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RESEARCH ARTICLE

UPDATE

Impact of the COVID-19 pandemic on routine surveillance for adults with chronic hepatitis B virus (HBV) infection in the UK [version 2; peer review: 2 approved]

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Open Peer Review

Approval Status ✓✓

Abstract

Background

To determine the impact of the COVID-19 pandemic on the population with chronic Hepatitis B virus (HBV) infection under hospital follow-up in the UK, we quantified the coverage and frequency of measurements of biomarkers used for routine surveillance (alanine transferase [ALT] and HBV viral load).

Methods

We used anonymized electronic health record data from the National Institute for Health Research (NIHR) Health Informatics Collaborative (HIC) pipeline representing five UK National Health Service (NHS) Trusts.

Results

We report significant reductions in surveillance of both biomarkers during the pandemic compared to pre-COVID-19 years, both in terms of the proportion of patients who had ≥1 measurement annually, and the mean number of measurements per patient.

Conclusions

These results demonstrate the real-time utility of HIC data in monitoring health-care provision, and support interventions to provide catch-up services to minimise the impact of the pandemic. Further investigation is required to determine whether these disruptions will be associated with increased rates of adverse chronic HBV outcomes.

Keywords
hepatitis B virus, HBV, epidemiology, virology, viral hepatitis, COVID-19

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version 2 (update) 15 Nov 2023		✓ view
version 1 11 Feb 2022	✓ view	

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Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Campbell C: Conceptualization, Formal Analysis, Investigation, Methodology, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Wang T**: Conceptualization, Investigation, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Smith DA**: Data Curation; **Freeman O**: Data Curation, Software; **Noble T**: Data Curation, Project Administration; **Várnai KA**: Data Curation, Methodology, Project Administration, Writing – Review & Editing; **Harris S**: Data Curation; **Salih H**: Data Curation; **Roadknight G**: Project Administration; **Little S**: Project Administration; **Glampson B**: Data Curation; **Mercuri L**: Data Curation; **Papadimitriou D**: Data Curation; **Jones CR**: Data Curation; **Taylor V**: Data Curation; **Chaudhry A**: Data Curation; **Phan H**: Data Curation; **Borca F**: Data Curation; **Olza J**: Data Curation; **Warricker F**: Data Curation; **Romão L**: Data Curation; **Ramlakhan D**: Data Curation; **English L**: Data Curation; **Klenerman P**: Data Curation; **Andersson MI**: Data Curation, Writing – Review & Editing; **Collier J**: Data Curation; **Nastouli E**: Data Curation; **Khakoo SI**: Data Curation; **Gelson W**: Data Curation, Investigation, Visualization, Writing – Review & Editing; **Cooke GS**: Data Curation, Visualization, Writing – Review & Editing; **Woods K**: Funding Acquisition, Project Administration; **Davies J**: Data Curation, Project Administration, Resources, Software, Writing – Review & Editing; **Barnes E**: Conceptualization, Data Curation, Methodology, Project Administration, Supervision, Writing – Review & Editing; **Matthews PC**: Conceptualization, Data Curation, Investigation, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

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Abbreviations

ALT	Alanine transferase
CHB	Chronic HBV
COVID-19	Coronavirus Disease 2019
GHSS	Global Health Sector Strategy
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HIC	Health Informatics Collaborative
NHS	National Health Service
NIHR	National Institute for Health Research
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VL	Viral load
WHO	World Health Organization

Introduction

Mortality and morbidity associated with the Coronavirus Disease 2019 (COVID-19) pandemic can be directly attributed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but also result from indirect impacts on other conditions.

In order to progress towards elimination targets for Hepatitis B virus (HBV) infection[1] there is an urgent need for improvement of surveillance and treatment coverage. This will necessitate enhanced screening, followed by surveillance of individuals with chronic HBV (CHB) to determine treatment eligibility. Clinical follow-up includes routine monitoring of liver enzymes (e.g., alanine transferase (ALT)), hepatitis B virus (HBV) DNA viral load (VL), elastography, ultrasound, and occasionally liver biopsy[2–4]. In those receiving antiviral treatment, laboratory parameters are monitored to ensure virologic suppression is achieved and maintained, and to identify complications.

