

Find the Missing Millions: Malaysia's experience with nationwide hepatitis C screening campaign in the general population

Rosaida Md Said¹ | Rozainanee Mohd Zain² | Huan-Keat Chan³  | Shahrul Aiman Soelar³ | Norhayati Rusli⁴ | Nazrila Hairizan Nasir⁵ | Rozita Zakaria⁶ | Muhammad Radzi Abu Hassan⁷

¹Medical Department, Hospital Ampang, Ampang, Malaysia

²Virology Unit, Infectious Disease Research Center, Institute for Medical Research, Kuala Lumpur, Malaysia

³Clinical Research Center, Sultanah Bahiyah Hospital, Alor Setar, Malaysia

⁴Disease Control Division, Ministry of Health, Putrajaya, Malaysia

⁵Family Health Development Division, Ministry of Health, Putrajaya, Malaysia

⁶Putrajaya Health Clinic, Putrajaya, Malaysia

⁷Medical Department, Hospital Sultanah Bahiyah, Alor Setar, Malaysia

Correspondence

Huan-Keat Chan, Clinical Research Center, Sultanah Bahiyah Hospital, 05460 Alor Setar, Kedah, Malaysia.
Email: huankeat123@yahoo.com

Abstract

Approximately 2.5% of the Malaysian population is currently living with hepatitis C virus (HCV) infection. Yet, the public awareness of the disease is limited and under-screening remains a major challenge. With the support of international non-for-profit organizations, the Ministry of Health in Malaysia recently launched a one-week nationwide hepatitis C screening campaign in conjunction with the World Hepatitis Day. For the first time, the rapid diagnostic test (RDT) for HCV screening was introduced in public health institutions. This campaign involved 49 hospitals and 38 health clinics across the country, targeting the adult general population with unknown HCV infection status. Of the 11 382 participants undergoing the RDT, 1.9% were found to be positive for hepatitis C antibody (anti-HCV) and were referred to on-site medical departments or nearby hospitals for confirmatory testing and treatment. Men, the Malay ethnic group, intranasal and injection drug users and ex-prisoners were shown to have higher odds of being positive for anti-HCV. In addition to serving as a model to educate the general population about the disease, this campaign demonstrates the feasibility of decentralizing HCV screening, particularly by promoting the use of RDT, and linking the HCV-infected patients to care in Malaysia.

KEYWORDS

diagnostic screening programmes, hepatitis C, Malaysia, point-of-care testing

1 | INTRODUCTION

Since the discovery of hepatitis C virus (HCV) back in 1989, hepatitis C has been a global public health concern.¹ Approximately 3% of the world population is currently infected with HCV. HCV

infection often develops into chronic hepatitis over time, claiming 350 000-500 000 lives annually.² Cirrhosis and hepatocellular carcinoma, two of the common life-threatening complications of chronic hepatitis, are estimated to have affected 30% and up to 8% of the HCV-infected individuals, respectively.^{3,4} However, at least one-third of the HCV-infected individuals in many countries, including Malaysia, are still unaware of their conditions.⁵⁻⁷ Meanwhile, less than half of them had received adequate medical care.⁶

Abbreviations: CIs, confidence intervals; CL, compulsory licence; CSOs, civil society organizations; DAAs, direct-acting antivirals; DNDi, Drugs for Neglected Diseases initiative; FIND, Foundation for Innovative New Diagnostics; HCV, hepatitis C virus; MOH, Ministry of Health; ORs, odds ratios; PWID, persons who inject drugs; RDT, rapid diagnostic test; TRIPS, Trade-Related Aspects of Intellectual Property Rights; WHO, World Health Organization.

Following the advent of the highly effective treatment with direct-acting antivirals (DAAs), the World Health Organization (WHO) has set a goal for the elimination of hepatitis C by 2030.⁸ As a country with approximately 2.5% of its population infected with HCV,⁹ Malaysia has been actively taking steps towards achieving this goal. Together with the Foundation for Innovative New Diagnostics (FIND) and the Drugs for Neglected Diseases initiative (DNDi), the Ministry of Health (MOH) in Malaysia is currently working on decentralizing HCV screening using a pre-qualified rapid diagnostic test (RDT) and linking the HCV-seropositive individuals to confirmatory testing and treatment. In 2017, the Malaysian government also invoked the Agreement on the Trade-Related Aspects of Intellectual Property Rights (TRIPS) and issued a compulsory licence (CL) for sofosbuvir,¹⁰ the backbone of a wide range of DAA-based regimens. This has since then allowed the use of the generic equivalent of sofosbuvir in public health institutions across the country.

