Appendix 4 (as supplied by authors): Backfilling Sensitivity Analyses

Intervals of RNA testing

In the absence of a treatment record, we assessed our backfilling approach by examining the interval between consecutive HCV RNA tests among the treatment backfilled individuals. Accordingly, we evaluated the interval between HCV RNA tests among the whole cohort and specifically among those who had backfilled treatment data.

Among those backfilled into the treatment group (n=509), 333 (65%) had one or more subsequent RNA tests within six months of each other following their first HCV RNA positive test record. Recognizing the potential lag time of HCV testing records within the linked administrative data, we also determined how many people had repeat RNA testing within 12 months and found that 405 (80%) of the backfilled population had such records. Therefore, we were confident that a minimum of 65% and likely upwards of 80% of those backfilled into the treatment stage did indeed receive antiviral therapy. While it is possible that some, or even all, of the others who were presumed to have been treated did not receive treatment, this would not significantly impact the overall results, as with 2,374 individuals with HCV genotyping, our data would still indicate a very large gap in the cascade of care at the point of treatment initiation.

In contrast, among individuals with an ODB record of a HCV prescription claim (n=493), 338 (69%) had one or multiple subsequent RNA tests within six months of each other following their first HCV RNA positive test record. Within 12 months following their first HCV RNA positive test record, 404 (82%) had multiple subsequent RNA tests. This shows that similar proportions were observed when comparing the intervals between RNA testing for individuals with a treatment record to the backfilled proportion.

Potential misclassification of individuals who may have spontaneously cleared infection rather than initiated treatment

One concern with the backfilling assumption is the potential misclassification of individuals who may have cleared the infection without treatment (spontaneous clearance). In addition to the HCV RNA testing

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interval information indicating probable treatment, from a clinical perspective and due to the asymptomatic nature of infection, it is relatively rare for individuals to present with acute infection. Once chronic, spontaneous clearance of HCV is very uncommon.[1] This is echoed in our spontaneous clearance group that we excluded from the HCV RNA positive stage and thus from stages further along the cascade of care (n=1,122 individuals). Within this group, only 145 (13%) presented as HCV RNA positive and then tested HCV RNA negative within a year without a treatment record. The majority (977 (87%)) were antibody-positive at index date and subsequently tested HCV RNA negative without record of an HCV RNA positive test or treatment in-between.

Relapse as an indicator of treatment

Relapse after antiviral therapy was relatively common in the interferon era, but rarely occurs with DAA-based treatment. Relapse is defined as becoming HCV RNA positive following an end-of-treatment response (HCV RNA negative) in the absence of reinfection. Distinguishing relapse from reinfection can be very challenging even with robust clinical data and is difficult from administrative data alone. We assumed that a positive HCV RNA test within 1 year after the end of treatment indicated virological relapse. It is possible that some of these individuals were reinfected shortly after completing treatment. It is much less of a concern that these individuals were never treated. Although it is possible to become transiently HCV RNA negative during acute HCV infection and subsequently develop chronic HCV, reports of this are rare and require very close surveillance to identify the interval of RNA negativity. Accordingly, it is very likely that HCV RNA positivity after documented HCV RNA negativity indicates treatment followed by relapse, or possibly reinfection, but indicates treatment in either scenario. Among the 509 individuals backfilled into the treatment and SVR stages, 24 (5%) tested HCV RNA positive again following an HCV RNA negative test, indicating potential relapse or reinfection. Among these 24 individuals, the majority (16 (67%)) tested positive within a year following the HCV RNA negative test date, which we presumed to indicate relapse but could also have been early post-treatment reinfection.

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Whether relapse or early reinfection, the data would still be highly suggestive of having received antiviral therapy.

Potential misclassification of treatment non-responders

In our backfilling assumption, we assumed that individuals had received treatment only if they were HCV RNA negative more than a year following their initial HCV RNA positive test. Non-responders were defined as those who received treatment, but did not exhibit a reduction in HCV viral load and thus did not become HCV RNA negative.

To infer the number of potential non-responders in the administrative data, similar to above, we can consider the interval of RNA testing for individuals who never tested HCV RNA negative following their initial positive HCV RNA test result. Among all individuals who had ever tested HCV RNA positive (n=2,715) (no exclusion criteria applied), 1,683 (62%) had no subsequent HCV RNA negative test record. Of the 1,683 individuals, 249 (15%) and 499 (30%) had at least one subsequent HCV RNA test within six months and within 12 months following their earliest HCV RNA positive result, respectively. Therefore, it is possible that the proportion of HCV RNA positive individuals who were treated may be slightly underestimated. Although inclusion of these individuals would not change the large gap observed in the cascade of care at the treatment initiation stage, this underestimation can serve to balance some of the concerns regarding the overestimation of the proportion treated using our backfilling approach.

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