Letter to the Editor

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# Cross-country migration linked to people who inject drugs challenges the long-term impact of national HCV elimination programmes

*To the Editor:*

As of 2018, the majority of Western European countries – including Spain – have lifted restrictions to therapy based on disease severity in the context of HCV infections.[1] Long overdue, most national elimination programmes now also include access to care for people who inject drugs (PWID),[2] who are at the core of ongoing HCV transmission.[3] Macías *et al.*[4] have recently shown in this *Journal* that high viral cure rates can be achieved in this group, hereby providing evidence that targeting PWID in treatment programmes is worthwhile. However, the extent to which such national efforts can reduce the HCV burden not only depends on the uptake into care and treatment success rates, it is also determined by the relative importance of within-country transmission and virus importation from elsewhere.

As the chronic nature of most HCV infections hampers reliably reconstructing contact networks from patient interviews, virus genetic data can be a valuable alternative source of information for elucidating the geographic history of virus lineages (*e.g.* 5,6). Using such data, we have recently shown that for the most prevalent subtype among PWID in Spain (40%,[7]), HCV1a, infections often link to infections abroad – in recent years >50% link to Western European countries, mostly European Union (EU) member states – as opposed to other infections within Spain.[8] Hence, reducing HCV1a prevalence and spread across Europe will help to consolidate the impact of Spanish efforts to reduce the HCV burden.

To investigate whether this is a general pattern that also holds for the second most prevalent subtype among PWID in Spain (26.5%,[7]), HCV3a, we analysed newly generated HCV3a genome data covering parts of the NS5A and/or NS5B genes from 196 HCV3a-infected patients sampled between April 2014 and April 2017 across Spain (GenBank: accession numbers MN227780 - MN228016). Of the 60% for whom information on the probable route of transmission was available, 81.8% reported injecting drug use. These sequences were complemented with a background dataset of publicly available data from GenBank (totalling 2752 taxa), and analysed as previously described.[5,8] The Ethics Committee of the San Cecilio Hospital, Granada, approved the study, and no informed consent was required as patient information was anonymised and de-identified prior to analysis.

As for HCV1a,[8] we found that the transmission network size structure is not dominated by a few large exclusively Spanish transmission networks, meaning that HCV3a transmission hot spots in Spain more often bridge to networks abroad rather than being connected domestically. Whereas we previously found an increasing importance of European lineages in seeding the HCV1a epidemic in Spain,[8] our current reconstructions showed that HCV3a virus movements from within the EU account for ~85% of all migrations towards Spain, with little fluctuation over time. The number of imported HCV3a infections per year from other EU member states – which is a lower bound estimate – has increased on average by 1 to 4 per year, totalling 125 (95% credible interval: 92–158) introductions (Fig. 1). The trend and magnitude are similar to those for HCV1a, for which the number of lineage introductions totals 114 (95% credible interval: 72–156) (Fig. 1).

The Spanish national strategy against HCV is based on a combination of factors, including a focus on increased screening and diagnosis, enhancing the treatment infrastructure, the availability of improved therapeutic regimens and targeting the groups at highest risk of transmitting HCV, including PWID.[9–11] Despite existing challenges and policy differences between regions, this multifactorial approach has led to Spain being one of the few countries in Europe that are reported to be on track to meet the World Health Organization HCV elimination targets by 2030.[12] As more recent subtype 1a and 3a infections are associated with illicit (injecting) drug use (*e.g.* 3), targeting this group that drives onwards spread, and for which Macías *et al.*[4] have demonstrated that treatment can be highly effective, is most desirable in many countries. However, across Europe, most countries have yet to embrace the universal treatment paradigm, and even more are yet to develop and implement a national strategy towards the elimination of HCV.[1] Our current and previous results[8] illustrate that in the absence of the latter, HCV will rapidly be re-seeded in the Spanish PWID population, challenging the long-term impact of the current Spanish intervention efforts. This demonstrates that there are beneficial scale-effects to implementing concurrent national efforts in the EU and elsewhere, without which the ultimate goal, namely eliminating HCV, will likely remain elusive.

## Conflict of interest

All authors have nothing to disclose, except for Federico Garcia, Joaquin Anton-Basantas and Miguel Angel Von Wichmann who report grants and personal fees from Viiv Healthcare, personal fees from Gilead, personal fees from Abbvie and/or personal fees from MSD and/or personal fees from Janssen, outside the submitted work; and Anne-Mieke Vandamme who reports grants from the Research Foundation Flanders (FWO), during the conduct of the study (as declared in the acknowledgments section).

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

Bram Vrancken and Lize Cuypers designed and developed the phylogenetic analysis pipeline, performed the phylogeographic analyses and wrote subsequent drafts of the manuscript. Natalia Chueca and Ana Belen Pérez were responsible for performing all

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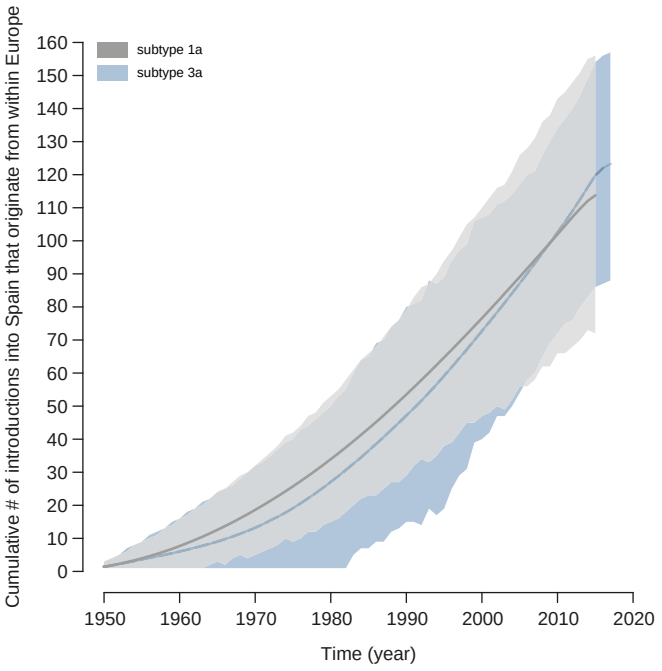


**Fig. 1. Frequent importation of HCV subtype 1a and 3a lineages into Spain mostly from other countries within the European Union.** The lines correspond to the average cumulative number of introduction events for these subtypes from other countries within the European Union into Spain, with the shaded areas indicating the uncertainty (95% credible interval). Grey colors pertain to subtype 1a, and blue colors to subtype 3a.

HCV sequencing experiments, and both assisted in writing the manuscript. Joaquin Anton-Basantas, Alberto de la Iglesia, Javier Fuentes, Juan Antonio Pineda, Francisco Téllez, Enrique Bernal, Pilar Rincón, Miguel Angel Von Wichman, Ana Fuentes, Francisco Vera, Antonio Rivero-Juárez, Miguel Jiménez provided samples from their clinical centre to be analysed within this study, and assisted in writing the manuscript. Anne-Mieke Vandamme provided substantial support to the phylogenetic computations and assisted extensively in writing the manuscript. Federico Garcia supervised the design of the analyses, the sequencing experiments and assisted extensively in writing the manuscript.

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## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.08.010.

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