Despite all the efforts made, the awareness of hepatitis C is still considerably lacking and under-screening remains a major challenge in Malaysia.^{11,12} Therefore, in collaboration with the FIND and DNDi, the MOH recently launched a one-week nationwide hepatitis C screening campaign. In addition to promoting the public awareness of the disease, this campaign aimed to provide insight into the effectiveness of a population-based screening programme in identifying HCV-infected individuals and the associated factors for HCV infection in the country.

2 | MATERIALS AND METHODS

The screening campaign was conducted between 15 and 21 July 2019 in conjunction with the World Hepatitis Day. Forty-nine public hospitals and 38 public health clinics located in all the 14 states in the country participated in this campaign.

The SD Bioline HCV rapid test kits (sensitivity = 99.3%; specificity = 98.1%) used in this campaign were provided by the FIND in support of the country's efforts to upscale the screening and treatment for hepatitis C.¹³ All the screening activities were performed in the existing health facilities by medical staff, including doctors, nurses and medical assistants, who had received training on the use of rapid test kits prior to the campaign. The adult population (≥ 18 years of age) with unknown HCV infection status was the main target of the campaign. The involved hospitals and clinics were also encouraged to reach out to at-risk groups in need of screening by engaging civil society organizations (CSOs).

Pre-test counselling was given to the individual participants who consented to be enrolled in the campaign, with the aim to inform them of the purpose of the screening, the data collection procedures and the measures taken to ensure confidentiality. Their information regarding sociodemographic characteristics and the exposure to risk factors of hepatitis C was gathered through an anonymous survey. The participants were required to complete a structured, self-administered questionnaire, which consisted

a list of risk factors of hepatitis C adopted from the Hepatitis C Elimination through Access to Diagnostics (HEAD-Start) project (Table 1).¹⁴ The survey was conducted in a designated area in each centre, and only trained medical staff were involved in the data collection.

The presence of hepatitis C antibody (anti-HCV) was mainly confirmed through the RDT, using capillary blood collected by finger-pricking with a lancet. Alternatively, venous blood was used as a sample for the RDT in the participants who required laboratory assessments for other medical conditions at the same time. Post-test counselling was also given to all the participants, mainly to inform them of the screening results and educate them about healthy lifestyle. Those who were positive for anti-HCV were subsequently referred to on-site medical departments or nearby hospitals for confirmatory testing and further management.

The data analysis was performed using the R-3.5.1 for Windows. All the categorical variables were summarized as frequencies and percentages. The backward stepwise multiple logistic regression analysis was applied to determine the factors associated with the anti-HCV status of the participants. This was preceded by the simple logistic regression analysis to identify the potential significant factors. It was ensured that multicollinearity and interaction were not present in the final model. The finding of the Hosmer-Lemeshow goodness-of-fit test, the overall correctly classified percentage and the area under the receiver operating characteristic curve were also used to confirm the model fitness. The final results were presented as crude and adjusted odds ratios (ORs), along with their corresponding 95% confidence intervals (CIs) and *P*-values.

3 | RESULTS

Of the 11 382 participants undergoing the RDT, nearly half were in the age range of 30-59 years. More than 60% of them were female and of Malay ethnicity. Having a history of invasive medical procedures (17.3%) and body piercing (12.4%) was found to be the most common risk factor of hepatitis C among the participants (Table 1). A total of 11,523 tests, including 141 (1.2%) repeated for invalid results, were performed. The majority (99.2%) of the participants provided a finger-prick sample for the RDT, while the rest were screened using their venous blood.

Two hundred and twenty (1.9%) of the participants were found to be positive for anti-HCV. Men were shown to have 6.42 times higher odds (95% CI: 3.94, 10.92) of being positive for anti-HCV as compared with women. The Malay ethnic group also had a higher tendency of being positive for anti-HCV than did the Chinese ethnic group (adjusted OR: 2.42; 95% CI: 1.28, 4.92). As they would be expected, intranasal illicit drug users (adjusted OR: 4.92; 95% CI: 2.77, 8.57), persons who inject drugs (PWID) (adjusted OR: 135.47; 95% CI: 88.94, 209.09) and ex-prisoners (adjusted OR: 2.34; 95% CI: 1.19, 4.64) were also more likely to be positive for anti-HCV (Table 2).

