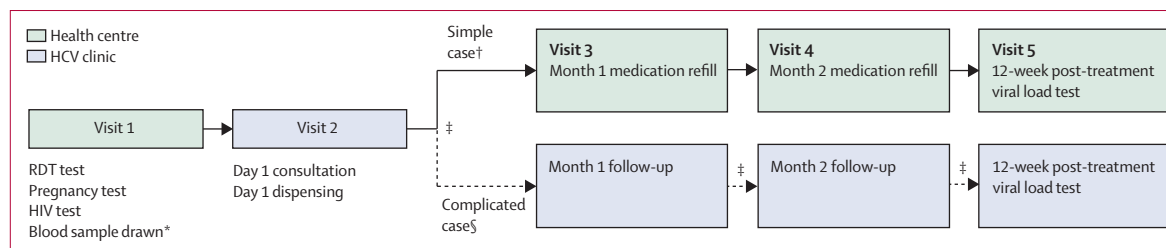


Figure 1: Treatment flows for simple and complicated cases evaluated at pretreatment consultation

Dotted lines indicate that visits might occur between visit 2 and month 1, months 1 and 2, and month 2 and 12-week post treatment viral load test. HBV=hepatitis B virus. HCV=hepatitis C virus. RDT=rapid diagnostic test. *Only patients with a positive HCV antibody result had a venous blood sample drawn for HCV viral load test.

†Simple cases were patients with only HCV infection without other conditions that required follow-up with a doctor. ‡Other visits might be required according to patient's condition and doctor's decision. §Complicated cases were patients with decompensated cirrhosis, HBV co-infection, previously treated with a direct-acting antiviral, or comorbidities that required medical attention.

