International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

Prevalence and Distribution of Naturally Occurring Antiviral Resistance-Associated Mutations in Treatment-Naïve Chronic Hepatitis B: A Systematic Review and Meta-Analysis

Usman Abdullahi Muhammad[1*], Elijah Ndakotsu Yisa[2], Baba Rasheedat Toyosi[3], Yakubu Firdausi[4], Isah Abubakar Aliyu[5], Abdullahi Mohammed[6], Abubakar Halima Sadiya[7]

*[1]Medical Laboratory Science Department, Faculty of Medical and Clinical Science, Newgate University Minna.
*[1]Medical Microbiology Department, Federal Medical Centre, Bida.
[2]College of Health Technology Minna, Niger State.
[3]Department of Medical Laboratory Science, Faculty of Health Sciences, Al-Hikmah University Ilorin, Kwara State.
[4]Federal Medical Centre Bida, Niger State.
[5]Department of Medical Laboratory Science, Bayero University, Kano.
[6]Medical Laboratory Science Department, Faculty of Medical and Clinical Science, Newgate University Minna.
[7]Jummai Babangida Neonatal and Maternal Hospital Minna

ABSTRACT

Background: Chronic hepatitis B virus (HBV) infection remains a major global public-health problem and an important cause of cirrhosis, hepatocellular carcinoma, and liver-related mortality. Although nucleos(t)ide analogue therapy has substantially improved management, antiviral resistance-associated mutations may occasionally be detected before treatment exposure.

Objective: To systematically determine the prevalence and distribution of established primary antiviral resistance-associated mutations among treatment-naïve patients with chronic HBV infection and to estimate the pooled prevalence of patients carrying at least one established primary resistance mutation.

Methods: A systematic review and meta-analysis were conducted using a patient-level endpoint defined as the presence of at least one established primary antiviral resistance-associated mutation in a unique treatment-naïve patient. Secondary or compensatory mutations were not counted as primary resistance when occurring alone. Studies using highly sensitive assays, including mutation-specific PCR and next-generation sequencing, were considered separately where appropriate. The review was structured according to PRISMA 2020.

Results: The current primary quantitative dataset comprised 42 cohorts involving 9,811 evaluable treatment-naïve participants, of whom 417 carried at least one qualifying primary resistance-associated mutation, giving a crude prevalence of 4.25%. The current random-effects synthesis estimated an overall pooled prevalence of 1.80% (95% CI, 1.04–3.09%). Between-study heterogeneity was very high (I^2=93.3%; τ^2=2.541; Q=616.02). The approximate 95% prediction interval was 0.08–30.41%.

Conclusion: Naturally occurring primary antiviral resistance-associated mutations are detectable in a minority of treatment-naïve patients with chronic HBV infection, but reported prevalence varies substantially according to population, geography, genotype, study design, and assay sensitivity. The pooled estimate should therefore not be interpreted as a universal prevalence applicable to every clinical setting.

KEYWORDS: hepatitis B virus, chronic hepatitis B, antiviral resistance, resistance-associated mutations, reverse transcriptase, treatment-naïve.

1. INTRODUCTION

Chronic hepatitis B virus (HBV) infection remains one of the most important chronic viral infections worldwide. HBV can cause acute and chronic disease, with chronic infection capable of progressing to fibrosis, cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC). The World Health Organization (WHO) estimated that approximately 254 million people were living with hepatitis B in 2022, while HBV-associated disease caused approximately 1.1 million deaths, predominantly from cirrhosis and HCC ([1]).

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

The burden of HBV is particularly important in low- and middle-income countries, including countries in sub-Saharan Africa and parts of Asia where transmission remains substantial and access to diagnosis and treatment is comparatively limited. Current international guidance emphasizes appropriate identification of patients requiring treatment and long-term monitoring of virological response and liver-disease progression ([1,2]).

The clinical management of chronic hepatitis B has changed considerably over the past two decades. Potent nucleos(t)ide analogues, particularly tenofovir and entecavir, have become important components of antiviral therapy because they strongly suppress HBV replication and have favourable resistance profiles compared with earlier agents ([1,2]).

Despite the high genetic barrier of contemporary therapies, antiviral resistance remains biologically and clinically relevant. HBV replicates through reverse transcription, and the viral polymerase lacks the proofreading mechanisms characteristic of many cellular DNA polymerases ([3]). Consequently, HBV populations exist as genetically heterogeneous viral quasispecies in which minority variants can arise spontaneously. Antiviral therapy can provide selective pressure that favours variants with reduced susceptibility to a particular drug ([4]).

Importantly, resistance-associated substitutions can occasionally be detected before a patient has received antiviral therapy. These variants are commonly referred to as naturally occurring, pre-existing, or baseline resistance-associated mutations. Their clinical significance depends on the specific mutation, viral genotype, accompanying substitutions, antiviral agent involved, variant frequency and assay used for detection ([5]).

Most clinically relevant HBV resistance substitutions occur in the polymerase reverse-transcriptase region. The best-characterized pathway involves rtM204I/V within the YMDD motif, which is strongly associated with resistance to lamivudine and related L-nucleoside analogues. The rtA181T/V pathway is associated with resistance to lamivudine and adefovir, while rtN236T is particularly associated with adefovir resistance ([6]).

Entecavir resistance is more complex. Clinically important entecavir resistance generally requires a pre-existing lamivudine-resistance backbone involving rtM204V/I and rtL180M together with additional substitutions at positions such as rtT184, rtS202 or rtM250. Therefore, isolated substitutions at these positions should not automatically be classified as clinically meaningful primary resistance ([7]).

Naturally occurring HBV RT mutations are not necessarily synonymous with clinically meaningful antiviral resistance. Several studies have demonstrated substantial genetic variation within the HBV polymerase among untreated individuals. However, the frequency of individual substitutions depends on HBV genotype, disease phase, geographic region, viral load, HBeAg status, sequencing method and the definition used for resistance ([8]).