TABLE 1 Patient characteristics and results of rapid diagnostic tests

Variables	Total n	RDT results		
		Negative	Positive	NA
		n (%)	n (%)	n (%)
Total	11 382	11 159 (98.0)	220 (1.9)	3 (0.0)
Age, years				
<30	2409	2379 (20.9)	28 (0.2)	2 (0.0)
30-39	3418	3344 (29.4)	73 (0.6)	1 (0.0)
40-49	2244	2182 (19.2)	62 (0.5)	0 (0.0)
50-59	1821	1778 (15.6)	43 (0.4)	0 (0.0)
≥60	1486	1472 (12.9)	14 (0.1)	0 (0.0)
NA	4	4 (0.0)	0 (0.0)	0 (0.0)
Gender				
Male	4293	4094 (36.0)	199 (1.7)	0 (0.0)
Female	7082	7058 (62.0)	21 (0.2)	3 (0.0)
NA	7	7 (0.1)	0 (0.0)	0 (0.0)
Ethnicity				
Malay	7116	6948 (61.0)	166 (1.5)	2 (0.0)
Chinese	1873	1856 (16.3)	17 (0.1)	0 (0.0)
Indian	769	760 (6.7)	8 (0.1)	1 (0.0)
Others	1617	1588 (14.0)	29 (0.3)	0 (0.0)
NA	7	7 (0.1)	0 (0.0)	0 (0.0)
Nationality				
Malaysian	11 294	11 072 (98.0)	219 (1.9)	3 (0.0)
Non-Malaysian	87	86 (98.9)	1 (1.1)	0 (0.0)
NA	1	1 (100.0)	0 (0.0)	0 (0.0)
History of invasive medical procedures				
Yes	1967	1924 (16.9)	43 (0.4)	0 (0.0)
No	9415	9235 (81.1)	177 (1.6)	3 (0.0)
History of body piercing				
Yes	1412	1386 (12.2)	25 (0.2)	1 (0.0)
No	9970	9773 (85.9)	195 (1.7)	2 (0.0)
History of receiving blood/blood products/clotting factor concentrations/organ transplant before 1994 ^a				
Yes	494	480 (4.2)	14 (0.1)	0 (0.0)
No	10 888	10 679 (93.8)	206 (1.8)	3 (0.0)
History of tattooing				
Yes	389	347 (3.0)	42 (0.4)	0 (0.0)
No	10 993	10 812 (95.0)	178 (1.6)	3 (0.0)
History of needle stick injury or mucosal exposure to HCV-infected blood				
Yes	267	262 (2.3)	5 (0.0)	0 (0.0)
No	11 115	10 897 (95.7)	215 (1.9)	3 (0.0)
History of intranasal illicit drug use				
Yes	238	165 (1.5)	73 (0.6)	0 (0.0)
No	11 144	10 994 (96.6)	147 (1.3)	3 (0.0)
History of injection drug use				

(Continues)

TABLE 1 (Continued)

