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Research article

Hepatitis B time series in Xinjiang, China (2006–2021): change point detection based on the Mann-Kendall-Sneyers test

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Abstract: Hepatitis B is a major global challenge, but there is a lack of epidemiological research on hepatitis B incidence from a change point perspective. This study aimed to fill this gap by identifying significant change points and trends in hepatitis time series in Xinjiang, China. The datasets were obtained from the Xinjiang Information System for Disease Control and Prevention. The Mann-Kendall-Sneyers (MKS) test was used to detect change points and trend changes on the hepatitis B time series of 14 regions in Xinjiang, and the effectiveness of this method was validated by comparing it with the binary segmentation (BS) and segment regression (SR) methods. Based on the results of change point analysis, the prevention and control policies and measures of hepatitis in Xinjiang were discussed. The results showed that 8 regions (57.1%) with at least one change fell within the 95% confidence interval (CI) in all 14 regions by the MKS test, where five regions (Turpan (TP), Hami (HM), Bayingolin (BG), Kyzylsu Kirgiz (KK), Altai (AT)) were identified at one change point, two change points existed for two regions (Aksu (AK), Hotan (HT)) and three change points was detected in 1 region (Bortala (BT)). Most of the change points occurred at both ends of the sequence. More change points indicated an upward trend in the front half of the sequence, while in the latter half, many change points indicated a downward trend prominently. Finally, in comparing the results of the three change point tests, the MKS test showed a 61.5% agreement (8/13) with the BS and SR.

Keywords: Hepatitis B; Change point; the MKS test; BS; SR

Abbreviations

MKS: Mann-Kendall-Sneyers; CI: confidence interval; BS: Binary Segmentation; SR: Segment regression; UQ: Urumqi; KM: Karamay; TP: Turpan; HM: Hami; CJ: Changji; BT: Bortala; BG: Bayingolin; AK: Aksu; KK: Kyzylsu Kirgiz; KS: Kashgar; HT: Hotan; YL: Yili; TC: Tacheng; AT: Altai

1. Introduction

Hepatitis B, caused by the hepatitis B virus infection, is a viral hepatitis disease characterized by symptoms such as decreased appetite, nausea, and pain in the liver area, and severe cases can lead to liver cirrhosis and liver cancer [1,2]. Hepatitis B virus infection is a global public health concern. According to the World Health Organization (WHO), in 2019, there were 296 million people worldwide living with chronic hepatitis B infection, resulting in 1.5 million new infections and 820,000 deaths [3]. China carries a high burden of the hepatitis B virus disease. According to the 2014 seroepidemiological survey of the hepatitis B virus, there are a total of 86 million hepatitis B virus infections in China, with an alarming 1 million reported cases of hepatitis B virus every year. Xinjiang, located in the northwest of mainland China, is one of the regions with high prevalence of hepatitis B virus. Epidemiological studies in Xinjiang are crucial for the prevention and control of this disease.

A change point refers to a point of sudden change in a time series. Change point analysis is the method of identifying the locations where these points occur in a sequence and it is currently widely applied in various scientific fields, such as bioinformatics [4,5], financial [6], hydrology [7], climatology [8], and others. Change point analysis should also receive attention in epidemiological research, as the results are highly relevant for future epidemiological studies and early warning systems for infectious diseases such as hepatitis B. By incorporating the findings into their analysis, researchers and public health officials can better monitor and respond to disease outbreaks, ultimately helping to prevent their spread and minimize their impact on public health. Since the last century, the Chinese government and health departments in Xinjiang have implemented a series of relevant policies for the prevention, control, and treatment of hepatitis B. By conducting change point analysis on hepatitis B time series, the effectiveness of these policies can be evaluated, which can help to develop adaptive prevention and control measures to prevent further outbreaks [9–11].

Compared to commonly used change point analysis models, such as linear regression models and Bayesian models, the MKS test offers several advantages. First, the MKS test is a non-parametric method, which means it does not rely on specific distribution assumptions, such as the normality of observed values. This makes it more robust and applicable to a wider range of datasets. Additionally, the MKS test is capable of identifying change points in time series data, while also detecting both linear and nonlinear monotonic trends, such as increasing or decreasing trends [12–14]. This flexibility enables it to capture complex patterns and variations in the data, providing a more comprehensive analysis. By being able to accurately identify change points and trends, the MKS test can serve as a valuable tool for long-term disease monitoring. Public health decision-makers can leverage this method to gain insights into the progression of diseases over time, identify critical points of change, and make informed decisions regarding intervention strategies.