Surveillance using VL and liver enzymes is recommended, typically at intervals of 3–12 months, and more frequently among males at older age, those with biochemically active hepatitis, risk factors for hepatocellular carcinoma (HCC), complications of liver disease, recent diagnosis, or changing treatment plans[5,6]. COVID-19-attributable disruptions to HBV elimination efforts have been broadly described[7,8], but we set out to quantify the specific impact on routine HBV surveillance in secondary care services in England using individual-level patient data.

Methods

We undertook longitudinal and cross-sectional analyses using routinely-collected individual-level secondary care data collected across five NHS Trusts in England by the National Institute for Health Research (NIHR) Health Informatics Collaborative (HIC), as previously described[9,10]. HBV treatment data were available from three NHS Trusts. We investigated how ALT and VL surveillance varied between pre-COVID-19 (years 2016–2019) to COVID-19 (year 2020 and part of 2021), comparing surveillance metrics in patients on and off antiviral therapy.

We calculated cumulative probabilities of undergoing ≥1 ALT and HBV DNA VL measurement each year using the Kaplan-Meier method, comparing probabilities across years using the log-rank test. We quantified the mean number of ALT and HBV DNA measurements per 100 patients, during pre-COVID-19 and COVID-19 years, with 95% CIs calculated using the normal distribution (whereby standard error (SE) is estimated by $\frac{s}{\sqrt{n}}$ with n denoting sample size and s denoting standard deviation). Official UK government COVID-19 incidence data are presented[11].

Ethics approval

The research database for the NIHR HIC viral hepatitis theme was approved by South Central - Oxford C Research Ethics Committee (REF Number: 21/SC/0060). All methods in this study were carried out in accordance with relevant guidelines and regulations. The requirement for written informed consent was waived by South Central - Oxford C Research Ethics Committee, because data has been anonymised before its use and the study is retrospective.

Results

Coverage of ALT and VL testing (proportion tested at least once a year)