Differences in laboratory methodology represent one of the major reasons why estimates of naturally occurring resistance vary between studies. Conventional population sequencing generally detects variants when they constitute a relatively substantial proportion of the viral population, whereas mutation-specific PCR, line-probe assays and deep-sequencing approaches can identify lower-frequency variants. Very-low-frequency variants may be analytically detectable without necessarily being clinically capable of producing treatment failure.

A previous major systematic review by ([9]) included 106 studies and 12,212 treatment-naïve patients and reported substantial prevalence of naturally occurring HBV resistance mutations. However, the literature has continued to expand, molecular technologies have evolved, and definitions of clinically meaningful resistance remain heterogeneous.

The present review therefore focuses specifically on unique treatment-naïve patients carrying at least one established primary antiviral resistance-associated mutation. This patient-level definition was selected to prevent double counting of individuals with multiple mutations and to improve clinical interpretability.

1.1 Research Question

What is the prevalence and distribution of established primary antiviral resistance-associated mutations among treatment-naïve patients with chronic HBV infection worldwide?

1.2 Objectives

- To identify studies reporting antiviral resistance-associated mutations among treatment-naïve patients with chronic HBV infection.
- To determine the prevalence of patients carrying at least one established primary resistance mutation.
- To identify the major primary resistance pathways reported in treatment-naïve patients.
- To examine geographic and assay-related differences in reported prevalence.

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

- To estimate the pooled prevalence of primary resistance using random-effects meta-analysis.
- To quantify between-study heterogeneity.
- To examine the potential influence of molecular assay sensitivity and cohort overlap on pooled estimates.
- To distinguish established primary resistance mutations from secondary, compensatory and uncertain mutations.

2. METHODS

2.1 Study design and reporting guideline

This study was designed as a systematic review and meta-analysis of observational studies reporting naturally occurring antiviral resistance-associated mutations in treatment-naïve patients with chronic HBV infection. The review was structured according to PRISMA 2020 ([10]), with consideration of PRISMA-S for reporting the literature-search component ([11]).

2.2 Eligibility criteria

Studies involving patients with chronic HBV infection who were treatment-naïve or had no previous exposure to nucleos(t)ide analogue therapy were eligible. Studies were required to provide molecular assessment of the HBV polymerase/reverse-transcriptase region and sufficient information to determine the number of unique patients with qualifying primary resistance mutations. Case reports and case series without an appropriate population denominator were not included in the quantitative synthesis.

2.3 Information sources and search strategy

Information source: PubMed was searched from inception to the final documented search date. Relevant reference lists were used as supplementary sources. The search scope should not be represented as a completed multi-database search.

2.4 Data extraction

Extracted fields included author, year, country, population, HBV genotype, treatment-naïve definition, enrolled sample size, evaluable/sequenced sample size, number of patients with qualifying primary RAMs, mutation type, assay, overlap status and meta-analysis decision.

2.5 Definition of primary resistance

The principal primary resistance pathways included rtM204V, rtM204I, rtM204S, rtA181V, rtA181T, rtA181S and rtN236T. Context-dependent entecavir resistance mutations at rtT184, rtS202 and rtM250 were considered only when accompanied by the required resistance background. Secondary or compensatory mutations such as rtL180M, rtV173L, rtL80I/V and rtV207I were not counted as primary resistance when isolated. Uncertain variants such as isolated rtI233V, rtQ215S, rtV214A and isolated rtS202, rtT184 or rtM250 substitutions were also excluded.

2.6 Handling multiple mutations

Patients carrying more than one qualifying mutation were counted once. The numerator therefore represented unique patients with at least one qualifying primary mutation rather than the sum of mutation categories.

2.7 Cohort overlap

Potential overlap was assessed using study location, recruitment period, sample size, institution, investigators, genotype distribution, and molecular methodology and publication characteristics. Where substantial overlap was suspected, the largest or most informative cohort was preferentially selected for the primary quantitative synthesis.

2.8 Statistical analysis

For each cohort, crude prevalence was calculated as x/n, where x was the number of unique patients with at least one qualifying primary RAM and n was the number of evaluable treatment-naïve patients. A 0.5 continuity correction was used for logit transformation in zero-event or sparse-event studies. A random-effects model was used because substantial clinical, geographic and methodological heterogeneity was expected. Heterogeneity was assessed using Cochran's Q, I^2 and τ^2. A 95% prediction interval was also calculated.

