Decentralized 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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• Analysis and interpretation of data: Meiwen Zhang, Daniel O’Keefe
• Drafting manuscript: Meiwen Zhang, Daniel O’Keefe
• Critical revision: Meiwen Zhang, Daniel O’Keefe, Jean-Philippe Dousset, Mickael Le Paih, Tonia Marquardt, Suna Balkan
• Meiwen Zhang, Daniel O’Keefe, and Jean-Philippe Dousset have verified the underlying data.

Ethic Committee Approval:

Cambodia National Ethical Committee for Health Research ethically approved the evaluation of this project (reference: NO. 240NECHR and NO. 031NECHR)
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ABSTRACT

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

Methods
The study cohort included adult residents of the HOD voluntarily screened between March 2018-January 2019 at local health centers. Serology testing was performed by rapid diagnosis test (SD Bioline®) with capillary blood. HCV viral load (VL) testing performed by GeneXpert®. Viremic patients (HCV VL>10IU/mL) received pre-treatment assessment by general practitioner and minimal treatment evaluation tests at the HOD referral hospital. Viremic patients, without additional complications, received all HCV-care follow-up at the local health centers, provided by nursing staff.

Findings
A total of 10425 (7.6% of the HOD’s estimated adult population) residents were screened. Among 540 (5.2%) patients diagnosed as HCV-viremic, linkage to treatment and follow-up care was strong, with 530 (98%) patients initiated onto treatment, 515 (97.2%) completing treatment, 466 (90.5%) completing follow-up, and 98.5% (n=459) achieving SVR12. Most initiated patients (91.5%, n=485) received followed-up at health center, and 8.5% (n=45) at the referral hospital.

Interpretation
This pilot project demonstrated that a highly simplified, decentralized model of HCV care can be integrated within a rural public health system in an LMIC, whilst maintaining high patient retention, treatment efficacy and safety. The project delivered care via highly accessible, decentralized primary health centers, using non-specialist clinical staff, thereby enhancing the efficient use of limited resources and maximizing the potential to test and treat individuals living with HCV.

Funding
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Word count: 298/300
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 rudimental health care via small, primary-care health centers, with tertiary care support provided by referral hospitals. At the health centers, most care is provided by nursing staff. From 2016-2018, 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 pre-treatment assessment and follow-up visits, and shifted many clinical tasks from doctors onto 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 decentralized model, responsive to the limited resources of the rural context is required. We have examined the care models of national HCV programs from Georgia, Mongolia, and Egypt. Although decentralized HCV care was applied, it was implemented with a vertical strategy tackling high disease burden – over 5% infected population.

Between December 1, 2019 and September 28, 2020, we searched studies in Pubmed using combinations of (“HCV” or “Hep C” or “hepatitis C”) and (“treatment” or DAA”) and (“decentralized” or “community” or “primary health care”), and conducted in low- and middle-income countries (LMIC) among general population. We did not limit the research type or language. Four studies were identified, including two implemented at village-level with decentralized HCV care centers in Egypt, and two implemented at primary health care centers in Pakistan and India, respectively. 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 demonstrated a highly simplified, decentralized model of HCV care, integrated within a public health system in an LMIC. The project greatly enhanced accessibility to HCV care among a rural population whilst maintaining high patient retention, treatment efficacy and safety. By further simplifying the Phnom Penh model, this project demonstrated the effectiveness of HCV care provided via rudimentary health facilities, without extensive pre-treatment assessment, largely by nursing staff. The project maximized the potential of existing health infrastructure and resources to test and treat individuals living with chronic HCV.

Implications of all the available evidence
The simplified, decentralized model of HCV care described here, 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 (e.g. treatment initiation by nursing staff) is currently being explored to reduce additional barriers to HCV care.
INTRODUCTION

1. In 2016, the World Health Organization (WHO) declared Hepatitis C infection as a public health problem and 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 confirmed HCV cases by 2030.¹ Recent developments in direct-acting antiviral (DAA) treatment for HCV have demonstrated high pan-genotypic efficacy and safety, opening the door for simplified models of HCV testing and treatment, delivered in decentralized settings by non-specialist clinical personnel.²⁻⁴ These improvements are particularly beneficial for low- and middle-income countries (LMICs), where scant resources need to be distributed efficiently. National HCV treatment programs using vertical strategies were also implemented in multiple LMICs (e.g. Georgia, Egypt and Mongolia).⁵⁻⁷ However, current efforts to address existing HCV epidemics in many LMICs are inadequate, as is clinical evidence from HCV programs in LMICs.⁸⁻⁹