To gain a better understanding of the epidemiology of hepatitis B in each region of Xinjiang, it is essential to investigate the change points and trend changes within the time series. The contributions of the paper are: (i) This paper stands out as the first to apply the MKS test to analyze time series data related to hepatitis B. By employing this innovative approach, the study introduces a fresh perspective to the field. (ii) This paper compares three change point detection methods to validate the MKS test. This comparative analysis adds credibility to the findings.

2. Materials and methods

2.1. Study area and data source

Xinjiang, located in the northwest of mainland China, is situated between longitudes 74° to 96° East and latitudes 34° to 49° North. It has vast territory and a large population. As of the end of 2022, Xinjiang's permanent resident population has reached 25.78 million. Daily data on hepatitis B cases in Xinjiang (excluding the Xinjiang Production and Construction Corps) from January 1, 2006, to December 31, 2021 were obtained from the Xinjiang Disease Prevention and Control Information System. The dataset includes information on patient age, place of residence, date of symptom onset, time and location of symptom confirmation. A quarterly time series was constructed based on the daily onset of symptoms. As the data used for analysis does not involve any patient privacy information, ethical approval or informed consent is deemed unnecessary.

2.2. Methods

2.2.1. Statistical spatial analysis

The MKS is a statistical method commonly used to identify change points in the temporal behavior of a series. It is particularly effective in detecting points where the trend shifts from a downward trajectory to an upward trajectory, or vice versa [15]. In the context of epidemic prevention and control, sudden changes in the incidence of a specific disease can often be attributed to various factors, including governmental policies and unforeseen events, although they may have different impacts [10]. Therefore, we aim to assess the potential of the MKS test in identifying change points in the time series data related to hepatitis B. The following section provides a detailed explanation of how the MKS test is applied to the hepatitis B time series data.

We've considered new quarterly cases as independent observations in a 64-quarter time series data. Let $\{x_i, i = 1, 2, \ldots, N\}$ be a time series, where N represents the total number of quarters observed. In our research, we have selected hepatitis B data spanning 16 years (equivalent to 64 quarters) from 14 regions in Xinjiang. Hence, we have 14 sequences of length $N = 64$ in our study. For each region, $n_i, i = 1, 2, \ldots, N$ denotes the total number of elements x_j preceding x_i , where $x_j < x_i$,

$$n_i = \#\{x_j : x_j < x_i, j = 1, 2, \ldots, i-1\}$$

Under the null hypothesis (there is no abrupt change point in the time series), the normally distributed statistic T_k is given by the following formula:

$$T_k = \sum_{i=2}^{k} n_i (k = 2, 3, \ldots, N)$$

and the mean and variance of T_k [16] are as follows

$$E(T_k) = \frac{1}{4}k(k-1),$$

$$var(T_k) = \frac{1}{72}k(k-1)(2k+5).$$

The normality assumption is valid already for $N \geqslant 10$ [17]. The normalized variable statistic U_f (the forward sequence) is given by

$$U_f = (T_k - E(T_k))/\sqrt{var(T_k)}$$

To search for the change points in possible trends, we calculated the backward sequence U_b using the same approach but with a reserved series $\{x_N, x_{N-1}, \ldots, x_1\}$,