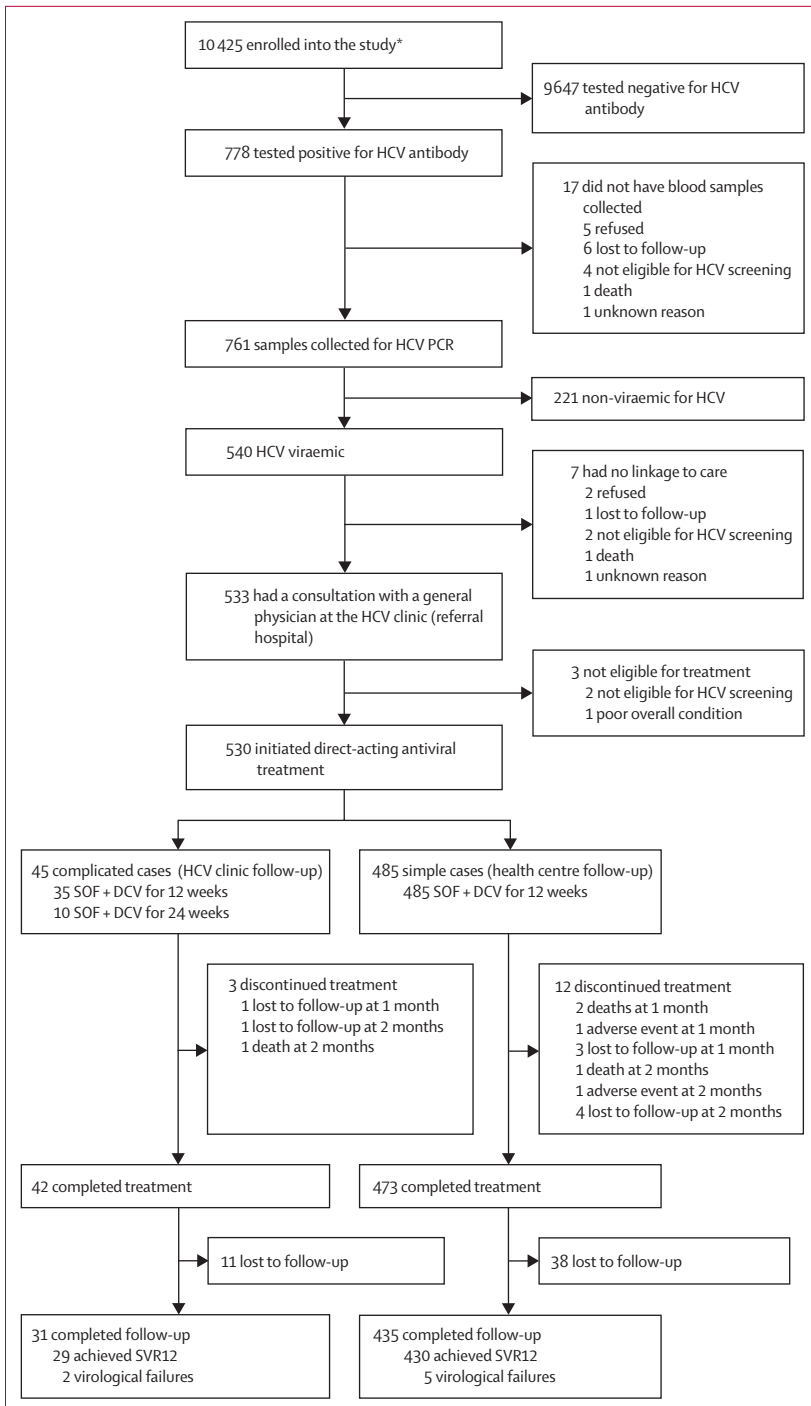


Figure 2: Study flowchart from enrollment to treatment outcomes

DCV=daclatasvir. HCV=hepatitis C virus. SOF=sofosbuvir. SVR12=sustained viral response at 12 weeks after treatment. *1650 patients received HCV care during the study period, but were not enrolled in the study, including four patients who opted out from the study, and 1646 non-residents of Moug Russei's health operational district.

of this project (240NECHR and 031NECHR). We used an opt-out consent design, which did not affect the provision of a person's HCV care. The study protocol is available on request, at msff-kh-comed@msf.paris.org.

Procedures

HCV screening started with pretest counselling, and HCV serology testing was done by a rapid diagnostic test (SD Bioline HCV, Standard Diagnostics, South Korea) with capillary blood (figure 1). If positive, venous blood sample was drawn immediately and transported on the same day to the referral hospital laboratory for HCV viral load testing done by GeneXpert (Cepheid, Sunnyvale, CA, USA). HCV viraemic (≥ 10 IU/mL, lower quantifiable range of GeneXpert) samples were also tested for hepatitis B virus (HBV) surface antigen (HbsAg). HCV viraemic results were informed via telephone the same day test results were available, and a consultation at the HCV clinic for treatment eligibility assessment was scheduled at the earliest available appointment. HCV treatment was provided according to a simplified care algorithm (figure 1), with all first consultations done by a general physician at the HCV clinic, and only the most necessary pretreatment assessments done, as stipulated by the project's medical standard operating procedures.

At pretreatment assessment, patients received liver fibrosis staging evaluation using FibroScan (Echosens, Paris, France). Serum creatinine testing was done only for patients aged 50 years or more, those who were positive for HbsAg, or those with a baseline FibroScan result of 20 kPa or more. HbsAg-positive patients also received alanine aminotransferase testing. Decompensated cirrhosis was diagnosed if a patient had any indications of liver decompensation: a history of using diuretics, gastrointestinal bleeding, encephalopathy, oedema, or ascites; or the current presence of abnormal vital signs, encephalopathy, oedema, ascites, or jaundice. Patients deemed eligible for treatment were prescribed sofosbuvir (400 mg) and daclatasvir (60 mg), to be taken orally once a day for 12 weeks, or 24 weeks (patients with decompensated cirrhosis or previously treated with a direct-acting antiviral).

Following pretreatment assessment, differentiated care was done according to the categorisation of patients as either simple or complicated cases (figure 1). Complicated cases were defined as those with decompensated cirrhosis, previously treated with a direct-acting antiviral, HBV co-infection, or other comorbidities requiring observation (eg, an estimated glomerular filtration rate < 30 mL/min per 1.73 m²). These patients were followed up at least once a month at the HCV clinic under the general physician's supervision, and provided with follow-up laboratory tests according to the patient's condition. Simple cases were defined as patients with only HCV infection without any other conditions that required follow-up with a physician. Patients designated as simple cases completed all follow-up at the health centre at which they were originally screened and supervised by nursing staff. These appointments included checking for treatment adherence and side-effects, and refill of medication at the second and third month of treatment. Patients could be referred back to the HCV clinic if there were health or treatment concerns.

	Antibody test		Viral load test			
	Total screening (N=10 425)	Antibody negative (n=9647)	Antibody positive (n=778)	Linkage to viral load test (n=761)	Non-viraemic (n=221)	Viraemic (n=540)
Sex*						
Male	3967 (38.1%)	3671 (38.1%)	296 (38.1%)	292 (38.4%)	79 (35.7%)	213 (39.4%)
Female	6457 (61.9%)	5976 (61.9%)	481 (61.9%)	469 (61.6%)	142 (64.3%)	327 (60.6%)
Age, years						
Median	44 (31-55) [†]	40 (31-54)	58 (50-63)	58 (50-63)	57 (48-64)	58 (50.5-63)
<45	5406 (51.9%)	5295 (54.9%)	111 (14.3%)	105 (13.8%)	43 (19.5%)	62 (11.5%)
45-54	2176 (20.9%)	1979 (20.5%)	197 (25.3%)	196 (25.8%)	52 (23.5%)	144 (26.7%)
55-64	1902 (18.2%)	1596 (16.5%)	306 (39.3%)	300 (39.4%)	78 (35.3%)	222 (41.1%)
≥65	941 (9.0%)	777 (8.1%)	164 (21.1%)	160 (21.0%)	48 (21.7%)	112 (20.7%)

Data are n (%) or median (IQR). HCV=hepatitis C virus. *One patient positive for HCV antibody did not provide information about their biological sex. †The median age of patients with negative and positive antibody test was significantly different (p<0.0001).