Data were available from 3768 patients for the year 2016; this increased to 5450 by the year 2021. In 2016, 74.1% (95% CI 72.7-75.5%) of individuals with CHB had ALT measured on ≥1 occasion throughout the year. This significantly decreased to 56.0% (95% CI 54.6-57.3%) in 2020 and 47.7% (95% CI 46.4-49.0%) in 2021, suggesting a negative impact of the COVID-19 pandemic on routine clinical? surveillance (Figure 1A). Similarly, throughout 2016, 68.4% (95% CI 66.9-69.9%) of patients had VL measured at least once, whilst this significantly decreased to 51.6% (95% CI 50.3-53.0%) in 2020 and 44.7% (95% CI 43.4-46.0%) in 2021 (Figure 1B). From 2016 to 2019, median time to ALT/VL surveillance ranged between 138 and 175 days (out of 365 total in one calendar year). Median time to surveillance significantly differed in 2020, with durations of 308 and 345 days in 2020 for ALT and VL, respectively (Log-rank $P < 0.0001$). In 2021, 47.7% and 44.7% of individuals achieved ALT and VL
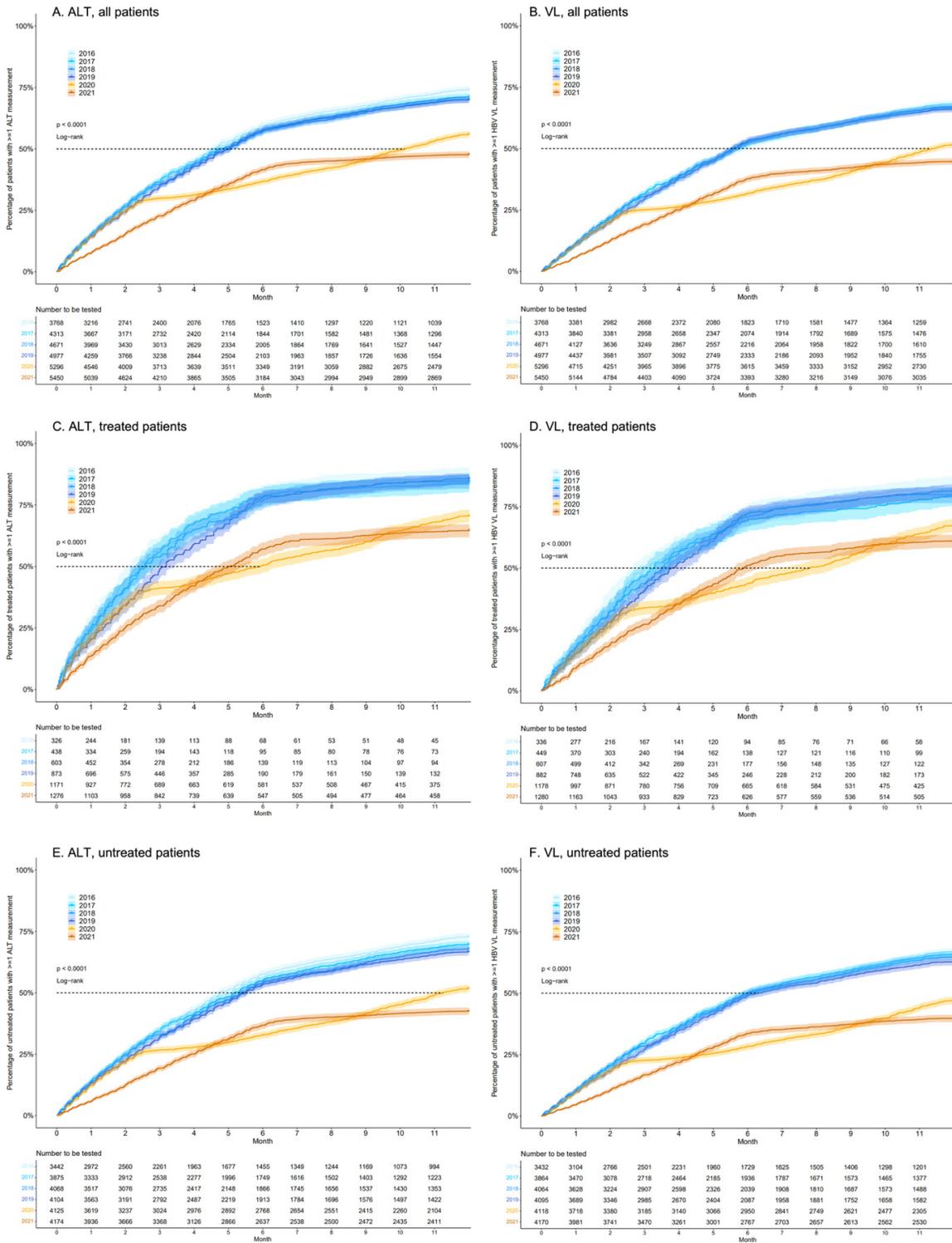
Figure 1. Kaplan-Meier plots demonstrating the cumulative proportion of adults with chronic Hepatitis B virus (HBV) infection undergoing routine laboratory surveillance. Plots show patients who have had ≥1 alanine transferase (ALT) (panels **A**, **C**, **E**) and ≥1 HBV DNA viral load (VL) (panels **B**, **D**, **F**) measurement each year for pre-COVID-19 (2016–19) and COVID-19 (2020 and part of 2021) years. For both ALT and VL, plots are stratified by treated (panels **C** and **D**, respectively) and untreated (panels **E** and **F**, respectively) patients. Dashed lines depict median time for 50% of the cohort to have the laboratory assessment undertaken. Cumulative probabilities for each year were calculated using the Kaplan-Meier method, comparing probabilities across years using the log-rank test, with 2016 serving as the reference/baseline year.

surveillance by the end of the calendar year, respectively. COVID-19 incidence data are displayed in Figure 2.

Coverage of ALT and VL testing stratified by treatment status

A subset of patients had treatment data available for years 2016 to 2021. Among treated patients, the proportion with ≥1 ALT measurement decreased significantly from 87.4% (95% CI 83.8-91.0%) in 2016 to 70.6% (95% CI 68.0-73.2%) in 2020, and 64.6% (95% CI 62.0-67.2%) in 2021 (Figure 1C). Untreated patients demonstrated a reduction from 72.9% (95% CI 71.4-74.4%) in 2016 to 51.8% (95% CI 50.3-53.3%) in 2020 and 42.5% (95% CI 41.0-44.0%) in 2021 (Figure 1E). In treated patients, median time to ALT surveillance ranged between 74 and 97 days from 2016-2019, and increased to 180 and 153 days in 2020 and 2021, respectively (Log-rank P < 0.0001). Differences in median time to surveillance were also observed in untreated patients, with median times to ALT surveillance ranging from 145 to 167 days during pre-COVID years and reaching 342 days in 2020 and with <50% individuals undergoing surveillance in 2021.