2. Cambodia has a modeled national HCV viremic prevalence of 1·6%, or an estimated 257,000 individuals.¹⁰ The majority (76%) of Cambodia’s population live in rural areas of the country.¹¹ Whilst there are no population-level HCV prevalence estimates for this rural population, a previous sample-specific study reported a 1.9% prevalence of chronic HCV.¹² Due to the majority of Cambodia’s population living in rural areas, and a HCV prevalence potentially comparable to that found in urban areas, it is fair to presume Cambodia’s rural population holds a considerable portion of the overall HCV burden. Despite this, access to HCV care is limited 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 cost to the patient, representing highly centralized provision of care.¹³ The time and cost of traveling to major cities represents a major barrier to receiving HCV care among those outside urban centers.¹⁴
3. Cambodia’s health system is structured as health operational districts (HOD), each covering approximately 100,000 to 200,000 population. Inhabitants in rural areas can access rudimentary clinical care at primary health care centers, provided mainly by nursing staff. The health centers sit below district referral hospitals generally situated in semi-urbanized areas of the HOD. Referral hospitals can provide limited services, often without advanced laboratories or specialist health staff, such as hepatologists. With these limited resources, there is a clear need to implement models of HCV care in Cambodia’s rural areas that maximize available resources, whilst also reaching as many infected people as possible.

4. In 2018, Médecins Sans Frontières (MSF), collaborating with the Cambodian Ministry of Health, implemented a pilot HCV screening and treatment program in Moung Russei HOD – a rural district in Battambang province, which is 230km from Phnom Penh, the capital city of Cambodia. Following implementation of an MSF-developed simplified HCV care model in a national hospital in Phnom Penh during 2016-2018, the Moung Russei project represented an even more simplified care model, suitable to the rural context. The project was implemented via Moung Russei’s primary health care centers and referral hospital, with care largely integrated within daily activities. The project was intended to explore the effectiveness of decentralized HCV care within a very limited resource context.

5. This study aims to:

1) Describe the demographic and disease prevalence characteristics of a patient cohort presenting for voluntary HCV testing at rural health centers and those subsequently accessing HCV treatment, and

2) Evaluate the efficacy and patient retention of a decentralized and simplified HCV care model implemented in a rural HOD in Cambodia.”

METHODS

Study design and participants
6. Moung Russei HOD has a total population of 213,392, composed of an adult population (≥18 years old) of 136,571 (64%) from 175 villages. Moung Russei HOD’s catchment area includes 13 health centers, each covering a catchment area with a median of 11 (IQR: 9, 13) villages and a population of 10001 (IQR: 7961, 12258) individuals, and supported by a district referral hospital in Moung Russei’s urban center. The median distance from any village to its corresponding catchment health center is 8km (IQR: 4, 14), and from any health center to the referral hospital is 10km (IQR: 7, 25).

7. The MSF pilot HCV testing and treatment project was implemented in March 2018. It was integrated in Moung Russei’s 13 rural health centers 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 centers and referral hospital. Voluntary HCV screening (with some restrictions, described below) was initiated for all patients presenting at health centers. Simple pre-treatment evaluation was performed at the HCV clinic, and differentiated follow-up was performed at either the health centers or the HCV clinic depending on the complexity of the patient’s treatment requirements (described below).

8. All screening material and DAAs were supplied by MSF. The health centers and referral hospital imposed a service fee for patients: 5,000 Riel (1.25 USD) for screening and 25,000 Riel (6.25 USD) for consultation. Fees were waived for patients holding Cambodian government identification card for low wage individual.

9. Four nurse supervisors were hired by MSF to coordinate patient management along the care continuum, logistics for the health centers, and some patient data collection.

10. This study cohort includes residents of Moung Russei HOD voluntarily screened between 12th March 2018-18th January 2019 at any health center. Although non-residents were also screened and treated in the project, they were not included in the study.
People aged ≥18 years 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 breast feeding and patients with tuberculosis were also ineligible for screening but were encouraged to return once eligible.

Cambodia NECHR ethically approved the evaluation of this project (reference: NO. 240NECHR and NO. 031NECHR). Opt-out consent was utilized, which did not affect the provision of a person’s HCV care.