Variables	Total n	RDT results		
		Negative n (%)	Positive n (%)	NA n (%)
Total	11 382	11 159 (98.0)	220 (1.9)	3 (0.0)
Yes	197	57 (0.5)	140 (1.2)	0 (0.0)
No	11 185	11 102 (97.5)	80 (0.7)	3 (0.0)
History of imprisonment				
Yes	134	76 (0.7)	58 (0.5)	0 (0.0)
No	11 248	11 083 (97.4)	162 (1.4)	3 (0.0)
History of chronic liver disease and/or hepatitis				
Yes	98	89 (0.8)	9 (0.1)	0 (0.0)
No	11 284	11 070 (97.3)	211 (1.9)	3 (0.0)
History of HIV infection				
Yes	86	77 (0.7)	9 (0.1)	0 (0.0)
No	11 296	11 082 (97.4)	211 (1.9)	3 (0.0)
History of having man-with-man sex				
Yes	74	68 (0.6)	6 (0.1)	0 (0.0)
No	11 308	11 091 (97.4)	214 (1.9)	3 (0.0)
History of having an HCV-infected partner				
Yes	55	53 (0.5)	2 (0.0)	0 (0.0)
No	11 327	11 106 (97.6)	218 (1.9)	3 (0.0)
History of working as a sex worker				
Yes	24	22 (0.2)	2 (0.0)	0 (0.0)
No	11 358	11 137 (97.8)	218 (1.9)	3 (0.0)
Long-term haemodialysis				
Yes	23	23 (0.2)	0 (0.0)	0 (0.0)
No	11,359	11,136 (97.8)	220 (1.9)	3 (0.0)
Born to an HCV-infected mother				
Yes	19	19 (0.2)	0 (0.0)	0 (0.0)
No	11 363	11 140 (97.9)	220 (1.9)	3 (0.0)
Being transgender				
Yes	16	14 (0.1)	2 (0.0)	0 (0.0)
No	11 366	11 145 (97.9)	218 (1.9)	3 (0.0)

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; NA, not available (incomplete documentation); RDT, rapid diagnostic test.

^aThe year in which viral hepatitis screening was mandated to be performed in blood, blood products, clotting factor concentrations and organ transplant.

4 | DISCUSSION

This campaign represents the first time that a highly sensitive and specific rapid test kit was introduced for HCV screening in public health institutions in Malaysia. The proportion of anti-HCV-positive patients found in this campaign (1.9%) was close to the estimated prevalence of hepatitis C in Malaysia (2.5%) and was remarkably higher than those reported in similar screening campaigns targeting the general population (0.6%-1.14%).^{15,16} While the increasing patient load poses a challenge to public hospitals, the finding indicates that, with adequate support and guidance, the decentralization

of hepatitis C management is possible in Malaysia. Apart from the expected risk factors of hepatitis C such as the history of injection drug use and imprisonment,¹⁷ the finding also demonstrates marked gender and ethnic differences in the anti-HCV status of the general population in Malaysia. Such information could help policymakers better understand the epidemiology of HCV infection in the country and provide them with a basis for targeted interventions.

While under-diagnosis remains the largest gap in the cascade of care for hepatitis C worldwide,¹⁸ this collaborative initiative could also serve as a model to improve the public awareness of the disease. In addition to the ongoing clinical trials, the success of this

TABLE 2 Factors associated with positive rapid diagnostic test results, and simple and multiple logistic regression analyses

Variables	Simple logistic regression			Multiple logistic regression ^a		
	Crude OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Gender						
Male	16.34	10.67, 26.42	<.001	6.42	3.94, 10.92	<.001
Female	1.00	-	-	1.00	-	-
Ethnicity						
Malay	2.61	1.63, 4.47	<.001	2.42	1.28, 4.92	.010
Chinese	1.00	-	-	1.00	-	-
Indian	1.15	0.47, 2.60	.747	2.50	0.87, 6.68	.074
Others	1.99	1.10, 3.72	.025	1.47	0.65, 3.42	.355
History of intranasal illicit drug use						
Yes	33.09	23.96, 45.47	<.001	4.92	2.77, 8.57	<.001
No	1.00	-	-	1.00	-	-
History of injection drug use						
Yes	340.85	235.03, 501.39	<.001	135.47	88.94, 209.09	<.001
No	1.00	-	-	1.00	-	-
History of imprisonment						
Yes	52.21	35.79, 75.92	<.001	2.34	1.19, 4.64	.014
No	1.00	-	-	1.00	-	-

Abbreviations: CI, confidence interval; OR, odds ratio.

^aOnly the participants with complete data for all the listed variables (n = 11 366) were included in the backward stepwise logistic regression analysis. Multicollinearity and interaction were checked and not found. The Hosmer-Lemeshow goodness-of-fit test (P = .417), overall correctly classified percentage (95.3%) and area under the receiver operating characteristic curve (92.4%) were applied to check the model fitness.

campaign suggests that using public health approaches to upscale the screening for hepatitis C could be a new form of long-term partnership between Malaysia and international non-for-profit organizations. Although risk-based screening, as demonstrated in a systematic review, is likely to be more cost-effective than population-based screening for hepatitis C as a long-term strategy in the real-world settings (<£30 000 vs >£30 000 per quality-adjusted life year),¹⁹ this campaign shows that the cost of a nationwide, population-based screening programme could be minimized through such a partnership. In fact, the total expenditure on this campaign was only MYR 71 500 (£13 280), a large portion (76.9%) of which was spent on the rapid test kits and funded by non-for-profit organizations.