The proportion of treated patients with VL measured decreased from 84.2% (95% CI 80.3-88.1%) in 2016 to 67.2% (95% CI 64.6-69.9%) in 2020 and 61.0% (95% CI 58.3-63.7%) in 2021 (Figure 1D). A decrease was also observed in untreated patients from 66.8% (95% CI 65.2-68.4%) in 2016 to 47.2% (95% CI 45.7-48.7%) in 2020 and 39.7% (95% CI 38.3-41.2%) in 2021 (Figure 1F). In both treated and untreated individuals, cumulative probabilities comparing time to ALT and HBV VL measurement significantly differed across calendar years (Log-rank P < 0.0001). Median time to VL surveillance in treated patients ranged between 91 and 115 days from 2016-2019, increased to 238 and 153 days in 2020 and accordingly reduced to 180 days in 2021 (Log-rank P < 0.0001). In untreated patients, median time to VL surveillance ranged from 183 to 192 days during pre-COVID years, whilst in both 2020 and 2021 <50% of individuals underwent VL surveillance (Log-rank P < 0.0001).

Frequency of ALT and VL testing

Pre-COVID, the mean number of ALT measurements varied from 19 (95% CI 19-19) to 24 (95% CI 24-24) per 100 patients per month, with annual dips in August and December suggesting an impact of holiday periods when clinic activity may be reduced (Figure 3A). Between March 2020 and December 2021, this range reduced to between 4 (95% CI 4-4) and 15 (95% CI 15-15), mean number of measurements per 100
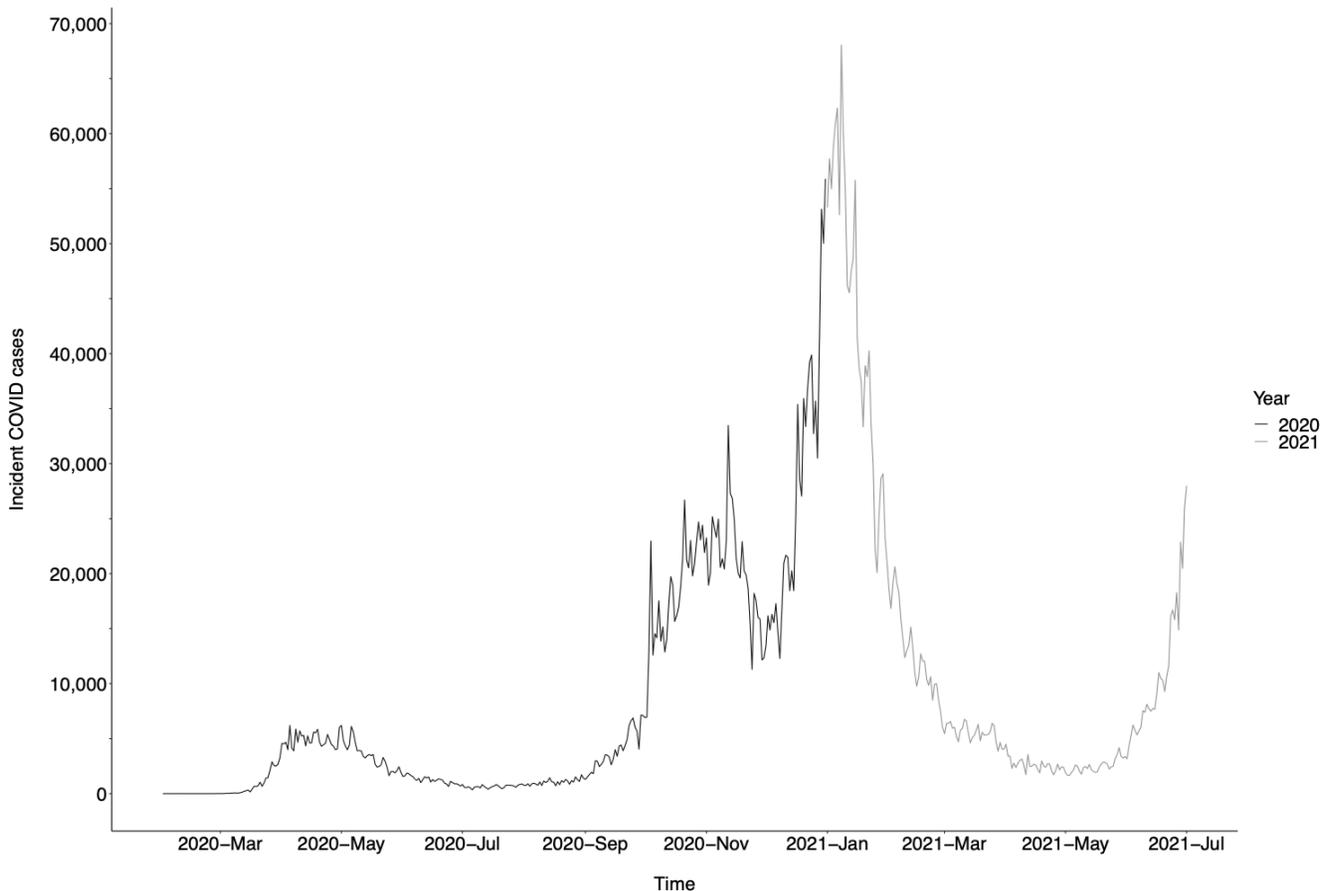