**Procedures**

HCV screening started with pre-test counseling, and HCV serology testing was performed by rapid diagnosis test (RDT, SD Bioline®) with capillary blood (Figure 1). If positive, venous blood sample was drawn immediately and transported same day to the referral hospital laboratory for HCV viral load (VL) testing performed by GeneXpert®. HCV viremic (≥10IU/ml, lower quantifiable range of GeneXpert®) samples were also tested for Hepatitis B virus (HBV) surface antigen (HbsAg). HCV viremic 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 performed by a general practitioner at the HCV clinic, and only the most necessary pre-treatment assessments performed, as stipulated by the project’s medical standard operating procedures (SOP).

At pre-treatment assessment, patients received liver fibrosis staging evaluation using FibroScan® (Echosens, France). Serum creatinine testing was performed only for patients ≥50 years, those HbsAg-
positive, or with a baseline fibroscan result $\geq 20$ kPa. HbsAg-positive patients also received alanine aminotransferase (ALT) testing.

16. Decompensated cirrhosis was diagnosed if a patient had any indications of liver decompensation; being 1. History of: Use of diuretics, gastrointestinal bleeding, encephalopathy, edema, ascites, and/or 2. Current presence of: Abnormal vital signs, encephalopathy, edema, ascites, or jaundice.

17. Patients deemed eligible were prescribed sofosbuvir (400mg) and daclatasvir (60mg) (SOF+DCV), to be taken orally and daily for 12 weeks, or 24 weeks (patients with decompensated cirrhosis or previously treated with DAA).

18. Following pre-treatment assessment, differentiated care was performed according to the categorization of patients as either “simple” or “complicated” cases (Figure 1). “Complicated” cases were those with decompensated cirrhosis, previously treated with DAA, HBV coinfection, or other comorbidities requiring observation (e.g. eGFR<30mL/min/1.73m$^2$). Complicated patients were followed up at least once a month at the HCV clinic under general practitioner supervision, and provided with follow-up laboratory tests according to the patient’s condition. Patients designated as simple cases completed all follow-up at the health center at which they were originally screened, supervised by nursing staff. These appointments included checking for treatment adherence and side effect, 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.

19. Several modifications were made to the project model following lessons learned via emerging international evidence and on-the-ground experience.
20. The second medical SOP (SOP2) was implemented in October 2018 (see appendix p1). SOP2 included two major updates, being: 1) the definition of positive HCV VL at screening changed from $\geq 10\text{IU/mL}$ to $\geq 1000\text{IU/mL}$ based on WHO recommendations; and 2) We trialed no longer using FibroScan during pre-treatment consultations to assist diagnosis of decompensated cirrhosis. The viability of this change in clinical practice was assessed by performing Fibroscan after pre-treatment consultation to confirm the doctor’s original assessment. No clinical decisions were ultimately changed as a result of confirmatory FibroScan results.

21. In January 2019, the four MSF nurse supervisors in Moung Russei were replaced by a single Ministry of Health nurse when the project rolled-out to a neighboring HOD. Whilst this study only included patients initiated prior to January 2019, 148 patients still required follow-up after the nurse replacement.

22. From March 2019, patient tracing was stopped for patients not presenting for PT12 testing. High SVR12 achievement had already been demonstrated by this time, and patient tracing caused significant staff workload. Remaining active patients ($n=93$) were still provided with a PT12 appointment, those missing the appointment ($n=27$, 29.0%) were not contacted.

**Outcomes**

23. HCV cure was defined as sustained virological response at 12-weeks post-treatment (SVR12), being HCV VL<10IU/mL. Treatment failure was defined as HCV VL $\geq 10\text{IU/mL}$. Patients experiencing treatment failure were tested for HCV viral load again six months after PT12 testing, with blood samples stored for potential HCV genotype and drug resistance testing. Patients who still failed viral clearance will be contacted for potential future re-treatment, should second line treatment become available.
24. Treatment safety was assessed for serious and non-serious adverse events at any time between treatment initiation and 12 weeks post-treatment (PT12) testing. Non-serious adverse events (AE/s) were defined as events leading to temporary or permanent treatment discontinuation or modification of treatment. Serious adverse events (SAE/s) were defined as events leading to hospitalization, prolonging existing hospitalization, or death. AEs and SAEs were classified regardless of their association with DAA treatment. All SAE cases were reported to the Cambodia National Ethical Committee for Health Research (NECHR) for external review.