Table 1: Screening outcomes from 13 health centres in the health operational district of Moug Russei (Battambang, Cambodia)

Several modifications were made to the project model following lessons learned via emerging international evidence and on-the-ground experience, which led to the second medical standard operating procedures being implemented on Oct 1, 2018. The second standard operating procedures included two major updates: the definition of positive HCV viral load at screening was changed from 10 IU/mL or greater to 1000 IU/mL or greater based on WHO's recommendations;²¹ and the use of FibroScan was no longer needed during pretreatment consultations to assist diagnosis of decompensated cirrhosis. The viability of this change in clinical practice was assessed by doing the FibroScan after pretreatment consultation to confirm the doctor's original assessment. No clinical decisions were ultimately changed as a result of confirmatory FibroScan results.

In Jan 18, 2019, the four MSF nurse supervisors in Moug Russei were replaced by a single Ministry of Health nurse when the project rolled out to a neighbouring health operational district. Although this study only included patients initiated before Jan 18, 2019, 148 patients still required follow-up after the nurse replacement.

From March 1, 2019, patient tracing was stopped for those not attending their 12-week post-treatment viral load test. High achievement of sustained virological response at 12 weeks after treatment had already been demonstrated by this time, and patient tracing caused substantial staff workload.¹⁹ Remaining active patients were still provided with an appointment for a 12-week post-treatment viral load test, however, those missing the appointment were not contacted.

Outcomes

HCV cure was defined as a sustained virological response at 12 weeks after treatment (HCV viral load <10 IU/mL). Treatment failure was defined as an HCV viral load of 10 IU/mL or more. Patients experiencing treatment failure were tested for HCV viral load again 6 months

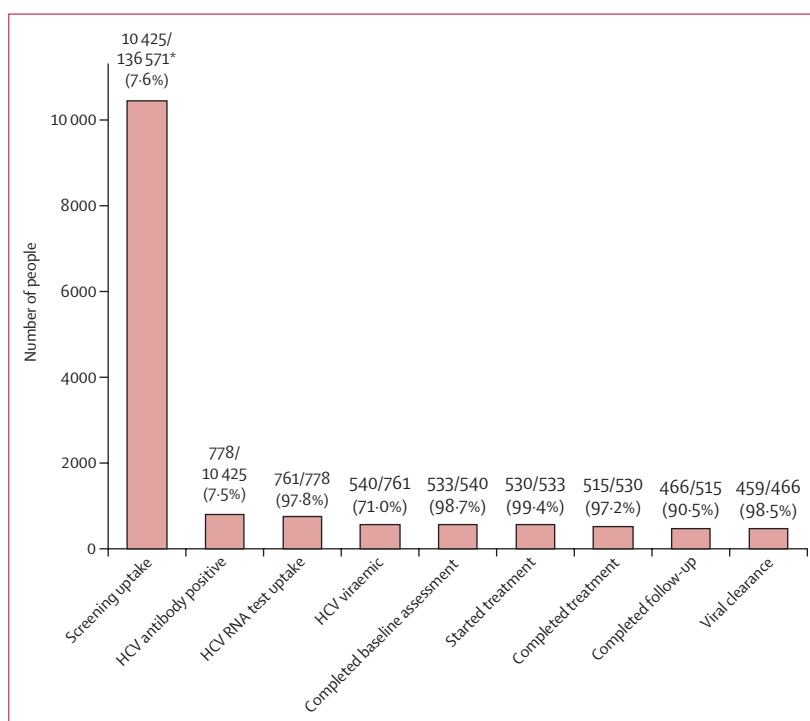


Figure 3: Cascade of project activity from screening uptake to cure in the health operational district of Moug Russei

HCV=hepatitis C virus. *The total adult population (age ≥18 years) of Moug Russei's health operational district.

after the 12-week post-treatment viral load test, with blood samples stored for potential HCV genotype and drug resistance testing. Patients who still did not achieve viral clearance would be contacted for potential future retreatment, should a second-line treatment become available.

Patients were assessed for serious and non-serious adverse events at any time between treatment initiation and 12 weeks post-treatment testing. Non-serious adverse events were defined as events leading to temporary or permanent treatment discontinuation or

modification of treatment. Serious adverse events were defined as events leading to hospitalisation, prolonging existing hospitalisation, or death. Both adverse events and serious adverse events were classified regardless of their association with direct-acting antiviral treatment. All serious adverse events were reported to the Cambodian NECHR for external review.

Statistical analysis

Data for screening and treatment were manually recorded via a paper-based system that was then electronically entered into the Research Electronic Data Capture system (Vanderbilt University, Nashville, TN, USA). Descriptive analysis was done using medians with IQRs for continuous variables and frequencies with percentages for categorical variables. Comparison between individuals with a positive or negative HCV serology result, and treatment follow-up locations, was done using the

See Online for appendix

Mann-Whitney *U* test for continuous variables, and Fisher's exact test or χ^2 test for categorical variables.