$$U_b = (T_k^{'} - E(T_k^{'}))/\sqrt{var(T_k^{'})}$$

where $T_k^{'}$ is similar to T_k,

$$T_k^{'} = \sum_{i=2}^{k} n_i^{'}(k = 2, 3, \ldots, N)$$

and

$$n_i^{'} = \#\{x_j : x_j < x_i, j = n, n-1, \ldots, n-i+1\}$$

The mean and variance of $T_k^{'}$ can be calculated by

$$E(T_k^{'}) = \frac{1}{4}(n-k)(n-k-1)$$

$$var(T_k^{'}) = \frac{1}{72}(n-k)(n-k-1)(2n-2k+5)$$

then, based on the two generated sequences (U_f and U_b) , we can find the change points of the time series $\{x_i\}, i = 1, 2, \ldots, N$. Initially, we consider the points of intersection between the two sequences as potential change points. However, it is important to note that not all change points represent abrupt changes in the time series because some change points may arise from a sudden shift in the mean value between two stable periods [18]. To address this issue, additional detection methods like the double mass curve can be used to evaluate outlier points [19]. In order to enhance the practicality of our proposed method and minimize errors, we apply a statistical filter that excludes intersection points falling outside the 95% CI ($Z - score = \pm 1.96, \alpha = 0.05$). This particular filter has been employed in relevant studies using the MKS technique [20]. It is worth mentioning that the MKS test is capable of detecting both monotonic trends and directional changes in the time series. For instance, an intersection point falling between the $Z - score$ of 0 and 1.96 reflects upward changes, while a point falling between $Z - score$ of -1.96 and 0 denotes a downward change. However, if a series follows an independent and identically distributed type, i.e, there is no trend that exists, the U_f and U_b plots are expected to fluctuate around the zero-line within the 95% CI.

3. Results

The data of this study was recorded with EXCEL 2022; the process of MKS and other change point analysis methods were performed by R (version 4.3.0) software. The significant level is 0.05.

A total of 670,681 cases of hepatitis B virus were reported in Xinjiang, China between January 1, 2006 and December 31, 2021. Figure 1 showed the study area and the quarterly reports of hepatitis B

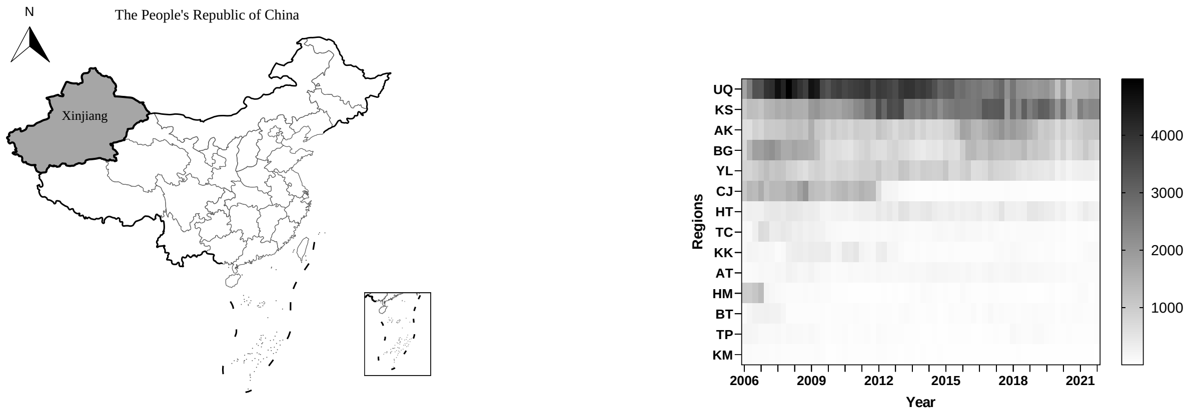

Figure 1. The geographical location of Xinjiang (left) and the number of quarterly hepatitis B reports in each region of Xinjiang, China from 2006 to 2021 (right).

cases in each region of Xinjiang, and the figure at right indicated a clear decline trend over time, but, of course, the number of cases still fluctuated in some regions, like Urumqi (UQ), Kashgar (KS), AK and so on. The top five regions with the highest number of hepatitis B reports were UQ, KS, AK, BG, Yili (YL), and the sum of cases (53,1803) in these five areas exceeded 79% of the total cases.

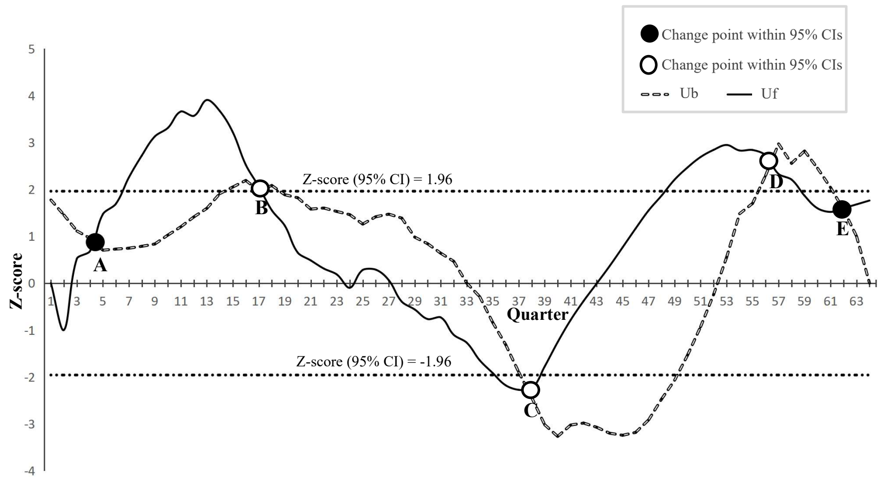

Figure 2. MKS test of new quarterly cases in Aksu with the identified change point (black dot) and the excluded change point (white dot). The solid line is the forward sequence, and the thicker dashed line is backward sequence.