**Statistical analysis**

25. Patient screening and treatment data was paper-based, then entered into Research Electronic Data Capture (REDCap, Vanderbilt University, USA). Descriptive analysis was conducted using medians with inter-quartile ranges [IQR] for continuous variables and frequencies with percentage for categorical variables. Comparison between patients with HCV serology positive or negative results, and treatment follow-up locations, was performed using Mann-Whitney U test for continuous variables, and Fisher’s exact test/Chi-square test for categorical variables.

26. SVR12 rate was calculated among patients experiencing pre-defined “known outcomes”. Known outcomes included achieving SVR12, treatment failure at PT12, treatment stoppage for any reason (AE, lost-to-follow-up (LTFU) up to treatment completion), and death at any point between initiation and PT12 testing. LTFU after treatment completion were not considered a known outcome and were excluded from treatment effectiveness analysis. All known outcomes other than SVR12 were considered as treatment failure in analysis. SVR12 rates are presented by baseline and clinical characteristics. 95% Confidence Intervals (95%CI) for SVR12 were calculated using the Clopper-Pearson method for exact binomial distribution. Independent variable associating with treatment
failure were not examined, due to the small number of failures. All analysis was performed using SAS Version 9·4 (2002-2012, SAS Institute Inc., NC, USA.).

Role of the funding source

Funding for the study was provided by Médecins Sans Frontières (MSF, https://www.msf.org/). MZ, DO’K, JC, PJ, SB, TM, JPD, and MLP were employed by MSF, and participated in planning the study, carrying out the research, and writing the report. MZ, DO’K, JC, SB, TM, JPD, and MLP had access to the raw data.

RESULTS

Screening uptake and linkage to treatment

During the study period, 10,425 individuals (7·6% of the estimated adult population in Moung Russei HOD) were voluntarily screened at the health centers (Figure 2). Across the 13 rural health centers, screening uptake varied between 1·9% -26·2% among the adult population (see appendix p2). Of patients screened, median age was 44 years (IQR: 31-55); 778 (7·5%) were HCV antibody positive (Table 1). Nearly all antibody positive patients (n=761, 97·8%) received HCV VL testing, and 71% (n=540) of those tested were HCV viremic (Figure 2). Median turnaround time from HCV antibody positive diagnosis to obtaining HCV VL result was 1 weekday (IQR: 0, 10). Antibody positive patients were significantly older (58 years) than negative patients (40 years, p<0·0001, Table 1). No other significant differences according to antibody or VL test results were found.

Treatment initiation

Very high patient retention between screening and treatment initiation was observed, with 98·7% (n=533) of viremic patients attending a baseline consultation at the HCV clinic (Figure 2, 3). Nearly all patients (99·4%, n=530) initiated DAA treatment. Median turnaround time from HCV diagnosis
to treatment initiation was 5 weekdays (IQR: 3, 8). Most patients were initiated under SOP1 (85·3%, n=452), and 14·7% (n=78) were initiated under SOP2 (see appendix p1).

304 Of those initiating treatment, the median age was 58 years (IQR: 50·3, 63) (Table 2). One patient was previously treated with pegylated-interferon and ribavrin, but all others (99·8%, n=529) were treatment naive. Eleven (2·1%) patients were co-infected with HBV. Among cirrhotic patients (n=131), 10 (1·9%) had decompensated cirrhosis and were prescribed SOF+DAC 24-week course. All other patients (98·1%, n=520) were prescribed SOF+DCV12-week course (Figure 2).

309 There were 485 (91·5%) simple cases and 45 (8·5%) complicated cases (Table 2). Patients diagnosed as simple case followed-up at the health centers were significantly younger (median age: 57 years vs. 60 years, p=0·0074), less were with cirrhosis (21·7% vs. 59·1%, p<0·0001), and more presented baseline HCV VL ≥1,000,000 IU/ml (62·9% vs. 40·0%, p=0·0026).

313 Patient follow-up and adverse events

314 Two (0·4%) AEs (fatigue and stomach upset), and five (0·9%) SAEs were reported among patients initiated into treatment. Among patients experiencing SAEs, four were considered simple cases at treatment initiation and one was considered a complicated case. All SAEs were determined by doctor evaluation as being unrelated to the patient’s HCV treatment. The causes of SAEs were infection (two cases), cardiovascular disease, panic attack, and one event with cause data missing.

319 Treatment outcomes

320 Five-hundred-and-fifteen (97·2% of those initiated) patients completed treatment (Figure 3). The remaining 15 non-completing patients included four deaths, two treatment discontinuations due to AE, and nine LTFUs (Figure 2). Treatment completion rate was >93% regardless of the patient being classified as a simple or a complicated case.
Following treatment completion, 466 (90.5%) patients returned for PT12 testing (Figure 3). Of these patients, 459 (98.5%) achieved SVR12.