It is also noteworthy that this campaign went beyond screening. Over the one-week period, all the anti-HCV-positive patients identified had been referred for confirmatory testing and, if necessary, further assessment of the need for treatment. As a sofosbuvir-based regimen is available at a cost of less than US\$300 per course while the CL is still valid,²⁰ it is timely for the MOH to massively scale up the hepatitis C treatment in Malaysia. Even though a follow-up is required to evaluate the commitment of the participants in this campaign to the subsequent management, linking the HCV-infected patients to early treatment is essential for Malaysia to achieve the WHO's elimination target by 2030. Besides complementing the routine screening, the additional value of this campaign in educating the

general population about the disease and familiarizing them with the services and treatment available in public health institutions should also not be overlooked.

Another point worth highlighting is the involvement of the medical staff of the MOH in this campaign. Although this clearly served as a means to minimize the operation cost of the campaign, it is arguable that the routine health services were not affected due to limited manpower. Hence, in order to optimize the resource utilization without compromising the quality of services in public health institutions, the MOH could consider integrating the viral hepatitis programme into the existing HIV infection programme, as highly recommended by the US Substance Abuse and Mental Health Services Administration.²¹ Moreover, it is important to acknowledge the contributions of CSOs in this campaign. Consistent with the previous findings,²² CSOs were found to play an active role in increasing the screening uptake among high-risk groups, particularly PWID and persons living with HIV. It is noted that the hospitals and clinics engaging CSOs were more likely to capture high-risk groups for HCV screening in this campaign. Again, this implies that multi-organizational participation is of great significance in pushing the agenda of hepatitis C elimination in Malaysia.

The major limitation of this screening campaign lies in its coverage, as the screening services might not be accessible to those who were unaware of this campaign or unable to make a visit to public health institutions. Therefore, the MOH has a plan to expand the

screening services to community-based outreach agencies and private health institutions in the second phase of the campaign. It was also challenging to have all the high-risk behaviours truthfully reported by using a self-administered questionnaire. Hence, in the next phase of the campaign, a one-to-one session in a private area could be introduced to obtain the history of high-risk behaviours of participants.

In conclusion, this nationwide HCV screening campaign represents a successful collaborative initiative between the MOH in Malaysia and international non-for-profit organizations. In addition to getting the general population acquainted with the disease and identifying more than 200 potentially HCV-infected individuals, this campaign demonstrates the feasibility of decentralizing HCV screening, especially by promoting the use of RDT, and linking the HCV-infected patients to care in Malaysia.

ACKNOWLEDGEMENTS

We would like to thank Datuk Dr Noor Hisham bin Abdullah, the Director-General of Health, Malaysia, for his support and advice throughout the conduct of the screening campaign. We would also like to thank the FIND and Unitaidd for providing us with the rapid diagnostic kits. The DNDi and Pharmaniaga are also acknowledged for their contribution to the transportation and distribution of the rapid diagnostic kits. We also appreciate all the assistance we received from the staff in the Ministry of Health, Malaysia.