The rate of sustained virological response after treatment at 12 weeks was calculated in patients with predefined known outcomes. These known outcomes included achieving the 12-week sustained virological response after treatment, treatment failure at the 12-week post-treatment viral load test, treatment stoppage for any reason (eg, adverse event, lost to follow-up up to treatment completion), and death at any point between initiation and the 12-week post-treatment viral load test. Those who were lost to follow-up after treatment completion were not considered a known outcome and were excluded from treatment effectiveness analysis. All known outcomes other than the sustained virological response at 12 weeks after treatment were considered as treatment failure in the analysis. Rates of sustained virological response after treatment at 12 weeks are presented by baseline and clinical characteristics. 95% CIs for these rates were calculated using the Clopper-Pearson method for exact binomial distribution. Independent variables associated with treatment failure were not examined because of the small number of failures. We did all the data analyses using SAS (version 9.4).

Role of the funding source

All screening material and direct-acting antivirals were supplied by the study funder. The funder had oversight and input over all aspects of the study.

Results

Between March 12, 2018, and Jan 18, 2019, 10 425 individuals (ie, 7.6% of the estimated adult population in the health operational district of Moug Russei) were voluntarily screened at 13 rural health centres (figure 2). Across these rural health centres, screening uptake varied between 1.9–26.2% among the adult population (appendix p 2). Of the 10 425 individuals screened, the median age was 44 years (IQR 31–55) and 778 (7.5%) were HCV-antibody positive (table 1; figure 3). 761 (97.8%) of 778 antibody-positive patients received HCV viral load testing, and 540 (71.0%) of those tested were HCV viraemic (figure 3). The median turnaround time from HCV antibody-positive diagnosis to obtaining HCV viral load result was 1 weekday (IQR 0–10). Antibody-positive patients were significantly older than antibody-negative patients (58 years vs 40 years; $p < 0.0001$; table 1). No other significant differences according to antibody or viral load test results were reported.

There was high patient retention between screening and treatment initiation, with 533 (98.7%) of 540 viraemic patients attending a baseline consultation at the HCV clinic (figure 3). 530 (99.4%) of 533 patients initiated direct-acting antiviral treatment. Median turnaround time from HCV diagnosis to treatment initiation was 5 weekdays (IQR 3–8). 452 (85.3%) of 530 patients were

	Simple case (n=485)	Complicated case (n=45)	Total (n=530)
Sex			
Female	291 (60.0%)	32 (71.1%)	323 (60.9%)
Male	194 (40.0%)	13 (28.9%)	207 (39.1%)
Age, years			
Median	57 (50–63)	60 (56–68)	58 (50–63)*
<45	58 (12.0%)	4 (8.9%)	62 (11.7%)
45–54	139 (28.7%)	5 (11.1%)	144 (27.2%)
55–64	197 (40.6%)	20 (44.4%)	217 (40.9%)
≥65	91 (18.8%)	16 (35.6%)	107 (20.2%)
FibroScan, kPa†			
Median	7.7 (5.4–13.0)	21.0 (7.4–39.5)	7.9 (5.5–14.0)
F0: 1	84/483 (17.4%)	4/44 (9.1%)	88/527 (16.7%)
F1: 2–8	135/483 (28.0%)	7/44 (15.9%)	142/527 (26.9%)
F2: 8–1–9	83/483 (17.2%)	2/44 (4.5%)	85/527 (16.1%)
F3: 9–1–14	76/483 (15.7%)	5/44 (11.4%)	81/527 (15.4%)
F4: ≥14.1‡	105/483 (21.7%)	26/44 (59.1%)	131/527 (24.9%)§
HCV viral load, IU/mL			
Median (log ₁₀)	14.6 (13.0–15.6)	13.4 (12.3–15.4)	14.5 (12.8–15.5)
≥1 000 000	305 (62.9%)	18 (40.0%)	323 (60.9%)¶
BMI, kg/cm²†			
Median	23.4 (20.8–26.3)	21.9 (19.7–25.4)	23.3 (20.8–26.3)
Normal: <23	222/481 (46.2%)	27/44 (61.4%)	249/525 (47.4%)
Overweight: 23–27.4	187/481 (38.9%)	9/44 (20.5%)	196/525 (37.3%)
Obese: ≥27.5	72/481 (15.0%)	8/44 (18.2%)	80/525 (15.3%)
Diabetes			
Diagnosed diabetes	36/485 (7.4%)	7/45 (15.6%)	43/530 (8.1%)
No history of diabetes but random blood sugar ≥200 mg/mL	14/485 (2.9%)	0	14/530 (2.6%)
Hypertension**			
	115/485 (23.7%)	15/45 (33.3%)	130/530 (24.5%)

Data are n (%), median (IQR), or n/N (%). BMI=body-mass index. HCV=hepatitis C virus. * $p=0.0074$. †Patients with missing data are not included. ‡We compared F4 (patients with cirrhosis) and F0–3 (patients with no cirrhosis). § $p < 0.0001$. ¶ $p=0.0026$. ||Previously diagnosed diabetes, with or without blood sugar controlled at baseline evaluation. **Previously diagnosed hypertension, with or without blood pressure controlled at baseline evaluation.