Four-hundred-eighty-one patients had known outcomes. Overall SVR12 rate was 95.4% (95%CI: 93.2, 97.1), with 96.2% (95%CI: 94, 97.8) and 85.3% (95%CI: 68.9, 95) among simple cases and complicated cases, respectively (Table 3). Across other baseline demographic and clinical characteristics, the SVR12 rate was consistently high (≥90%), except among patients with F4 cirrhosis (89.3%), diabetes history or baseline RBS ≥ 200mg/mL (89.1%), and patients initiated under SOP2 (82.4%).

**DISCUSSION**

This pilot project demonstrated high levels of patient retention, treatment efficacy and safety using a highly simplified model of non-specialist service delivery, in a rural, low-resource context via a decentralized 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.

The WHO has recommended simplified, decentralized models of diagnosis and treatment under a “treat-all” approach. By decentralizing HCV testing and treatment into rudimentary settings, the HCV project improved patient access. Two-thousand-three-hundred-and-eighty-three screenings of the HOD residents at the first month of implementation, and 9,048 in the first six months, shows the demand for HCV service (see appendix p3). A higher viremic rate in our study (5.2%) compared with the previous study conducted in the HOD (1.9%), suggests many patients knew their HCV positive status prior to presenting for screening. Two health centers unilaterally organized information campaigns, increasing their screening uptake. These campaigns were not a formal part of the project, but would likely be an effective strategy for similar interventions (see appendix p2).
38. The greater geographical accessibility, rapid, point-of-care diagnostics and reductions in patient consultations resulted in very high patient linkage and retention. Without a comparison group, the efficacy of our model could only be compared against real-world studies, in which case, our results are comparable or even improve upon other, similar real-world studies. Further, the model significantly reduced burden on staff, clinical and financial resources. Especially, the reduction in pre-treatment assessments suited the basic laboratory capacity, and task shifting most responsibilities onto nursing staff expanded the potential work force for HCV care. These improvements greatly increased programmatic coverage and the number of individuals that 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 performing initiation assessments in the health centers and immediately initiating uncomplicated cases.

39. SVR12 achievement was high (>=90%) across all patient sub-groups, except among patients with cirrhosis, followed-up at the HCV clinic (complicated case), initiated under SOP2, and with diabetes history or baseline high RBS. Unsurprisingly, patients with cirrhosis or diagnosed as complicated cases who had follow-up at the HCV clinic had lower SVR12 achievement. Liver cirrhosis is associated with increased risk of virological failure, with decompensated cirrhosis associated with a higher risk of death. Among complicated cases, 60% had liver cirrhosis, and of these, 37% had decompensated cirrhosis. Similarly, a higher percentage of patients with diabetes or high baseline RBS and initiated under SOP2 were among complicated cases compared with simple cases. Individuals living with HCV experience increased risk of developing diabetes, which in turn accelerates fibrosis progression.

40. The difference in treatment effectiveness between SOP1 and SOP2 is unlikely related to the exclusion of Fibroscan in determining simple and complicated cases. No clinical decisions were altered based on Fibroscan results that were used to validate the pre-treatment evaluation. The difference in
effectiveness rates between SOP1 & SOP2 are therefore potentially related to two factors. First, the adoption of SOP2, 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 LTFU during treatment (11·8% vs. SOP1: 0·7%, appendix p4). When only assessing patients who completed follow-up, 97·7% achieved viral clearance among SOP2 patients. Second, a significantly higher proportion of patients with decompensated cirrhosis presented during the second SOP compared to the first SOP (5.1% vs. 1.3%, p=0.045), which is related with higher risk of failure (see appendix p1). The reasons for higher percentage of decompensated cirrhotic patients during the SOP2 period, are unclear. Even so, with the inclusion of these patients good effectiveness rate (93·3%) maintained, after accounting for the increased LTFU 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 the resource limited context. While the examinations for fibrosis are unavailable or inaccessible, HCV treatment could still be initiated with high efficacy. However, we do recognize the importance of diagnosing liver cirrhosis to guide clinical decisions, follow-up of liver cirrhosis, and monitor hepatocellular carcinoma.