ORCID

Huan-Keat Chan  <https://orcid.org/0000-0001-6710-7257>

REFERENCES

- Houghton M. Hepatitis C. Virus: 30 years after its discovery. *Cold Spring Harb Perspect Med*. 2019;9(12):a037069.
- Moosavy SH, Davoodian P, Nazarnezhad MA, Nejatizadeh A, Eftekhari E, Mahboobi H. Epidemiology, transmission, diagnosis, and outcome of hepatitis C virus infection. *Electron Physician*. 2017;9(10):5646-5656.
- Gordon SC, Lamerato LE, Rupp LB, et al. Prevalence of cirrhosis in hepatitis C patients in the chronic hepatitis cohort study (CHeCS): a retrospective and prospective observational study. *Am J Gastroenterol*. 2015;110(8):1169-1177; quiz 1178.
- Baumert TF, Juhling F, Ono A, Hoshida Y. Hepatitis C-related hepatocellular carcinoma in the era of new generation antivirals. *BMC Med*. 2017;15(1):52-52.
- Holmberg SD. Hepatitis C virus and the infectious diseases community. *Clin Infect Dis*. 2012;55(Suppl 1):S1-S2.
- Cheng PN, Chiu YC, Chiu HC, Chien SC. The characteristics of residents with unawareness of hepatitis C virus infection in community. *PLoS ONE*. 2018;13(2):e0193251.
- World Hepatitis Alliance. HCV Quest Country-Specific Report – Malaysia. 2015. <https://www.worldhepatitisalliance.org/hcv-quest-global-patient-survey-malaysia-ms-report>. Accessed 16 December 2019.
- Popping S, Bade D, Boucher C, et al. The global campaign to eliminate HBV and HCV infection: International Viral Hepatitis Elimination Meeting and core indicators for development towards the 2030 elimination goals. *J Virus Erad*. 2019;5(1):60-66.
- McDonald SA, Dahlui M, Mohamed R, Naning H, Shabaruddin FH, Kamarulzaman A. Projections of the current and future disease burden of hepatitis C virus infection in Malaysia. *PLoS ONE*. 2015;10(6):e0128091.
- Ooms G, Hanefeld J. Threat of compulsory licenses could increase access to essential medicines. *BMJ*. 2019;365:2098.
- Muhamad Radzi AH, Tan SS, Mohamed R, et al. Hepatitis screening and treatment campaign in Malaysia-validation of low-cost point of care screening tests and nucleic acid tests for hepatitis B and C. *Euroasian J Hepatogastroenterol*. 2018;8(2):101-107.
- Raihan R. Hepatitis in Malaysia: past, present, and future. *Euroasian J Hepatogastroenterol*. 2016;6(1):52-55.
- Abbott. SD Bioline HCV (product sheet). 2019. <https://www.alere.com/en/home/product-details/sd-bioline-hcv.html>. Accessed 16 December 2019.
- Drugs for Neglected Diseases initiative. FIND and DNDi team up to support Malaysian MOH efforts to simplify and decentralize hepatitis C screening & treatment. 2018. <https://www.dndi.org/2018/media-centre/press-releases/find-dndi-malaysianmoh-efforts-hepatitis-c-screening-treatment/>. Accessed 16 December 2019.
- Kileng H, Gutteberg T, Goll R, Paulssen EJ. Screening for hepatitis C in a general adult population in a low-prevalence area: the Tromsø study. *BMC Infect Dis*. 2019;19(1):189.
- Gomez-Escolar Viejo L, Garcia Herola A, Saez Lloret I, et al. Screening of hepatitis C virus infection in adult general population in Spain. *Eur J Gastroenterol Hepatol*. 2018;30(9):1077-1081.
- Mohd Suan MA, Said SM, Lim PY, Azman AZF, Abu Hassan MR. Risk factors for hepatitis C infection among adult patients in Kedah state, Malaysia: A case-control study. *PLoS ONE*. 2019;14(10):e0224459.
- Terrault NA. Hepatitis C elimination: challenges with under-diagnosis and under-treatment. *F1000Res*. 2019;8:54. pii: F1000 Faculty Rev-54.
- Coward S, Leggett L, Kaplan GG, Clement F. Cost-effectiveness of screening for hepatitis C virus: a systematic review of economic evaluations. *BMJ Open*. 2016;6(9):e011821.
- Hassan MRA, Chan HK. Comment on: "Projections of the health-care costs and disease burden due to hepatitis C infection under different treatment policies in Malaysia, 2018-2040". *Appl Health Econ Health Policy*. 2019;18(1):139-140.
- Center for Substance Abuse Treatment. *Addressing Viral Hepatitis in People with Substance Use Disorders*. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2011; 61-72.
- Maistat L, Kravchenko N, Reddy A. Hepatitis C in Eastern Europe and Central Asia: A survey of epidemiology, treatment access and civil society activity in eleven countries. *Hepatol Med Policy*. 2017;2:9.

How to cite this article: Md Said R, Mohd Zain R, Chan H-K, et al. Find the Missing Millions: Malaysia's experience with nationwide hepatitis C screening campaign in the general population. *J Viral Hepat*. 2020;00:1-6. <https://doi.org/10.1111/jvh.13267>