Table 2: Baseline characteristics of patients initiating HCV treatment

initiated under the first standard operating procedures, and 78 (14.7%) of 530 were initiated under the second standard operating procedures (appendix p 1).

Of those initiating treatment, the median age was 58 years (IQR 50–63; table 2). One (0.2%) of 530 patients was previously treated with pegylated interferon and ribavirin, and the other 529 (99.8%) were treatment naive. 11 (2.1%) of 530 patients were co-infected with HBV. 131 (24.9%) of 530 patients had liver cirrhosis. Ten (1.9%) of 530 had decompensated cirrhosis and were prescribed a 24-week course of sofosbuvir plus daclatasvir. The other 520 (98.1%) patients were prescribed a 12-week course of sofosbuvir plus daclatasvir (figure 2).

485 (91.5%) of 530 patients were defined as simple cases and 45 (8.5%) were complicated cases (table 2). Patients who were diagnosed as a simple case were followed up at the health centres and were significantly younger than those who were diagnosed as a complicated case ($p=0.0074$). The percentage of patients with cirrhosis was lower in those diagnosed with a simple case than in those with a complicated case ($p<0.0001$), and baseline HCV viral load of 1 000 000 IU/mL or more was higher in the simple cases than in the complicated cases ($p=0.0026$).

Two (0.4%) adverse events (fatigue [$n=1$] and stomach upset [$n=1$]), and five (0.9%) serious adverse events were reported among patients who initiated treatment. Among the five patients who had a serious adverse event, four (80%) were considered to be simple cases at treatment initiation and one (20%) was considered to be a complicated case. All serious adverse events were determined by the doctors' evaluation as being unrelated to the patient's HCV treatment. The causes of serious adverse events were infection ($n=2$), cardiovascular disease ($n=1$), and panic attack ($n=1$), with data missing for one of the causes of serious adverse events.

515 (97.2%) of 530 patients completed treatment (figure 3). The other 15 (2.8%) patients did not complete treatment because of death ($n=4$), treatment discontinuation due to an adverse event ($n=2$), and being lost to follow-up ($n=9$; figure 2). Patients who did not complete treatment were considered to be treatment failures. Treatment completion rate was more than 93% regardless of the patient being classified as a simple or a complicated case. After treatment completion, 466 (90.5%) of 515 patients returned for a 12-week post-treatment viral load test (figure 3). Of these 466 patients, 459 (98.5%) achieved a sustained virological response at 12 weeks after treatment.

481 patients had known outcomes. The overall rate of sustained virological response at 12 weeks after treatment was 95.4% (95% CI 93.2–97.1), with 96.2% (94.0–97.8) among simple cases and 85.3% (68.9–95.0) among complicated cases (table 3). Across other baseline demographic and clinical characteristics, the sustained virological response at 12 weeks after treatment was consistently high ($\geq 90\%$), except among patients with

	Number of patients achieving SVR12	Number of patients with known outcomes*	SVR12 (95% CI)
Total	459	481	95.4% (93.2–97.1)
Sex			
Male	168	181	92.8% (88.0–96.1)
Female	291	300	97.0% (94.4–98.6)
Age, years			
<50	107	108	99.1% (94.9–100)
≥ 50	352	373	94.4% (91.5–96.5)
Cirrhosis status†			
F0–3	356	366	97.3% (96.0–98.7)
F4	100	112	89.3% (82.0–94.3)
HCV viral load, IU/mL			
<1 000 000	177	185	95.7% (91.7–98.1)
$\geq 1 000 000$	282	296	95.3% (92.2–97.4)
BMI, kg/cm ² ‡			
<23	210	222	94.6% (90.7–97.2)
≥ 23	246	255	96.5% (93.4–98.4)
Diabetes			
Diabetes history or baseline random blood sugar ≥ 200 mg/mL	41	46	89.1% (76.4–96.4)
No diabetes history nor random blood sugar ≥ 200 mg/mL	418	435	96.1% (93.8–97.7)
Hypertension			
Diagnosed hypertension	106	116	91.4% (84.7–95.8)
No history of hypertension	353	365	96.7% (94.3–98.3)
Co-infection			
HCV mono-infection	449	470	95.5% (93.3–97.2)
HBV co-infection	10	11	90.9% (58.7–99.8)
Case definition			
Simple case	430	447	96.2% (94.0–97.8)
Complicated case	29	34	85.3% (68.9–95)
SOP used for the treatment initiation‡			
First SOP	417	430	97.0% (94.9–98.4)
Second SOP	42	51	82.4% (69.1–91.6)

BMI=body-mass index. HBV=hepatitis B virus. HCV=hepatitis C virus. SOP=standard operational procedure. SVR12=sustained virological response at 12 weeks after treatment. *Known outcomes include achieving SVR12, treatment failure at the 12-week post-treatment viral load test, treatment stoppage for any reason (adverse event, loss to follow-up before treatment completion), and death at any point between initiation and the 12-week post-treatment viral load test. †Patients missing or without valid results for BMI and FibroScan were not shown. ‡Patients initiated before Oct 1, 2018, were under the care of the first SOP, and patients initiated after were under the care of the second SOP.