Limitations

Many non-residents of Moung Russei HOD presented for HCV screening (non-Moung Russei residents represented 49% of treatment initiations, but only constituted 15% of all patients screened during the first six months of implementation). Although they were not included in this study, this unexpectedly large number of patients, who very likely knew their HCV-positive status and traveled specially to Moung 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 Moung Russei HOD. However, without the presentation of these patients, the project may have been able to test and treat a much larger number of Moung Russei residents, thereby potentially limiting the numbers reported here.

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

44. The difference in HCV prevalence among patients presenting for screening, and the estimated prevalence for the wider HOD population suggests many presenting patients already knew their HCV status, or suspected themselves at risk of HCV positivity. This knowledge may have motivated them to seek screening and treatment, and therefore represents a potential bias in patient recruitment. It’s therefore possible that our study cohort is not entirely representative of the general population within the HOD. Even so, among the 10,425 patients screened as part of this study, only 761 were antibody positive, and 540 RNA positive, meaning a substantial majority of patients screened probably did not know their HCV status, and were still motivated to attend the health center, very likely due to the availability of the service.

**Conclusion**

45. This pilot project demonstrated that a highly simplified model of HCV care can be integrated within a rural public health system in an LMIC, enhancing accessibility, whilst maintaining short turnaround times, high patient retention, treatment efficacy and safety. The use of rapid diagnostics, non-specialist
clinical staff, minimal treatment evaluation tests including removal of fibrosis evaluation, and follow-up consultations, primarily delivered in highly accessible, decentralized rural health centers, maximized the number of patients tested and treated, whilst making efficient use of limited resources. If the WHO’s global elimination targets for viral hepatitis are to be reached, innovative methods of delivering HCV care are required, particularly outside of urban centers. This project provides a model that can be replicated in similar rural contexts in LMICs.

DATA SHARING STATEMENT

46. 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 (available at: http://fieldresearch.msf.org/msf/handle/10144/306501). Requests for access to data should be made to data.sharing@msf.org.

47. The study protocol is available on request for the medical coordinator of the project, at: msff-kh-comed@msf.paris.org.
References


Table 1. Screening outcomes (n=10425) from 13 health centers in Moung Russei health operational district, Battambang Province, Cambodia, March 2018- January 2019, by sex and age, n (%)

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<tr>
<td>45-54</td>
<td>2176 (20·9)</td>
<td>1979 (20·5)</td>
<td>197 (25·3)</td>
<td>196 (25·8)</td>
</tr>
<tr>
<td>55-64</td>
<td>1902 (18·2)</td>
<td>1596 (16·5)</td>
<td>306 (39·3)</td>
<td>300 (39·4)</td>
</tr>
<tr>
<td>65 and above</td>
<td>941 (9·0)</td>
<td>777 (8·1)</td>
<td>164 (21·1)</td>
<td>160 (21)</td>
</tr>
<tr>
<td>Total</td>
<td>10425</td>
<td>9647</td>
<td>778</td>
<td>761</td>
</tr>
</tbody>
</table>

& One HCV antibody positive patient missed information of sex.
** The median age of patients with negative and positive antibody test is significantly different, p<0·0001.
Table 2. Baseline characteristics among patients initiating HCV treatment (n=485) at the referral hospital, Moung RusseiHOD, Cambodia, March 2018- January 2019, by simple and complicated cases