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

3. RESULTS

3.1 PRISMA 2020-style flow

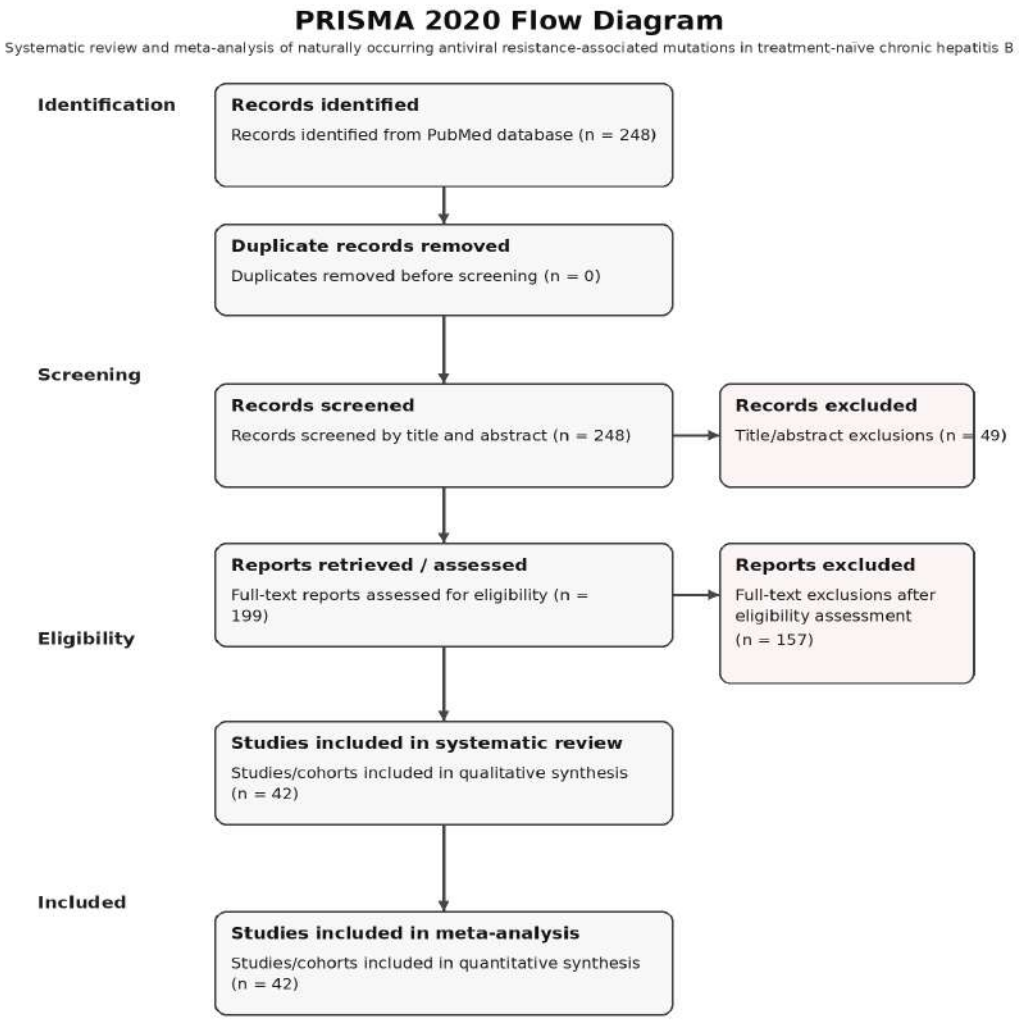


Figure 1. PRISMA 2020-style flow

3.2. Primary meta-analysis

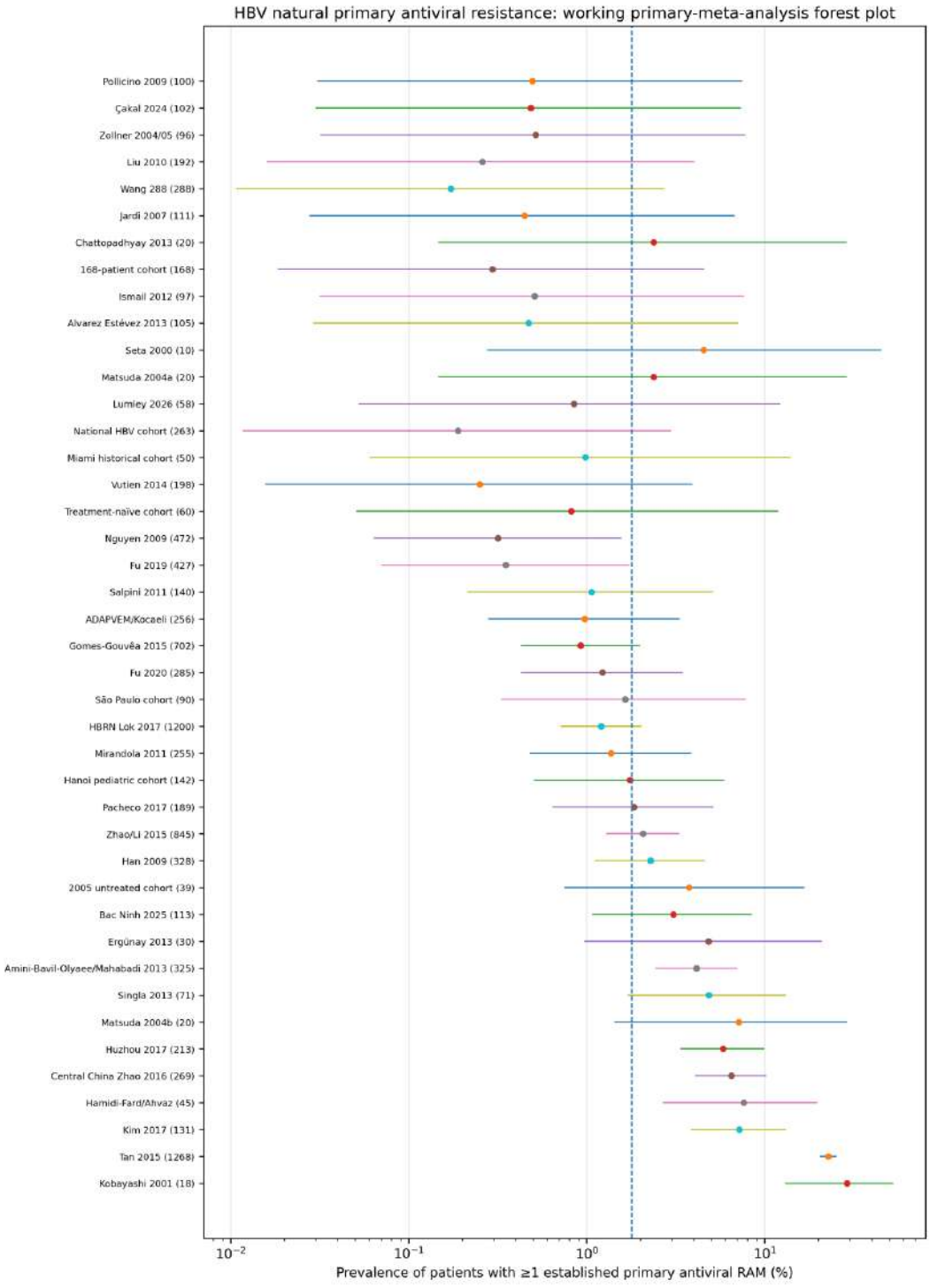
The current primary quantitative dataset comprised 42 cohorts, 9,811 evaluable treatment-naïve participants and 417 patients with at least one qualifying primary RAM. The random-effects logit model with a 0.5 continuity correction produced a pooled prevalence of 1.80% (95% CI 1.04%–3.09%), with I^2=93.3% and τ^2=2.541. The crude proportion was 4.25%. The wide heterogeneity indicates that the pooled estimate should be interpreted alongside assay method, cohort characteristics and overlap sensitivity analyses.