Figure 2. UK coronavirus disease 2019 (COVID-19) incidence, displayed as number of incident daily COVID-19 cases[12]. Data from March 2020 to July 2021 are displayed.
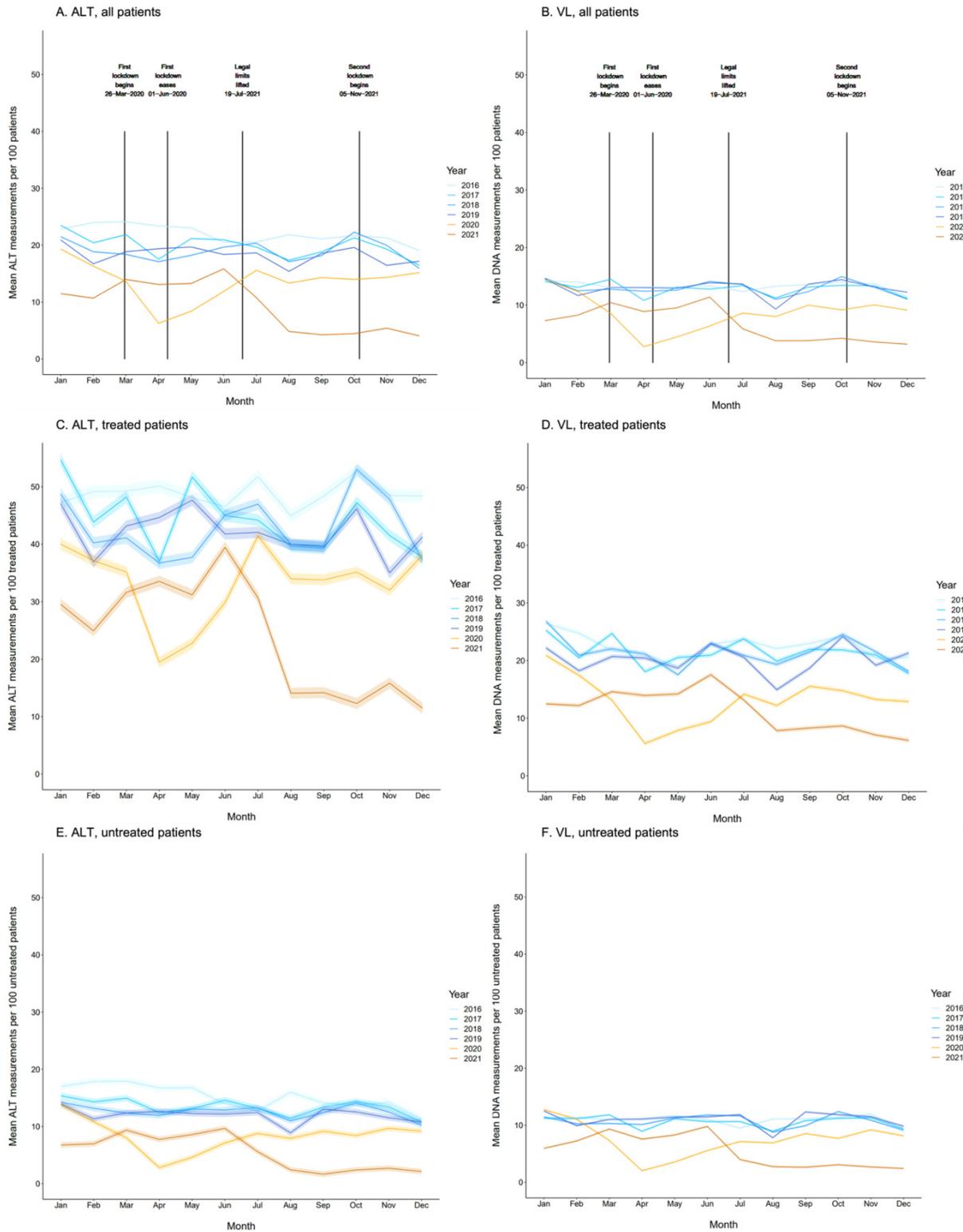
Figure 3. Mean numbers of ALT and HBV DNA VL measurements per 100 patients per month during pre-COVID-19coronavirus disease 2019 (COVID-19, 2016–19) and COVID-19 (2020 and part of 2021) periods. Data are shown overall and stratified by treatment status for both viral load (VL, panels **A**, **C**, **E**) and alanine transferase (ALT, panels **B**, **D**, **F**). Dates of UK national COVID-19 lockdowns are denoted in overall plots. 95% CIs were calculated using the normal distribution (whereby standard error (SE) is estimated by $\frac{s}{\sqrt{n}}$ with n denoting sample size and s denoting standard deviation).