For the hepatitis B time series of each region in Xinjiang, the two sequences (U_f and U_b) were generated by the MKS test. Here, we presented a detailed account of the MKS test results using the AK region as an illustrative example in Figure 2. The forward and backward sequences were represented by a solid line and the thicker dashed line, respectively. The points where two sequences intersected formed the initial set of change points. In this specific case of AK in Figure 2, five points of intersection were initially detected. As mentioned in the previous section, the thresholds of 95% CI ($Z-score = \pm 1.96$), two finer dashed lines in Figure 2, were set as the statistical filter and only change points within the thresholds were retained. Therefore, Quarter 17 (Point B in Figure 2, $Z-score = 5$) , Quarter 38 (Point C in Figure 2, $Z - score = -2.25$), and Quarter 56 (Point D in Figure 2, $Z - score = 2.72$) were excluded, as it fell beyond the established thresholds. Only Quarter 5 (Point A in Figure 2, $Z - score = 1.46$) and Week 62 (Point E in Figure 2, $Z - score = 1.59$) were identified as final change points with statistical confidence, and because both point A and E were between the $Z - score$ of 0 and 1.96, the trend of these two changes were upward.

Through the utilization of the MKS test on quarterly new hepatitis B cases in 14 regions, we have determined 8 regions (57.1%) with at least one change that falls within the 95% CI. In Figure 3, we mapped out the emergence of the change points for these 8 regions. Five regions (TP, HM, BG, KK, AT) were identified at one change point, two change points existed for 2 regions (AK, HT), and three change points was detected in 1 region (BT). While for the remaining regions that did not pass the qualifications, they showed no change points within the 95% CI, but they did display at least one change point above the 95% CI. Furthermore, as seen in Figure 3, most of the change points occur at both ends of the sequence and there are more change points indicating an upward trend in the front half of the sequence, while in the latter half of the sequence, many change points indicating a downward trend are more prominent.

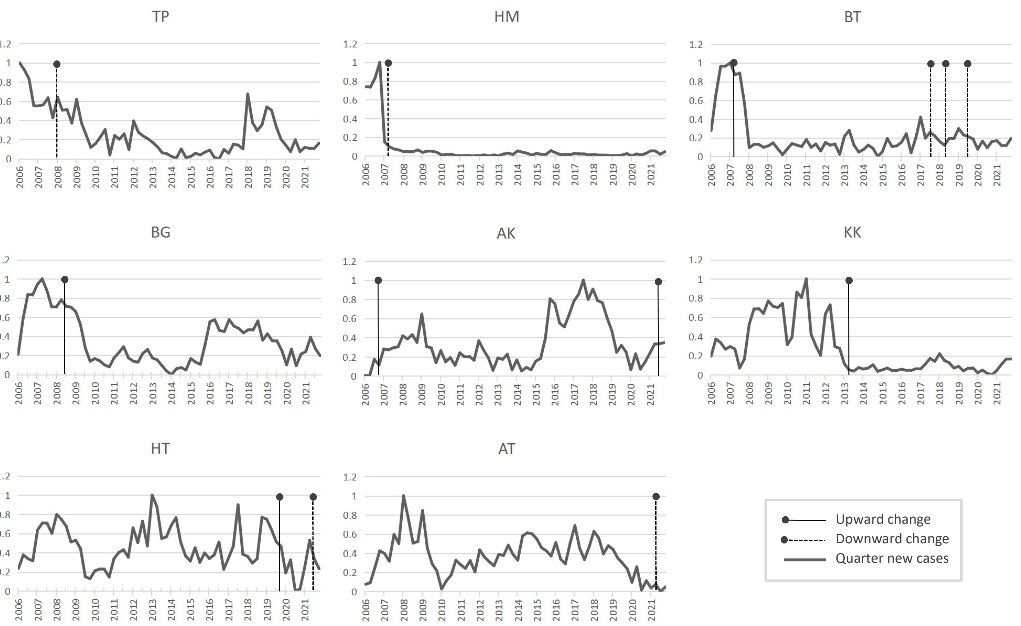

Figure 3. Regions with at least one change point detected. The horizontal axis is the quarterly time; the vertical axis is the quarterly new cases normalized to 0–100% with respect to the maximum quarterly new cases in each region