Table 1.Overall quantitative findings

Parameter	Result
Number of primary cohorts	42
Evaluable participants	9,811
Patients with ≥1 primary RAM	417
Crude prevalence	4.25%
Random-effects pooled prevalence	1.80%

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

95% CI	1.04–3.09%
I^2	93.3%
τ^2	2.541
Q	616.02
Approximate 95% prediction interval	0.08–30.41%



International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

3.3 Distribution of primary RAM prevalence

The prevalence of qualifying primary RAMs differed considerably between cohorts. Several studies reported no qualifying primary RAMs, whereas substantially higher prevalence was observed in several historical cohorts using highly sensitive mutation-specific approaches. The wide range of observed prevalence was one of the principal findings of the review.

3.4 Major primary resistance mutations

The most frequently represented resistance pathway was the rtM204 pathway, including rtM204I and rtM204V. Other qualifying pathways involved rtA181T, rtA181V, rtA181S and rtN236T, together with context-dependent combinations involving established resistance backgrounds.

Table2. Resistance mutations

Category	Examples	Rule
Primary resistance-associated	rtM204V/I; rtA181T/V; rtN236T; recognized rtT184, rtS202, rtM250 variants; selected pathway-defining substitutions	Exact substitution and combination retained; pathway context flagged.
Controversial/pathway-dependent	rtA194T and other substitutions with inconsistent evidence	Not automatically equivalent to established resistance; sensitivity analysis.
Secondary/compensatory	rtL80I/V; rtV173L; rtL180M when background/compensatory	Extract separately; not counted alone unless predefined.
Putative/uncertain	rtI233V; rtV207I/M; rtV214A; rtQ215S/H/P/R	Narrative/exploratory synthesis only.

3.5. Assay-stratified analysis

Between-study heterogeneity was extremely high (I^2=93.3%; Q=616.02; τ^2=2.541), indicating that most of the variability in observed study estimates was attributable to differences between studies rather than sampling error alone.

Assay method is a major potential source of heterogeneity. The locked analysis contains 37 conventional-sequencing cohorts, four INNO-LiPA cohorts and one NGS cohort. Conventional sequencing yielded a pooled prevalence of 1.97% (95% CI 1.36%–2.85%), whereas INNO-LiPA yielded 3.90% (95% CI 0.92%–15.02%). The single NGS cohort had zero events and was not meta-analytically pooled because k=1 is insufficient for a meaningful subgroup estimate.

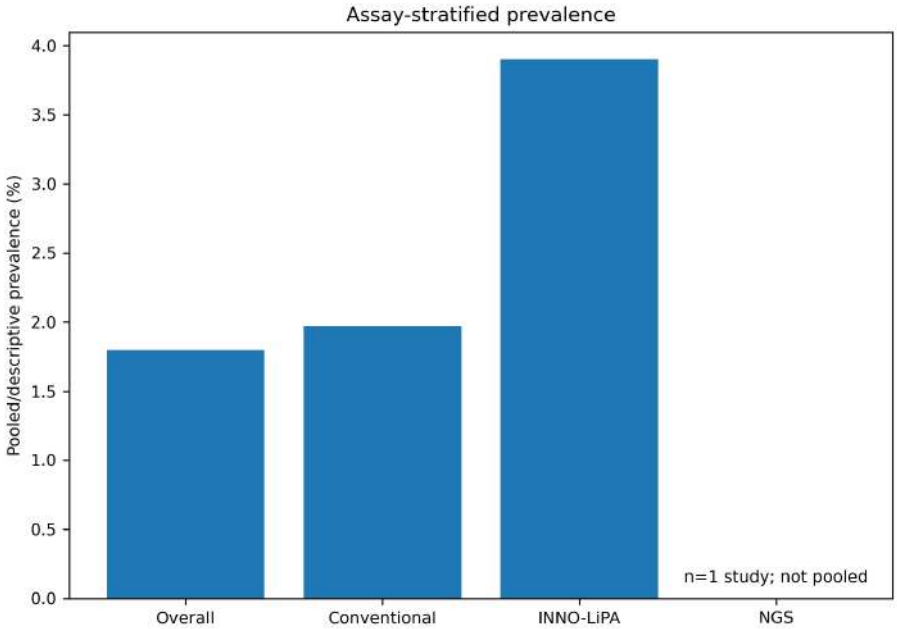


Figure 2. Assay-stratified prevalence. NGS is shown descriptively only because one study was available.

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

Table 3. Assay-stratified prevalence

Assay	K	N	Events	Pooled	95% CI	I^2	Interpretation
All selected assays	42	9811	417	1.80%	1.04%–3.09%	93.3%	Random-effects logit
Conventional	37	7762	110	1.97%	1.36%–2.85%	69.0%	Random-effects logit
INNO-LiPA	4	1991	307	3.90%	0.92%–15.02%	95.7%	Random-effects logit
NGS	1	58	0	Not pooled	—	—	One study; descriptive only

3.6 Assay-related variation

The dataset included conventional sequencing, INNO-LiPA and highly sensitive sequencing/PCR studies. Manually calculated crude assay-group prevalences were approximately 1.42% for conventional sequencing, 15.42% for INNO-LiPA and 0.00% for the small NGS category. The NGS figure should not be interpreted as evidence that NGS detects no resistance because the number of independent NGS cohorts in the primary dataset is too small for a reliable pooled estimate.

Table 4. Assay-related variation

Assays	Count of Study/cohort	Sum of Evaluable_n	Sum of Primary_RAM_positive	CRUDE
Conventional	37	7762	110	1.42%
INNO-LiPA	4	1991	307	15.42%
NGS	1	58	0	0.00%
Grand Total	42	9811	417	

3.7 Geographic distribution

The evidence originated from Europe, East and Southeast Asia, South Asia, the Middle East, North America, Latin America and Africa. China contributed a particularly large component of the evidence base, while studies from Japan, South Korea, Taiwan, Turkey, Iran, India, Spain, Italy, Vietnam, Brazil, Mexico, the United States, Canada, Morocco and African countries also contributed.