<table>
<thead>
<tr>
<th></th>
<th>Simple case</th>
<th>Complicated case</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>485 (100)</td>
<td>45 (100)</td>
<td>530 (100)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>291 (60)</td>
<td>32 (71·1)</td>
<td>323 (60·9)</td>
</tr>
<tr>
<td>Male</td>
<td>194 (40)</td>
<td>13 (28·9)</td>
<td>207 (39·1)</td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td>58 (50·3, 63)*</td>
</tr>
<tr>
<td>&lt;45</td>
<td>58 (12)</td>
<td>4 (8·9)</td>
<td>62 (11·7)</td>
</tr>
<tr>
<td>45-54</td>
<td>139 (28·6)</td>
<td>5 (11·1)</td>
<td>144 (27·2)</td>
</tr>
<tr>
<td>55-64</td>
<td>197 (40·6)</td>
<td>20 (44·4)</td>
<td>217 (40·9)</td>
</tr>
<tr>
<td>≥65</td>
<td>91 (18·8)</td>
<td>16 (35·6)</td>
<td>107 (20·2)</td>
</tr>
<tr>
<td><strong>FS (kPa) (n=527)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>7·7 (5·4, 13)</td>
<td>21 (7·4, 39·5)</td>
<td>7·9 (5·5, 14)</td>
</tr>
<tr>
<td>F0: 1kPa</td>
<td>84 (17·4)</td>
<td>4 (9·1)</td>
<td>88 (16·7)</td>
</tr>
<tr>
<td>F1: 2-8kPa</td>
<td>135 (28)</td>
<td>7 (15·9)</td>
<td>142 (26·9)</td>
</tr>
<tr>
<td>F2: 8-1-9kPa</td>
<td>83 (17·2)</td>
<td>2 (4·5)</td>
<td>85 (16·1)</td>
</tr>
<tr>
<td>F3: 9-1-14kPa</td>
<td>76 (15·7)</td>
<td>5 (11·4)</td>
<td>81 (15·4)</td>
</tr>
<tr>
<td>F4: ≥14-1kPa^</td>
<td>105 (21·7)</td>
<td>26 (59·1)</td>
<td>131 (24·9)**</td>
</tr>
<tr>
<td><strong>HCV viral load</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(IU/mL)</td>
<td>14·6 (13, 15·6)</td>
<td>13·4 (12·3, 15·4)</td>
<td>14·5 (12·8, 15·5)</td>
</tr>
<tr>
<td>≥1 million</td>
<td>305 (62·9)</td>
<td>18 (40)</td>
<td>323 (60·9)**</td>
</tr>
<tr>
<td><strong>BMI (kg/cm²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=525)**</td>
<td>23·4 (20·8, 26·3)</td>
<td>21·9 (19·7, 25·4)</td>
<td>23·3 (20·8, 26·3)</td>
</tr>
<tr>
<td>Normal: &lt;23</td>
<td>222 (46·1)</td>
<td>27 (61·4)</td>
<td>249 (47·4)</td>
</tr>
<tr>
<td>Overweight: 23-27·4</td>
<td>187 (38·9)</td>
<td>9 (20·4)</td>
<td>196 (37·3)</td>
</tr>
<tr>
<td>Obese: ≥27·5</td>
<td>72 (15·0)</td>
<td>8 (18·2)</td>
<td>80 (15·3)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed Diabetes^&amp;</td>
<td>36 (7·4)</td>
<td>7 (15·6)</td>
<td>43 (8·1)</td>
</tr>
<tr>
<td>No history of diabetes</td>
<td>14 (2·9)</td>
<td>..</td>
<td>14 (2·6)</td>
</tr>
<tr>
<td>but RBS≥200mg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension^$</strong></td>
<td>115 (23·7)</td>
<td>15 (33·3)</td>
<td>130 (24·5)</td>
</tr>
</tbody>
</table>

*p=0.0074, ** p<0.0001, ***p=0.0026

^ Patients with missing data is not included here.

^ It was compared between F4 (cirrhotic) and F0-F3 (non-cirrhotic) patients.

^& Previously diagnosed diabetes, with/without blood sugar controlled at baseline evaluation.

^$ Previously diagnosed hypertension, with/without blood pressure controlled at baseline evaluation.