patients per month remaining lower in these years as compared to pre-COVID years. The same trend was observed for VL (Figure 3B), with mean numbers of measurements ranging from 9 (95% CI 9-9) to 15 (95% CI 15-15) per 100 patients pre-COVID, and from 3 (95% CI 3-3) to 11 (95% CI 11-12) during the COVID period, with nadirs of 3 measurements per 100 patients (95% CI 3-3) in April 2020 and December 2021.

Frequency of testing by HBV treatment status

VL and ALT measurements were more frequent in treated (Figure 3 C, D) compared to untreated (Figure 3 E, F) patients throughout the study period. In treated patients pre-COVID, mean number of ALT measurements fluctuated between and within years but remained >35 measurements per 100 patients per month (Figure 3C); hence, treated patients had ALT measured on average once every 4 months (in keeping with the routine interval for clinic visits in patients on treatment).

Mean numbers of ALT monthly tests fluctuated between 1 (95% CI 10-13) and 42 (95% CI 40-43) per 100 patients during the COVID-19 period but were generally significantly lower compared to pre-COVID years. This pattern was also observed for VL, with mean numbers of measurements ranging from 15 (95% CI 15-15) to 27 (95% CI 26-27) during pre-COVID years and 6 (95% CI 5-6) to 18 (95% CI 17-18) during the COVID period (Figure 3D).

In untreated patients pre-COVID, mean number of ALT measurements per 100 patients per month ranged from 64 (95% CI 64-65) to 99 (95% CI 98-99), with a drop in the COVID period to between 23 (95% CI 22-23) and 74 (95% CI 73-74) (Figure 3E). This pattern was also observed for VL, with pre-COVID and COVID measurements ranging from 8 (95% CI 8-8) to 12 (95% CI 12-13) and from 2 (95% CI 2-2) to 13 (95% CI 13-13) measurements per 100 patients, respectively (Figure 3F).

Discussion/conclusions

These data demonstrate the negative impact of the COVID-19 pandemic on routine clinical surveillance for patients with CHB infection in the UK. Reduction in rates of surveillance closely track SARS-CoV-2 incidence and thus periods of population lock-down.

During lockdown periods, much clinical care was switched to telemedicine[13,14], intended to maintain contact between patients and healthcare providers, but at the detriment of laboratory monitoring. Although patients may have an option to attend phlebotomy appointments, services have been stretched, and clinicians and/or patients may have elected to defer routine blood tests. Telephone appointments are impractical for certain patients, and contact may have been lost altogether – for example, for those who do not communicate confidently in English. Furthermore, CHB patients who left the UK early in the course of the pandemic may have been unable to return due to travel restrictions, thereby foregoing routine surveillance.