Table 5. Geographic distribution

Country	Count of Study/cohort	Sum of Evaluable_n	Sum of Primary_RAM_positive	Crude Prevalence
Brazil	3	981	10	1.02%
China	10	4283	345	8.06%
Germany	1	96	0	0.00%
India	3	188	3	1.60%
Iran	2	370	16	4.32%
Italy	3	495	4	0.81%
Japan	4	68	6	8.82%
Mexico	1	39	1	2.56%
Morocco	1	60	0	0.00%
South Korea	1	131	9	6.87%
Spain	2	216	0	0.00%
Turkey	3	388	3	0.77%
Uganda	1	58	0	0.00%
UK	1	263	0	0.00%
USA	4	1920	15	0.78%
Vietnam	2	255	5	1.96%
Grand Total	42	9811	417	

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

3.8. Leave-one-study-out sensitivity analysis

Each of the 42 primary cohorts was omitted in turn and the same random-effects logit model was recalculated. The pooled prevalence ranged from 1.64% to 1.96%. The lowest estimate occurred after omitting Kobayashi 2001 (1.64%), while the highest occurred after omitting Tan 2015 (1.96%). No single omission produced a reversal of the overall conclusion that natural primary RAMs are detectable but highly heterogeneous.

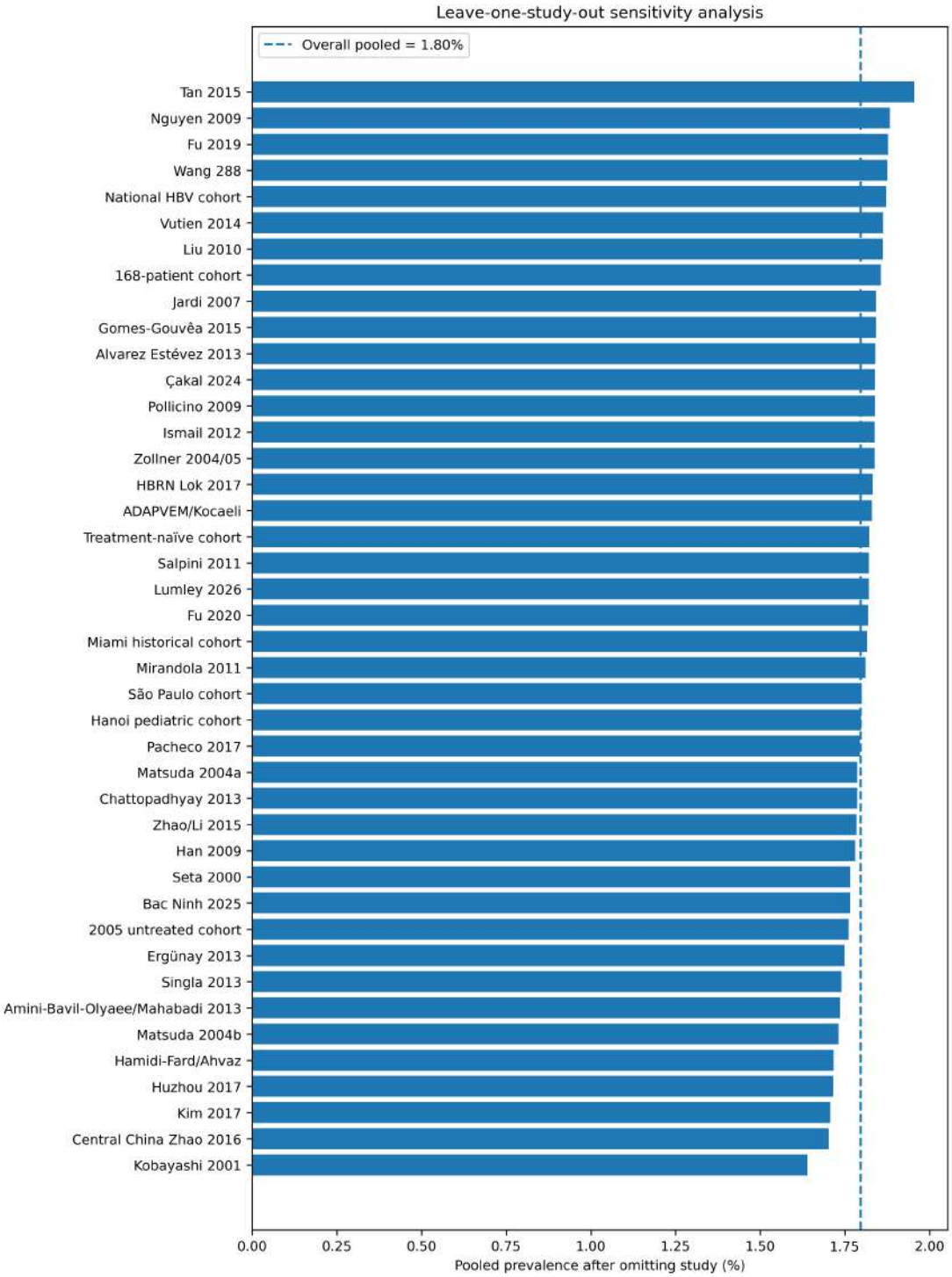


Figure 3. Leave-one-study-out pooled prevalence. The dashed line represents the overall pooled estimate.