To validate the effectiveness of the MKS test, a comparison was made with two commonly used methods for detecting multiple change points in time series data: binary segmentation (BS) [21] and the segmented regression (SR) model [22] (Table 1). The BS method employs a likelihood-based approach to search for change points by minimizing a cost function over various possible numbers and locations of change points. It also utilizes an efficient pruning technique to enhance computational efficiency [10, 23]. The SR method analyzes the time series using a regression model with multiple

Table 1. Summary of the detected change points by the three methods.

Region	MKS				BS					SR				
	CP-1	CP-2	CP-3	CP-4	CP-1	CP-2	CP-3	CP-4	CP-5	CP-1	CP-2	CP-3	CP-4	CP-5
UQ					38	55				7	17	38		
KM					15	33				10	27			
TP	9				14	55	61			10	27	45	54	
HM	6				7	16				6	16			
CJ					25					25				
BT	6	47	50	55	6	50	56			4	7	22	55	
BG	11				12	40	51			5	10	14	39	51
AK	4	62			2	15	38	53	61	5	14	38	52	60
KK	30				8	28				8	13	20	28	
KS					20					20	31			
HT	56	62			34	56				11	34	55		
YL					49	61				5	34	48		
TC					15	50				14	44	50		
AT	61				60					7	35	61		

segments. In this approach, the time series is divided into segments and a regression model is fitted to each segment to estimate its parameters. The *changepoint* [24] package in R software was used for the BS method, while the segmented [22, 25, 26] package was employed for the SR method. Summary of the detected change point by these three methods can be outlined in Table 1. One is considered to be confirmed if a change point identified by MKS is validated by another method within a two-quarter period. In Table 1, out of the 13 change points identified by the MKS test, the MKS test exhibits a 69.5% agreement (9/13) with the BS method, a 76.9% agreement (10/13) with the SR model, and a 61.5% agreement (8/13) with the BS and SR. It is worth mentioning that the SR exhibits a 64.5% agreement (20/31) with the SR method based on the SR method.

4. Discussion

Change point analysis and trend analysis are commonly used in finance [27, 28], hydrology [29], climatology [30], and many other fields. However, we firmly believe that they also have very important applications in epidemic prevention and control. Once the changes are identified in the hepatitis B time series, they can provide critical epidemiological information, especially in the temporal dimension. Combined with the infectious disease prevention and control policies implemented by government agencies, these results will provide numerical evidence for evaluating the effectiveness of policies, thereby providing effective basis for the prevention and control of local diseases.

Although the global hepatitis B vaccination program, which began in the 1990s, has significantly reduced the incidence of hepatitis B, it remains one of the most pressing global public health issues to date. Xinjiang, China, due to its vast territory and large population, is still confronted with significant challenges in preventing and controlling hepatitis B.

Figure 4 illustrates the number of hepatitis B cases in Xinjiang, China, as well as some hepatitis B prevention and control policies released by the Chinese health authorities. The results indicate an overall decreasing trend in hepatitis B incidence in Xinjiang over time, which may be associated with the effectiveness of China hepatitis B control measures and treatment protocols. Nevertheless, we can-not ignore the significant fluctuations evident in this sequence, which implies that the prevention and control of this disease in Xinjiang still requires attention. In conjunction with the change point analysis results, change points were observed in most regions of Xinjiang, with a majority of them appearing at the two ends of the sequence (TP, HM, BT, BG, AK, HT, and AT), and those at the beginning of the sequence mostly tend to exhibit an upward trend mostly (BT, BG, and AK), which can be explained by the policies issued by the nation. The national regulation on free hepatitis B vaccinations for newborns was enforced in 2005. In our research range, it was a critical time period from 2006 to 2008 for these regulations to be promoted nationwide, thus the rising trend of change points is not difficult to comprehend. Moreover, the downward trend of change points located at the end of the time series (BT, HT, and AT) is more prominent, indicating that the effectiveness of prevention and control is more evident after years of implementing a series of policies against hepatitis B. Meanwhile, the small increasing trends in confirmed hepatitis B cases observed at the end of the time series should not be ignored (AK), as it might be the intensified efforts in disease prevention and control in the AK region since 2020. This includes enhanced monitoring and testing for major diseases, leading to an improved screening rate for significant illnesses like hepatitis B. This also suggests that for diseases with high incidence, highly infectious, and widespread prevalence, effective prevention and control should be carried out with precision and persistent efforts.

