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Title:

Hepatitis C and the absence of genomic data in low income countries; a barrier on the road to eradication?

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Following the development of highly effective direct acting antiviral (DAA) compounds for the treatment of the hepatitis C virus (HCV), the World Health Organisation (WHO) has set out plans for eradication by 2030. Many barriers must be surmounted before this can be achieved, including buy-in from governments and policy-makers, reduced drug costs and improved infrastructure for the pathway from diagnosis to treatment. A comprehensive set of guidelines were produced by WHO in 2014, updated in 2016 and are due to be revised later this year.[1] It is likely that they will be substantially improved following the addition of pan-genotypic regimens; this is of particular importance in low and middle income countries (LMICs) where the cost of genotyping may be prohibitively high. In such areas, information on HCV prevalence and serotype is extremely limited.[2] Very little data on circulating genetic strains and polymorphisms that may be associated with resistance to DAAs are available. One of the most variable of the RNA viruses, HCV has 7 distinct genotypes differing from each other by up to 30% with 86 subtypes varying by 10-25% at the nucleotide level. Direct-acting antiviral drugs have improved sustained virological response rates significantly to over 95% in trials in high income countries (HICs), but variants associated with drug resistance have emerged both *in vitro* and in clinical trials, leading guidance to recommend resistance testing in treatment failure and in selected regimens at baseline.[4] Variation in HCV sequences could affect both diagnostic assays and treatment outcomes.

In this study, we used HCV-GLUE, a new linked dataset and suite of analysis tools for HCV sequence data. We identified > 30,000 sequences from NCBI which encode the NS3, NS5A and NS5B viral proteins (the targets of DAAs), and mapped these by geographical regions.[5] This revealed huge gaps in sequence data in the majority of LMICs and some HICs (Figure 1). For example, only 15 sequences spanning NS5B are available for the whole sub-Saharan Africa region (Figure 1F). More work to investigate circulating genotypes is needed to inform local governments and policymakers who are developing the infrastructure for the diagnosis and treatment of HCV in these regions in order to facilitate eradication of the disease. Resistance associated variants (RAVs) could present a barrier to the WHO plan for eradication of HCV by 2030 and vigilance is required to monitor transmitted viral strains as treatment roll-out occurs.

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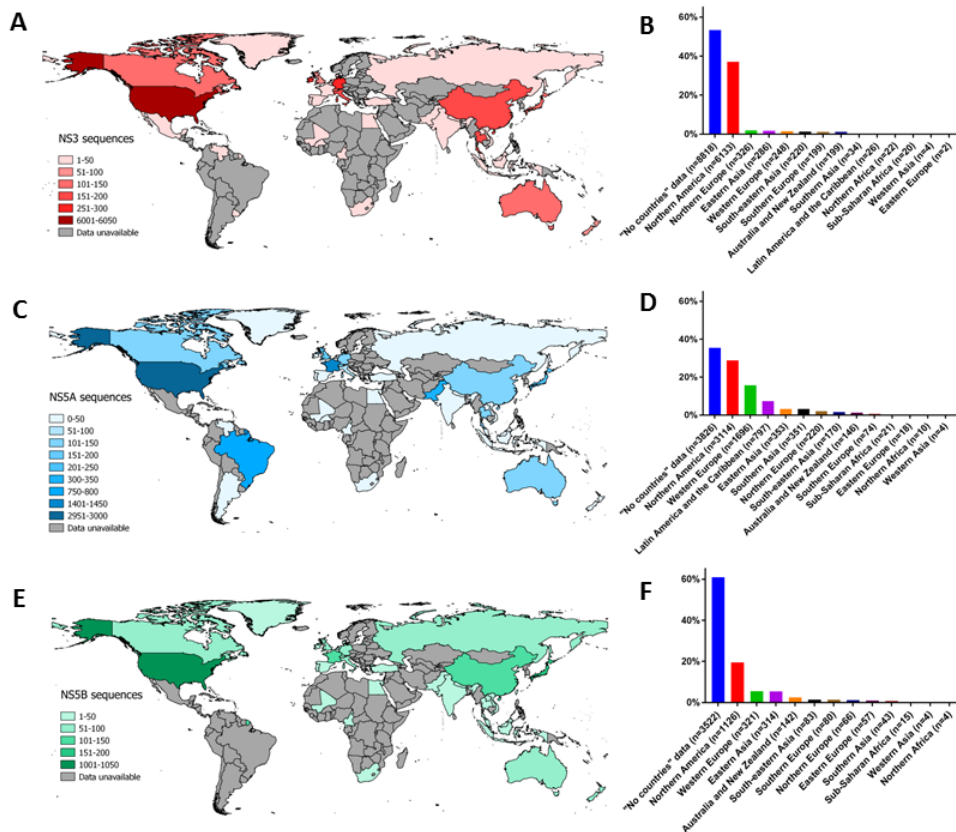
Figure 1. Global distribution of HCV sequence data based on the genes of DAA treatment targets. (A) NS3 protease sequences by country (B) Abundance of NS3 sequences by UN sub-regions. (C) NS5A sequences by country. (D)Abundance of NS5A sequences by UN sub-regions. (E) NS5B sequences by country. (F) Abundance of NS5B sequences by UN sub-regions.