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

Table 6. Leave-one-study-out sensitivity results

Study removed	Pooled prevalence	95% CI	I^2	Q
Pollicino 2009	1.84%	1.06%–3.17%	93.5%	611.03
Salpini 2011	1.82%	1.05%–3.15%	93.4%	607.49
Mirandola 2011	1.81%	1.04%–3.14%	93.3%	600.08
ADAPVEM/Kocaeli	1.83%	1.05%–3.16%	93.3%	600.65
Ergünay 2013	1.75%	1.00%–3.03%	93.5%	615.01
Çakal 2024	1.84%	1.06%–3.17%	93.5%	610.97
Zollner 2004/05	1.84%	1.06%–3.17%	93.5%	611.16
Han 2009	1.78%	1.02%–3.09%	93.3%	596.43
Liu 2010	1.86%	1.07%–3.21%	93.4%	608.76
Tan 2015	1.96%	1.37%–2.78%	70.8%	136.77
Zhao/Li 2015	1.79%	1.02%–3.10%	92.9%	562.97
Central China Zhao 2016	1.70%	0.96%–3.02%	93.5%	611.22
Huzhou 2017	1.72%	0.97%–3.02%	93.5%	611.03
Fu 2019	1.88%	1.08%–3.23%	93.3%	597.52
Fu 2020	1.82%	1.05%–3.14%	93.3%	598.33
Wang 288	1.88%	1.08%–3.23%	93.4%	607.13
168-patient cohort	1.86%	1.07%–3.20%	93.4%	609.26
Kim 2017	1.71%	0.97%–3.00%	93.5%	614.45
Singla 2013	1.74%	0.99%–3.03%	93.5%	613.68
Chattopadhyay 2013	1.79%	1.03%–3.09%	93.5%	614.81
Ismail 2012	1.84%	1.06%–3.17%	93.5%	611.13
Amini-Bavil-Olyaee/Mahabadi 2013	1.74%	0.98%–3.05%	93.4%	602.55
Hamidi-Fard/Ahvaz	1.72%	0.98%–2.99%	93.5%	615.60
Jardi 2007	1.84%	1.06%–3.18%	93.5%	610.70
Alvarez Estévez 2013	1.84%	1.06%–3.18%	93.5%	610.88
Matsuda 2004a	1.79%	1.03%–3.09%	93.5%	614.81
Matsuda 2004b	1.73%	0.99%–3.00%	93.5%	615.77
Kobayashi 2001	1.64%	0.94%–2.85%	93.4%	609.93
Seta 2000	1.77%	1.02%–3.05%	93.5%	615.63
Gomes-Gouvêa 2015	1.84%	1.07%–3.17%	93.0%	573.91
Pacheco 2017	1.79%	1.03%–3.11%	93.4%	604.33
São Paulo cohort	1.80%	1.03%–3.12%	93.4%	610.39
Nguyen 2009	1.88%	1.09%–3.24%	93.3%	596.45
Vutien 2014	1.86%	1.07%–3.21%	93.4%	608.64
HBRN Lok 2017	1.83%	1.06%–3.14%	92.6%	539.55
Miami historical cohort	1.82%	1.05%–3.14%	93.5%	612.98
2005 untreated cohort	1.76%	1.01%–3.05%	93.5%	614.25
National HBV cohort	1.87%	1.08%–3.22%	93.4%	607.51
Hanoi pediatric cohort	1.80%	1.03%–3.11%	93.4%	607.19
Bac Ninh 2025	1.77%	1.01%–3.07%	93.4%	610.12
Lumley 2026	1.82%	1.05%–3.14%	93.5%	612.60
Treatment-naïve cohort	1.82%	1.05%–3.15%	93.5%	612.52

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

3.9. Overlap sensitivity analysis

Potential cohort overlap was identified within the Turkish Kocaeli/ADAPVEM family, the Brazilian cohorts, and the Northern California cohorts. The primary analysis retains the selected cohorts already adjudicated for the working dataset. Two additional scenarios were evaluated: exclusion of every primary cohort explicitly flagged for possible overlap, and retention of the largest cohort within each flagged family.

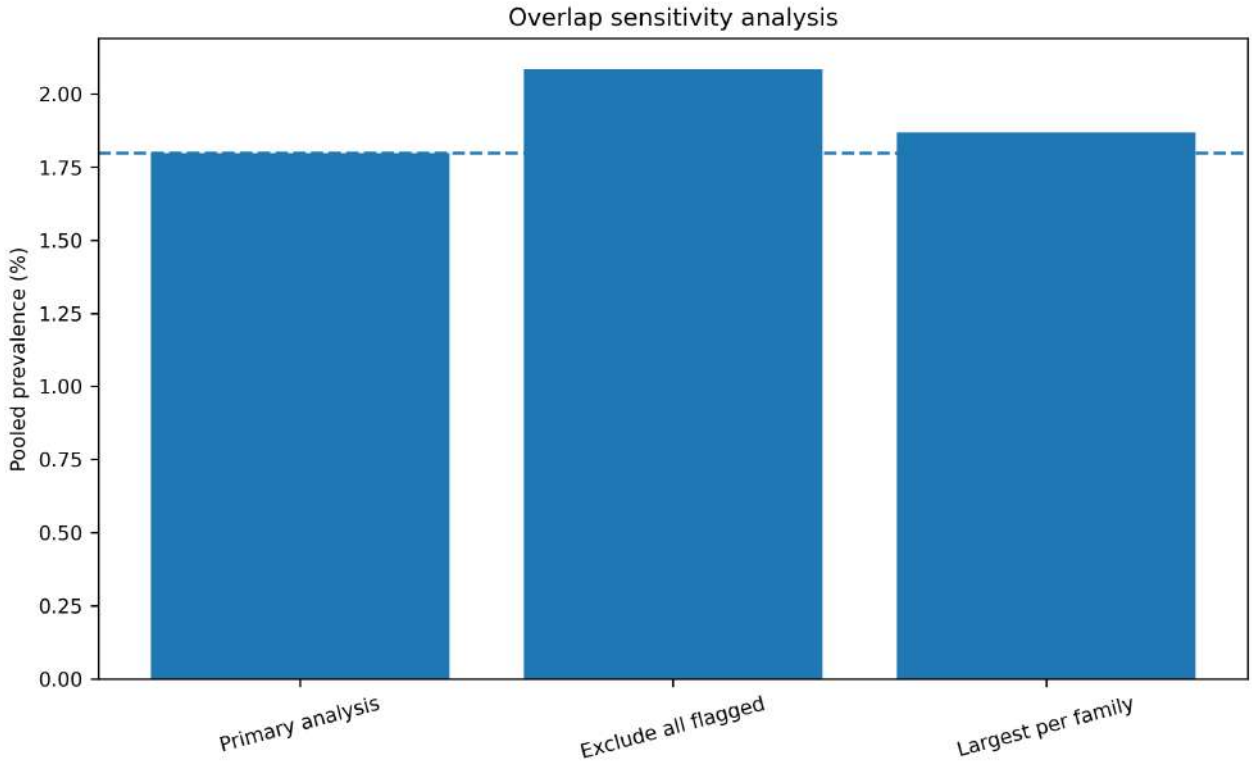


Figure 4. Overlap sensitivity analysis.