FS: FibroScan; VL: viral load; BMI: body-mess-index; RBS: random blood sugar.
Table 3. SVR12 rate among patients with known outcomes (n=481), Moung Russei HOD, Cambodia, March 2018- January 2019, by baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SVR12/patients with known outcomes*</th>
<th>SVR12% (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>459/ 481</td>
<td>95·4 (93·2, 97·1)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>168/ 181</td>
<td>92·8 (88, 96·1)</td>
</tr>
<tr>
<td>Female</td>
<td>291/ 300</td>
<td>97 (94·4, 98·6)</td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>107/ 108</td>
<td>99·1 (94·9, 100)</td>
</tr>
<tr>
<td>≥50</td>
<td>352/ 373</td>
<td>94·4 (91·5, 96·5)</td>
</tr>
<tr>
<td><strong>Cirrhosis status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0-F3</td>
<td>356/ 366</td>
<td>97·3 (96·0, 98·7)</td>
</tr>
<tr>
<td>F4</td>
<td>100/ 112</td>
<td>89·3 (82·0, 94·3)</td>
</tr>
<tr>
<td><strong>HCV viral load (IU/mL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1,000,000</td>
<td>177/ 185</td>
<td>95·7 (91·7, 98·1)</td>
</tr>
<tr>
<td>≥1,000,000</td>
<td>282/ 296</td>
<td>95·3 (92·2, 97·4)</td>
</tr>
<tr>
<td><strong>BMI (kg/cm²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;23</td>
<td>210/ 222</td>
<td>94·6 (90·7, 97·2)</td>
</tr>
<tr>
<td>≥23</td>
<td>246/ 255</td>
<td>96·5 (93·4, 98·4)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes history or baseline RBS≥200mg/mL</td>
<td>41/ 46</td>
<td>89·1 (76·4, 96·4)</td>
</tr>
<tr>
<td>No diabetes history nor RBS≥200mg/mL</td>
<td>418/ 435</td>
<td>96·1 (93·8, 97·7)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed hypertension</td>
<td>106/ 116</td>
<td>91·4 (84·7, 95·8)</td>
</tr>
<tr>
<td>No history of hypertension</td>
<td>353/ 365</td>
<td>96·7 (94·3, 98·3)</td>
</tr>
<tr>
<td><strong>Coinfection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV monoinfection</td>
<td>449/ 470</td>
<td>95·5 (93·3, 97·2)</td>
</tr>
<tr>
<td>HBV coinfection</td>
<td>10/ 11</td>
<td>90·9 (58·7, 99·8)</td>
</tr>
<tr>
<td><strong>Case definition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple case</td>
<td>430/ 447</td>
<td>96·2 (94, 97·8)</td>
</tr>
<tr>
<td>Complicated case</td>
<td>29/ 34</td>
<td>85·3 (68·9, 95)</td>
</tr>
<tr>
<td><strong>SOP used for the treatment initiation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOP1</td>
<td>417/ 430</td>
<td>97 (94·9, 98·4)</td>
</tr>
<tr>
<td>SOP2</td>
<td>42/ 51</td>
<td>82·4 (69·1, 91·6)</td>
</tr>
</tbody>
</table>

* Known outcomes include: achieving SVR12, treatment failure at PT12, treatment stoppage for any reason (adverse event, lost-to-follow-up up to treatment completion), and death at any point between initiation and PT12 testing.

† Patients missing or without valid result of BMI and FibroScan were not shown.

§ Patients initiated before 1 Oct 2018 was under the care of SOP1, and patients initiated after was under the care of SOP2.

SVR12: post-treatment 12 weeks; RBS: random blood sugar; SOP: standard operational procedure
**Figure 1. Treatment flows for simple and complicated cases evaluated at pre-treatment consultation**

- Only patients with positive HCV antibody result were down venous blood sample for HCV viral load test.
- Simple case were patients with only HCV infection without conditions as the complicated case that required follow-up with a doctor.
- Complicated cases were patients with decompensated cirrhosis, HBV co-infection, previously treated with DAA, and comorbidities that required medical attention.
- Other visits might required according to patient’s condition and doctor’s decision.
Enrolled in the study^ 
\[N=10425\]

RDT HCV antibody positive 
\[N=778 \ (7.5\%\)]

Sample collected for HCV PCR 
\[n=761 \ (97.8\%)\]

HCV viremic 
\[N=540 \ (71.0\%)\]

Consultation with GP at HCV clinic (RH) 
\[N=533 \ (98.7\%)\]

Initiated DAA 
\[N=530 \ (99.4\%)\]

Blood sample not collected \((n=17)\): 
- Refused: \(n=5\)
- LTFU: \(n=6\)
- Not eligible for screening: \(n=4\)
- Death: \(1\)
- Unknown: \(n=1\)

No linkage to care \((n=7)\):
- Refused: \(n=2\)
- LTFU: \(n=1\)
- Not eligible for screening: \(n=2\)
- Death: \(n=1\)
- Unknown: \(n=1\)

Not eligible for treatment \((n=3)\):
- Not eligible for screening: \(n=2\)
- Poor overall condition: \(n=1\)

**Figure 2. Study flowchart from enrollment to treatment outcomes following the screening and follow-up pathways**

^1650 patients received HCV care during the study period, but were not enrolled in the study, including: 4 patients opt-out from the study, and 1646 non-residents of Moung Russei Health Operational District.

HC: health center; SOF+DCV: sofosbuvir and daclatasvir; 12w: 12 weeks; 24w: 24 weeks; LTFU: lost-to-follow-up; M1: treatment month 1; M2: treatment month 2; SVR12: sustained viral response at 12 weeks post-treatment.
Figure 3. Cascade of project activity from screening uptake to cure in Moung Russei health operational district

& The total Moung Russei health operational district adult population (age ≥18years).