Table 3: SVR12 among patients with known outcomes

F4 cirrhosis, a history of diabetes or baseline random blood sugar of 200 mg/mL or more, and patients initiated under the second standard operating procedures (table 3).

Discussion

This pilot project showed high patient retention, treatment efficacy, and safety using a highly simplified model of non-specialist service delivery, in a rural, low-resource context via a decentralised approach, embedded within the existing health-care system. As a result, this model of care was incorporated in the Cambodian

Government's National Strategic plan on Viral Hepatitis C Infection Control in December, 2019.²²

WHO has recommended simplified, decentralised models of diagnosis and treatment under a treat-all approach for HCV.²¹ By decentralising HCV testing and treatment into rudimentary settings, this HCV project improved patient access. 2383 screenings of the residents in the health operational district at the first month of implementation, and 9048 in the first 6 months, shows the demand for HCV services (appendix p 3). A higher viraemic rate in our study (5.2%) compared with the previous study done in the health operational district (1.9%) suggests many patients knew or suspect their HCV-positive status before presenting for screening.¹² Although the study did not intend to evaluate the factors associated with screening uptake, a future exploration of the characteristics among individuals and services that encourage and discourage HCV screening would inform more effective service provision. There was increased screening uptake at the two health centres that initiated project information campaigns (outside of formal project procedures). Although not formally evaluated in our study, these campaigns would possibly be an effective strategy for similar interventions (appendix p 2).

The greater geographical accessibility, rapid, point-of-care diagnostics, and reductions in patient consultations resulted in high patient linkage and retention. Without a comparison group, the efficacy of our model could only be compared with real-world studies, in which case our results are comparable or even improve upon other similar real-world studies.^{2,4,23} Furthermore, the model substantially reduced burden on staff, as well as clinical and financial resources. More specifically, the reduction in pretreatment assessments complemented the basic laboratory capacity, and task shifting of most responsibilities onto nursing staff expanded the potential workforce for HCV care. These improvements greatly increased programmatic coverage and the number of individuals who could be tested and treated. In addition, further model simplification could be feasible by providing the entire treatment medication course to reduce follow-up appointments, and with nursing staff doing initiation assessments in the health centres and immediately initiating treatment of uncomplicated cases.^{24,25}

The rate of patients achieving a sustained virological response at 12 weeks after treatment was high ($\geq 90\%$) across all patient subgroups, except among those with cirrhosis, those who were followed up at the HCV clinic (ie, complicated case), those initiated under the second standard operating procedures, and those with a history of diabetes or a high baseline random blood sugar value. Unsurprisingly, patients with cirrhosis or diagnosed as complicated cases who had a follow-up at the HCV clinic had achieved a lower sustained virological response at 12 weeks after treatment. Liver cirrhosis is associated with

increased risk of virological failure, with decompensated cirrhosis associated with a higher risk of death.^{21,26} Among complicated cases, about 60% had liver cirrhosis, and of these, about 37% had decompensated cirrhosis. Similarly, a higher percentage of patients with diabetes or a high baseline random blood sugar value who were initiated under the second standard operating procedures were identified as complicated cases compared with simple cases. Individuals living with HCV experience increased risk of developing diabetes, which in turn accelerates fibrosis progression.^{27,28}

The difference in treatment effectiveness between the first and second standard operating procedures is unlikely to be related to the exclusion of FibroScan in determining simple and complicated cases. No clinical decisions were altered on the basis of FibroScan results that were used to validate the pretreatment evaluation. The difference in effectiveness rates between both standard operating procedures are therefore potentially related to two factors. First, the adoption of the second standard operating procedures coincided with a later period in the project when the four MSF nurses were replaced with one Ministry of Health nurse, who could not alone cover all patient tracing, which led to an increased number of patients lost to follow-up during treatment (11.8% for the second standard operating procedures vs 0.7% for the first standard operating procedures; appendix p 4). Nevertheless, the total number of patients lost to follow-up during treatment was small ($n=9$). Consequently, we do not have sufficient statistical power to analyse the associations with those lost-to follow-up. When only assessing patients who completed follow-up, 97.7% achieved viral clearance among patients in the second standard operating procedures, which is comparable to that of the first standard operating procedure (98.6%; appendix p 4). Second, a significantly higher proportion of patients with decompensated cirrhosis presented during the second standard operating procedure (5.1%) compared with the first standard operating procedure (1.3%), which is associated with a higher risk of treatment failure (appendix p 1). The reasons for a higher percentage of patients with decompensated cirrhosis during the second period of the standard operating procedures are unclear. Even so, with the inclusion of these patients, there was a 93.3% sustained virologic response after 12 weeks post treatment (appendix p 4), was maintained, after accounting for the increased lost-to-follow-up rate.