Table 7. Overlap sensitivity analysis

Scenario	K	N	Events	Pooled	95% CI	I^2	τ^2
Primary analysis (all 42 selected cohorts)	42	9811	417	1.80%	1.04%–3.09%	93.3%	2.541
Exclude all cohorts flagged for possible overlap	36	7904	404	2.08%	1.17%–3.67%	93.2%	2.330
Retain the largest cohort in each flagged family	39	9334	413	1.87%	1.06%–3.27%	93.6%	2.528

3.9 Prediction interval

The approximate 95% prediction interval was 0.08% to 30.41%. This broad interval indicates that a future study from a population comparable to the evidence base could plausibly produce prevalence substantially below or above the pooled estimate.

4. DISCUSSION

This systematic review and meta-analysis demonstrate that established primary antiviral resistance-associated mutations can be detected in treatment-naïve patients with chronic HBV infection, but their prevalence varies markedly across populations and molecular methodologies. Across 42 quantitative cohorts comprising 9,811 evaluable participants, 417 patients had at least one qualifying primary RAM, corresponding to a crude prevalence of 4.25%. The random-effects pooled prevalence was lower, at 1.80%

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

(95% CI, 1.04–3.09%), but the very high heterogeneity (I^2=93.3%) demonstrates that the pooled estimate cannot adequately describe every clinical population. ([9]) conducted a large systematic review and meta-analysis involving 106 studies and 12,212 treatment-naïve patients and reported substantial natural resistance mutation prevalence. The present review differs by using a stricter patient-level definition of primary resistance. Rather than treating every reported resistance-associated substitution as equivalent, the present analysis separates established primary resistance from secondary/compensatory and uncertain variants. ([8]) similarly emphasized that naturally occurring RT mutations are influenced by geography, genotype, HBeAg status, viral load, disease progression and detection methodology.

The crude prevalence of 4.25% treats all participants as one combined population, whereas the meta-analysis considers each cohort as an individual estimate and incorporates within-study uncertainty and between-study heterogeneity. Several high-prevalence studies were relatively small, while large cohorts with low prevalence contributed substantial information. Both statistics should therefore be reported.

The high heterogeneity is biologically plausible given differences in HBV genotype, geographic region, study period, treatment-naïve definition, patient selection, disease phase, sequencing technology, detection thresholds, mutation classification, sample size and cohort overlap. The rtM204I/V pathway was the most important primary resistance pathway identified. The mutation occurs in the YMDD motif and is strongly associated with resistance to lamivudine and related L-nucleoside analogues. The presence of rtM204V/I before treatment has biological significance, particularly when an antiviral affected by this pathway is considered.

The rtA181 pathway is another important primary resistance pathway and is associated with resistance to lamivudine and adefovir. Some studies in the dataset identified these substitutions in individuals without documented antiviral exposure. rtN236T represents a separate resistance pathway particularly associated with adefovir. Its occurrence in treatment-naïve individuals is less frequent than rtM204I/V in many populations, but it remains an established primary resistance mechanism.

A major methodological strength is the decision not to equate all RT substitutions with primary resistance. Mutations such as rtL180M, rtV173L, rtL80I/V and rtV207I can be important in resistance pathways but do not have the same evidence for primary resistance when found alone. Conservative classification reduces inflation of prevalence. The review indicates that molecular methodology is an important determinant of reported prevalence. Conventional sequencing generally identifies relatively abundant variants, whereas highly sensitive PCR and deep sequencing can identify lower-frequency variants. Detection of a very-low-frequency mutation does not necessarily mean that the variant will dominate during therapy. Future NGS studies should therefore report variant frequency, sequencing depth, quality thresholds and minimum allele-frequency criteria. Current guidelines emphasize potent agents with high genetic barriers to resistance, particularly tenofovir and entecavir ([1,2]). ([12]) found that resistance to modern agents is uncommon, particularly in treatment-naïve populations. Thus, baseline resistance findings should be interpreted in the context of the specific antiviral, mutation frequency, genotype, treatment history, adherence and virological response.

The findings are particularly relevant to countries with high HBV prevalence and limited access to molecular testing. WHO guidance emphasizes expanding diagnosis and access to effective treatment rather than requiring universal resistance testing before therapy. The results support strengthening molecular surveillance and treatment-outcome monitoring, particularly in high-burden regions. ([13]) studied 113 treatment-naïve patients in Bac Ninh, Vietnam and reported a broad RT resistance-associated mutation prevalence of 32.7%. However, most of these mutations involved rtV207M, illustrating why broad resistance-associated mutation counts are not equivalent to the strict primary-RAM endpoint used in the present review. Strengths include patient-level counting, conservative resistance classification, retention of zero-event studies, explicit consideration of cohort overlap, attention to assay sensitivity, and inclusion of contemporary evidence.

Limitations include very high heterogeneity, inconsistent definitions of treatment-naïve status, variation in molecular sensitivity, historical cohorts, incomplete patient-level reporting, possible cohort overlap and potential publication or reporting bias.

5. Implications for Future Research

• Future studies should clearly report the number enrolled, number successfully sequenced, exact treatment history, HBV genotype, sequencing method, sequencing depth, minimum variant-frequency threshold and number of unique patients with each mutation.

• Researchers should distinguish primary resistance mutations from putative, secondary and compensatory RT substitutions.