The impact of the pandemic was seen across treated and untreated individuals. However, the impact on ALT measurement was greater in those on treatment during lockdowns.

We were unable to investigate how imaging-based surveillance strategies were impacted due to lack of complete elastography and ultrasound data in our current dataset. Furthermore, as complications of CHB evolve over the long-term (months to years), it is not yet possible to quantify how service disruptions may impact incidence of HCC and other adverse endpoints. Surveillance disruption may be associated with an increased risk of CHB progression and delays in starting antiviral therapy. Further prospective data are required to determine the impact on long-term outcomes.

Our data represent only five large, urban centres, in the South East of England; trends may differ across settings and additional data will be required to determine the extent to which our observations apply in other regions. HIC data collection is being expanded[10], providing enhanced opportunities to incorporate a wider view of the UK over time. Effort and resources are required to refine telemedicine services and optimise access to laboratory surveillance[15], re-establish face-to-face services and catch-up on monitoring and interventions. Future analyses are warranted to investigate how imaging surveillance and telemedicine service uptake have been impacted when these data become available in the NIHR HIC database. Longitudinal follow-up is warranted to ascertain how COVID-attributable disruptions will impact the incidence of HCC and other relevant endpoints, and to ensure activity is re-aligned to support progress to elimination goals.

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Open Peer Review

Current Peer Review Status: ✓ ✓

Version 2

Reviewer Report 25 April 2024

https://doi.org/10.21956/wellcomeopenres.21838.r75872

✓   **James Van Yperen** [ID]

University of Sussex, Brighton, England, UK

The authors present a study on the impact of the COVID-19 pandemic on routine surveillance for adults with a chronic hepatitis B virus infection in the UK. The authors use the Kaplan-Meier method (typically used for survival analysis) to analyse the cumulative probability of patients getting at least 1 test (either monitoring alanine transferase or virus DNA load) over the course of a year, generating estimates for 2016 up to 2021, and used a log-rank statistical test to compare these. Applying standard exploratory data analysis techniques, they provide statistics on the coverage of the two different tests, stratified by whether a patient has received treatment. The data used in the manuscript is not publicly available but can be made available by request to the steering committee (details available in the manuscript).

The manuscript is well-written, but please thoroughly check for typos. The tests are appropriate, the results well represented and clear. Here are some scientific comments that could improve the manuscript:

1. Are surveillance levels going back to normal levels now? And if not, why do the authors think that is?
2. How could this drop in surveillance levels be mitigated in future pandemics causing lockdowns? For example, using home tests to check the viral load?
3. It would be interesting to see the distribution of the number of measurements per patient over the year. This could shed light on behaviour (e.g., lockdown caused a bimodal distribution with some not getting any measurements and some getting a lot).
4. I am not sure what Figure 2 is adding to the manuscript right now, other than a reminder on the COVID-19 cases?
5. The "methods" summary is not indicative of what methods you employed for your analysis, it should include the statistical methods and tests employed.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Mathematical modelling; mathematics of public health; operational research; nowcasting and forecasting using mathematics; systems modelling

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

- -

Version 1

Reviewer Report 28 February 2023

https://doi.org/10.21956/wellcomeopenres.19374.r54846

✔ **Dorcas Obiri-Yeboah** (iD)
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Thank you for the manuscript. This paper focused on how the pandemic impacted routine care for CHBV patients on treatment and those not on treatment. A number of articles have been published which looked at similar issues for other patients like HIV clients and other sin routine care prior to the pandemic. I am happy about the approach used here where the dataset set used is verifiable and the number of data points is large enough. The analysis has been done rigorously enough and clearly brings out the fact that laboratory services were very much negatively impacted compared with other aspects which telemedicine provided a solution.

I am very happy and did not see any significant point to make to improve this manuscript. It is well written. The authors could propose or give some suggestions as to how this impact particularly on laboratory services could be mitigated in future similar situations. That would be helpful. And again what do you consider as further research that could offer more insight into what has been reported here? I am also wondering why the team did not look at the laboratory results where available and see if there was any trend pre- and during the pandemic? That could have implications for the care received.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Virology, infectious disease epidemiology, laboratory science

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.