Based on these findings, fibrosis evaluation should not be mandatory for HCV treatment initiation. Due to the expense and examination capacity required, necessitating fibrosis assessment represents a barrier to HCV treatment in a resource limited context. When examinations for fibrosis are unavailable or inaccessible, HCV treatment can still be initiated with high efficacy. However, we do recognise the importance of diagnosing liver cirrhosis to guide clinical decisions, follow-up, and monitoring for hepatocellular carcinoma.

Many non-residents of Moug Russei's health operational district presented for HCV screening (non-Moug Russei residents represented 49% of treatment initiations, but only constituted 15% of all patients screened during the first 6 months of implementation). Although they were not included in this study, this unexpectedly large number of patients, who most likely knew their HCV-positive status and travelled specifically to Moug Russei for treatment, represented an otherwise disproportionate burden on the planned capacity of the project. For these reasons, HCV testing and treatment, and this subsequent project evaluation, was restricted to residents of Moug Russei's health operational district. However, without the presentation of these patients, the project might have been able to test and treat a much larger number of Moug Russei residents, thereby potentially limiting the numbers reported in this study.

The high standard of care provided here is contingent on a certain level of resource allocation, which might not be replicable in settings with small public health budgets. This limitation is potentially reflected in the increased loss to follow-up rate following the removal of the MSF nurses. With this lesson learned, during project expansion, health centre staff were provided more tools for case monitoring and village volunteers started supporting patient tracing. Further, care quality could be improved through enhancing the public health system. Cambodia's national strategic plan on viral hepatitis has subsequently made a commitment to treat patients with cirrhosis and monitor hepatocellular carcinoma.²⁰

The difference in HCV prevalence among patients presenting for screening, and the estimated prevalence for the wider health operational district population suggests many presenting patients already knew their HCV status, or suspected themselves at risk of HCV positivity. This knowledge might have motivated them to seek screening and treatment, and therefore represents a potential bias in patient recruitment. It is therefore possible that our study cohort is not entirely representative of the general population within the health operational district. Even so, among the 10425 patients screened as part of this study, only 761 were antibody positive, and 540 RNA positive, suggesting a substantial number of patients screened probably did not know their HCV status, and were still motivated to attend the health centre, which was most likely due to the availability of the service.

In conclusion, our pilot project showed that a highly simplified model of HCV care can be integrated within a rural public health system in a low-income or middle-income country, enhancing accessibility, while maintaining short turnaround times, high patient retention, treatment efficacy, and safety. The use of rapid diagnostics, non-specialist clinical staff, and minimal treatment evaluation tests (including removal of fibrosis evaluation) and follow-up consultation—primarily delivered in highly accessible, decentralised rural health centres—maximised the number of patients tested and treated, and made

efficient use of the scarce resources available. If WHO's global elimination targets for viral hepatitis are to be reached, innovative methods of delivering HCV care are required, particularly outside of urban centres. This project provides a model that can be replicated in similar rural contexts in low-income and middle-income countries.

Contributors

MZ, J-PD, and MLP conceived and designed the study. MZ, JC, KS, VB, and PJ acquired the data. MZ and DO'K analysed and interpreted the data, and drafted the manuscript. MZ, DO'K, SB, TM, J-PD, and MLP critically revised the manuscript. MZ, DO'K, and J-PD verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MZ, DO'K, JC, PJ, SB, TM, J-PD, and MLP were employed by Médecins Sans Frontières. All other authors declare no competing interests.

Data sharing

Médecins Sans Frontières (MSF) has a managed access system for data sharing that respects MSF's legal and ethical obligations to its patients to collect, manage, and protect their data responsibly. Ethical risks include, but are not limited to, the nature of MSF operations and target populations being such that data collected are often highly sensitive. Data are available on request in accordance with MSF's data sharing policy. Requests for access to data should be made to data.sharing@msf.org.