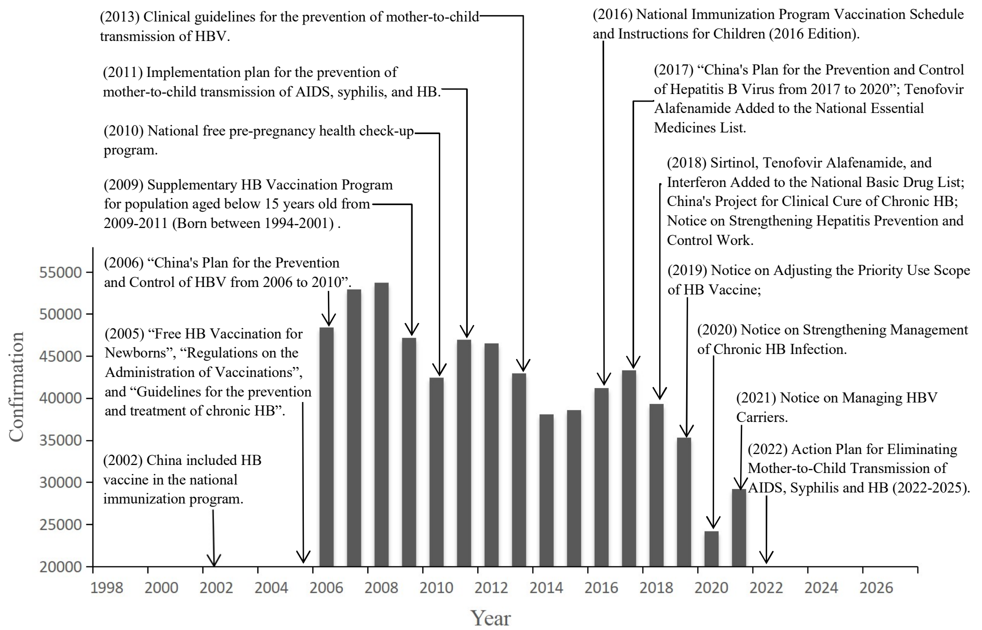

Figure 4. The number of hepatitis B cases in Xinjiang, China, and some hepatitis B prevention and control policies released by the Chinese health authorities.

In comparing the results of the three change point tests, the consistency of change point identification across all three methods was over 60%. It is noteworthy that both the BS and SR methods were able to identify at least one change point for each region. Nevertheless, these methods have certain limitations, as they do not provide a clear indication of the direction of change associated with the detected points. However, the advantage of the MKS method is its ability to determine the direction of change associated with the identified change points while detecting them. In addition, the MKS method failed to identify any change points in 6 out of the 13 regions, and even in the remaining regions, the number of detected change points was lower compared to the BS and SR methods. These findings imply that the MKS test is a relatively conservative approach to detecting change points. It primarily focuses on identifying abrupt changes while avoiding false-positive results. This conservative nature can be adjusted by modifying the filter width for the MKS test and offering potential for further investigation in enhancing its performance.

5. Conclusions

As an efficient and easily implementable method for identifying change points that can detect changes in direction, MKS testing can be used for pattern recognition in initial data analysis. Of course, combining it with other change points testing methods can mutually verify the results and increase their reliability. Furthermore, although the changes in some hepatitis B sequences in Xinjiang have been decreasing in recent years (e.g., BT, AT), there are still areas where they are increasing (e.g., AK). Furthermore, despite a significant drop in reported hepatitis B cases in many areas since early 2020, this result should not be taken optimistically as it is highly likely that the Coronavirus disease 2019 has led to an underestimation of the number of cases, due to factors such as lockdown preventing access to timely medical care. It might lead to the burden of hepatitis B in various regions, and the incidence rate might increase in the coming years [31, 32]. Based on these findings, we hope that local health departments in all regions of Xinjiang can continue to vigorously promote accurate prevention and control of hepatitis B.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Ethical approval and informed consent

The data utilized in this study comprises anonymized information directly reported from the Xinjiang Disease Prevention and Control Information System. It does not include any specific patient identifiers that could lead to the identification of individual patients. Consequently, ethical approval or informed consent is deemed unnecessary.

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Conflict of interest

The authors declare no conflicts of interest.

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