• NGS studies should report the biological and clinical rationale for their minimum allele-frequency threshold rather than treating analytical detection as equivalent to clinically meaningful resistance.

• Large prospective multicentre studies in Africa and other underrepresented regions are particularly important for defining contemporary baseline resistance prevalence.

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

5. CONCLUSION

Naturally occurring antiviral resistance-associated mutations are present in a proportion of treatment-naïve patients with chronic HBV infection. In the current synthesis of 42 cohorts involving 9,811 evaluable patients, 417 patients carried at least one established primary resistance-associated mutation, corresponding to a crude prevalence of 4.25%. The random-effects pooled prevalence was 1.80% (95% CI, 1.04–3.09%). However, the extremely high heterogeneity (I^2=93.3%) and wide prediction interval (0.08–30.41%) demonstrate that there is no single prevalence that adequately represents all HBV populations.

The findings reinforce the importance of distinguishing established primary resistance mutations from secondary, compensatory and uncertain RT substitutions. They also demonstrate why highly sensitive molecular methods may produce considerably higher estimates of baseline HBV resistance than conventional sequencing. In the era of potent high-genetic-barrier antiviral agents such as tenofovir and entecavir, naturally occurring resistance remains clinically relevant but should not be interpreted as synonymous with inevitable treatment failure ([1,2]).

6. DECLARATIONS

Ethics approval

Not applicable. This study used data from previously published studies and did not involve direct recruitment or interaction with human participants.

Consent for participation

Not applicable.

Consent for publication

Not applicable.

Data availability

The extracted study-level dataset and meta-analysis calculations should be provided as supplementary material upon submission, subject to journal requirements.

Conflict of interest

The authors should declare any actual or potential conflicts of interest.

Funding

No external funding was received for this study, unless otherwise applicable.

REFERENCES

1. World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. World Health Organization. 2024
2. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of hepatitis B virus infection. Journal of Hepatology. 2025;83(2):502–583. https://doi.org/10.1016/j.jhep.2025.03.018
3. Qian F, Zou W, Qin J, Li D. Naturally occurring genotypic drug-resistant mutations of HBV in Huzhou, China: a single-center study. Infect Drug Resist. 2017;10:507-509. doi:10.2147/IDR.S149992. PMID:29276396.
4. Zhu B, Wang T, Wei X, Zhuo Y, Liu A, Zhang G. Accumulation of mutations in reverse transcriptase of hepatitis B virus is associated with liver disease severity in treatment-naïve Chinese patients with chronic hepatitis B. Adv Clin Exp Med. 2017;26(7):1123-1129. doi:10.17219/acem/63998. PMID:29211361.
5. Ismail AM, Samuel P, Eapen CE, Kannangai R, Abraham P. Antiviral resistance mutations and genotype-associated amino acid substitutions in treatment-naïve hepatitis B virus-infected individuals from the Indian subcontinent. Intervirology. 2012;55(1):36-44. doi:10.1159/000323521. PMID:21311172.
6. Locarnini, S., & Mason, W. S. Cellular and virological mechanisms of HBV drug resistance. Journal of Hepatology. 2006;44(2):422–431.
7. Locarnini, S., & Zoulim, F. Molecular genetics of HBV infection. Antiviral Therapy. 2016;21(7), 1–12.
8. Choi, Y. M., Lee, S. Y., & Kim, B. J. Naturally occurring hepatitis B virus reverse transcriptase mutations related to potential antiviral drug resistance and liver disease progression. World Journal of Gastroenterology. 2018:24(16), 1708–1724. https://doi.org/10.3748/wjg.v24.i16.1708

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 09 Issue 11 November 2026
DOI: 10.47191/ijcsrr/V9-i11-19, Impact Factor: 8.048
IJCSRR @ 2026
www.ijcsrr.org

9. Zhang, Q., Cao, F., & Zhang, W. Incidence of natural resistance mutations in naïve chronic hepatitis B patients: A systematic review and meta-analysis. Journal of Gastroenterology and Hepatology. 2015;30(10), 1529–1538. https://doi.org/10.1111/jgh.12831
10. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., Stewart, L. A., Thomas, J., Tricco, A. C., Welch, V. A., Whiting, P., & Moher, D. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372, n71. https://doi.org/10.1136/bmj.n71
11. Rethlefsen, M. L., Kirtley, S., Waffenschmidt, S., Ayala, A. P., Moher, D., Page, M. J., Koffel, J. B., & PRISMA-S Group. PRISMA-S: An extension to the PRISMA statement for reporting literature searches in systematic reviews. Systematic Reviews. 2021;10, 39.
12. Lumley, S. F., Delphin, M., Mokaya, J. F., Tan, C. S. C., Martyn, E., Anderson, M., Li, K. C., Waddilove, E., Sukali, G., Downs, L. O., Said, K., Okanda, D., Campbell, C., Harriss, E., Shimakawa, Y., & Matthews, P. C. A systematic review and meta-analysis of the risk of hepatitis B virus (HBV) resistance in people treated with entecavir or tenofovir. Journal of Clinical Virology.2024;174, 105711. https://doi.org/10.1016/j.jcv.2024.105711
13. Hoang MC, Duong HQ, Le VD, Nguyen TTN, Ngo VL, Dang TH. Hepatitis B virus genotypes and antiviral drug resistance mutations in treatment-naïve patients with chronic hepatitis B in Bac Ninh, Vietnam: a cross-sectional study. Ther Adv Infect Dis. 2025;12:20499361251344784. doi:10.1177/20499361251344784. PMID:40529960.

Cite this Article: Muhammad, U.A., Yisa, E.N., Toyosi, B.R., Firdausi, Y., Aliyu, I.A., Mohammed, A., Sadiya, A.H. (2026). Prevalence and Distribution of Naturally Occurring Antiviral Resistance-Associated Mutations in Treatment-Naïve Chronic Hepatitis B: A Systematic Review and Meta-Analysis. International Journal of Current Science Research and Review, 9(11), pp. 5709-5721. DOI: https://doi.org/10.47191/ijcsrr/V9-i11-19