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References

- 1 WHO. Combating hepatitis B and C to reach elimination by 2030. Geneva: World Health Organization, 2016.
- 2 Dhiman RK, Grover GS, Premkumar M, et al. Decentralized care with generic direct-acting antivirals in the management of chronic hepatitis C in a public health care setting. *J Hepatol* 2019; **71**: 1076–85.
- 3 Shih G, Soliman R, Mikhail NN, Easterbrook P. An educate, test and treat model towards elimination of hepatitis C infection in Egypt: feasibility and effectiveness in 73 villages. *J Hepatol* 2019; **72**: 658–69.
- 4 Capileno YA, Van den Bergh R, Donchunk D, et al. Management of chronic hepatitis C at a primary health clinic in the high-burden context of Karachi, Pakistan. *PLoS One* 2017; **12**: e0175562.
- 5 Hutin Y, Luhmann N, Easterbrook P. Evaluating the impact of Georgia's hepatitis C elimination plan: lessons learned for the global initiative. *Lancet Glob Health* 2020; **8**: e163–64.
- 6 El-Akel W, El-Sayed MH, El Kassas M, et al. National treatment programme of hepatitis C in Egypt: hepatitis C virus model of care. *J Viral Hepat* 2017; **24**: 262–67.
- 7 Dashdorj N, Dashdorj N, Bungert AS, et al. Hepatitis prevention, control, and elimination program in Mongolia: national hepatitis elimination program in a country with the highest burden of viral hepatitis in the world. *J Hepatol* 2017; **66**: S412–13.
- 8 WHO. Global hepatitis report 2017. Geneva: World Health Organization, 2017.
- 9 Heffernan A, Cooke GS, Nayagam S, Thursz M, Hallett TB. Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. *Lancet* 2019; **393**: 1319–29.
- 10 Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol* 2017; **2**: 161–76.

For MSF's data sharing policy see <http://fieldresearch.msf.org/msf/handle/10144/306501>

- 11 World Bank. Rural population (% of total population)—Cambodia. 2019. <https://data.worldbank.org/indicator/SP.RUR.TOTL.ZS?locations=KH> (accessed May 13, 2020).
- 12 Lynch E, Falq G, Sun C, et al. Hepatitis C viraemic and seroprevalence and risk factors for positivity in Northwest Cambodia: a household cross-sectional serosurvey. *BMC Infect Dis* 2021; **21**: 223.
- 13 WHO. Mission report: viral hepatitis epidemiology and situation assessment in Cambodia. Phnom Penh: World Health Organization, 2017.
- 14 Kelly C, Hulme C, Farragher T, Clarke G. Are differences in travel time or distance to healthcare for adults in global north countries associated with an impact on health outcomes? A systematic review. *BMJ Open* 2016; **6**: e013059.
- 15 Cambodia Ministry of Health. Guidelines for developing operational districts. Phnom Penh: Cambodia Ministry of Health, 1997.
- 16 Cambodia Ministry of Health. Guidelines on minimum package of activities for health center development. Phnom Penh: Cambodia Ministry of Health, 2018.
- 17 Cambodia Ministry of Health. Guidelines on complementary package of activities for referral hospital development. Phnom Penh: Cambodia Ministry of Health, 2014.
- 18 Perrone LA, Voeurung V, Sek S, et al. Implementation research: a mentoring programme to improve laboratory quality in Cambodia. *Bull World Health Organ* 2016; **94**: 743–51.
- 19 Zhang M, O’Keefe D, Iwamoto M, et al. High sustained viral response rate in patients with hepatitis C using generic sofosbuvir and daclatasvir in Phnom Penh, Cambodia. *J Viral Hepat* 2020; **27**: 886–95.
- 20 Battambang provincial Health Department. Health coverage plan for Battambang province 2019. Phnom Penh: Cambodia Ministry of Health, 2019.
- 21 WHO. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva: World Health Organization, 2018.
- 22 Cambodia Ministry of health. National strategic plan for viral hepatitis B and C infection control in Cambodia 2020–24. Phnom Penh: Cambodia Ministry of Health, 2019.
- 23 Shiha G, Metwally AM, Soliman R, Elbasiony M, Mikhail NNH, Easterbrook P. An educate, test, and treat programme towards elimination of hepatitis C infection in Egypt: a community-based demonstration project. *Lancet Gastroenterol Hepatol* 2018; **3**: 778–89.
- 24 Overton K, Clegg J, Pekin F, et al. Outcomes of a nurse-led model of care for hepatitis C assessment and treatment with direct-acting antivirals in the custodial setting. *Int J Drug Policy* 2019; **72**: 123–28.
- 25 Dore GJ, Feld JJ, Thompson A, et al. Simplified monitoring for hepatitis C virus treatment with glecaprevir plus pibrentasvir, a randomised non-inferiority trial. *J Hepatol* 2019; **72**: 431–40.
- 26 Perazzo H, Castro R, Luz PM, et al. Effectiveness of generic direct-acting agents for the treatment of hepatitis C: systematic review and meta-analysis. *Bull World Health Organ* 2020; **98**: 188–97.
- 27 Hammerstad SS, Grock SF, Lee HJ, Hasham A, Sundaram N, Tomer Y. Diabetes and hepatitis C: a two-way association. *Front Endocrinol* 2015; **6**: 134.
- 28 Fabiani S, Fallahi P, Ferrari SM, Miccoli M, Antonelli A. Hepatitis C virus infection and development of type 2 diabetes mellitus: systematic review and meta-analysis of the literature. *Rev Endocr Metab Disord* 2018; **19**: 405–20.