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# Two-Decade Evaluation of Pediatric Hepatitis B Immunization: Shifting Immune Kinetics and Metabolic/Clinical Predictors of Vaccine Non-Response

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**ABSTRACT:** **Background**: Hepatitis B remains a major public health threat associated with risks of cirrhosis and hepatocellular carcinoma. In Algeria, a country of intermediate endemicity (prevalence of 2% to 8%), vaccination was integrated into the Expanded Program on Immunization (EPI) in 2000. This study evaluates the effectiveness of this national strategy by measuring the post-vaccination immune response within a pediatric cohort in the Constantine region.

**Materials and Methods**: A retrospective, observational, cross-sectional study was conducted on 551 vaccinated children in the Constantine region. Quantitative measurement of anti-HBs antibodies was performed using an ELISA technique (seroprotection threshold set at >=10 IU/L) at the Constantine University Hospital. HBsAg, anti-HBc, HBeAg, and anti-HBe markers were also screened to assess viral circulation. Data were analyzed using SPSS v.21 software (statistical significance threshold set at $p < 0.05$).

**Results**: The overall vaccine seroprotection rate was 89.84% (n = 495), of whom 57.35% exhibited strong immunity (>100 IU/L). Older age at testing ($p < 0.001$), birth weight abnormalities ($p < 0.001$), non-compliance with the vaccination schedule ($p < 0.001$), and positive maternal HBsAg status ($p < 0.001$) significantly influenced post-vaccination immunization. Seroprevalences of 1.27% for HBsAg (7/551) and 2.18% for anti-HBc (12/551) were observed, indicating breakthrough infections or vertical transmission. Among children born to HBsAg-positive mothers, specific comorbidities such as type 1 diabetes ($p < 0.001$) and biological anemia ($p < 0.011$) were strongly associated with serological non-response.

**Conclusion**: The Algerian EPI ensures robust overall immunological coverage. Nevertheless, the insufficient seroprotection rate observed in children exposed to vertical transmission necessitates the implementation of systematic prenatal screening, rigorous post-vaccination serological follow-up, and standardized immunoprophylaxis (combining vaccine and specific immunoglobulins) within the first 24 hours of life. Finally, personalized management of children suffering from metabolic or hematological comorbidities is indispensable to optimize the overall efficiency of this national program.

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**RESEARCH HIGHLIGHTS**

- **Protection rate reached 89.84%** among 551 children in Constantine.
- **Vaccine protection drops over time**, down to 24.39% after 15 years.
- **Maternal hepatitis B infection** causes 72.73% of vaccine failures.
- **Maternal screening** and birth dose within 24 hours are recommended.
- **A challenge dose** distinguishes antibody loss from vaccine failure.

## 1. INTRODUCTION

Hepatitis B, caused by a DNA virus belonging to the Hepadnaviridae family, constitutes a major global public health challenge. It is responsible for severe complications, notably cirrhosis and hepatocellular carcinoma (HCC), causing nearly 820,000 deaths annually **[1]**. In the face of this challenge, systematic vaccination of newborns represents the most effective strategic lever for eradicating viral transmission **[2]**. In this context, evaluating the post-vaccination immune response is a critical strategic step to validate the efficacy of immunization programs, guarantee the sustainability of collective protection, and guide prevention policies **[3]**.

Public health officials have ranked the reduction of vaccine-preventable diseases among the ten greatest achievements of the 21st century, of which the hepatitis B vaccine is an integral part. Hepatitis B vaccination is indicated to prevent active infection by the virus, which can lead to chronic liver failure and hepatocellular carcinoma **[4]**. The hepatitis B virus (HBV) vaccine is the first vaccine capable of reducing cancer incidence. In 1992, the World Health Organization (WHO) recommended universal vaccination against HBV. It should be possible to eradicate the disease by applying this recommendation on a global scale **[5]**.

The first licensed hepatitis B vaccine was developed by purifying the hepatitis B surface antigen (HBsAg) from the plasma of chronic HBsAg carriers. Subsequently, recombinant DNA technology enabled the development of a recombinant hepatitis B vaccine. A series of three vaccine doses can confer long-term protection, exceeding 30 years according to some authors **[6]**. Globally, the WHO estimates the number of chronic HBV carriers at 296 million **[1]**. Algeria is historically classified as an intermediate endemicity zone, with HBsAg prevalence ranging between 2% and 8% in the general population **[7]**. The Ministry of Health integrated the recombinant vaccine into the National Immunization Program (NIP) in the year 2000 to break the chains of horizontal and vertical transmission. The current schedule relies on the administration of four doses (at birth, 2, 4, and 12 months), aiming for early and durable seroprotection **[8]**.

### 1.2. The Challenge of Immune Escape and Non-Response

The core objective of this study lies in analyzing the actual immunogenicity of the vaccine within a local pediatric cohort after two decades of EPI implementation. Despite the intrinsic efficacy of recombinant vaccines, international literature reports a vaccine non-response rate of 5% to 10%, defined by an anti-HBs antibody titer below the threshold of 10 IU/L **[9]**. Furthermore, the natural decline of antibody titers over time after primary vaccination raises the question of the persistence of immunological memory **[10] [11]**. In Algeria, although vaccine coverage is extensive, monitoring the immune response in children is crucial to identify clinical or biological variables that may compromise the effectiveness of the national program.

### 1.3. Objectives of the Study

The primary objective of this study is to evaluate anti-HBs antibody titers in a representative pediatric cohort from the Constantine region. Secondary objectives aim to identify clinical, chronological, and biological factors correlated with the absence of this post-vaccination sero-immunization. This approach is part of an effort to validate the real-world effectiveness of the Algerian EPI, using the Constantine region as a 'sentinel model' whose results can inform the management of immunological protection at a national level.

## 2. PATIENTS AND METHODS

The rigor of the methodological approach is fundamental to evaluating the actual effectiveness of the National Immunization Program (NIP) in Algeria. In an intermediate endemicity epidemiological context, the validity of immunogenicity data

depends on a strict standardization of selection criteria and measurement procedures, allowing for precise quantification of serological protection within the pediatric population of the Constantine region in eastern Algeria **[10]**.

### 2.1. Setting, Study Type, and Population

This research is based on a retrospective, cross-sectional, and observational study protocol conducted over a three-year period starting January 1, 2022. The study was conducted in the Constantine region and included a cohort of 551 randomly recruited children. To guarantee data homogeneity, the following inclusion criteria were applied:
1. Children who received a complete vaccination schedule against hepatitis B virus (HBV).

2. Documented absence of congenital or acquired immunodeficiency.
3. A minimum delay of one month after the administration of the last vaccine dose to ensure stabilized immune kinetics.

### 2.2. Data Collection and Variables Studied

Information was comprehensively collected by reviewing vaccination records and clinical files. The variables selected for analysis include:

- Demographic data: Sex, age at the time of serological quantification, and geographical origin.
- Neonatal parameters: Birth weight (identifying low birth weight/hypotrophia < 2000 g and macrosomia > 4000 g) and type of breastfeeding (exclusive maternal, artificial, or mixed).

- Clinical profile: Presence of chronic pathologies such as diabetes mellitus and anemia.
- Biological markers: Maternal serological status (HBsAg) and child's virological profile (HBsAg, anti-HBc, HBeAg, anti-HBe, HCV, and HIV).

### 2.3. Biological Procedures and Outcome Criteria

Serological quantification of anti-HBs antibodies was performed in the Microbiology Department of the Constantine University Hospital (CHUC) using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) technique. The primary outcome criterion to define serological protection was an anti-HBs antibody titer [more than or equal to] 10 IU/L. Subjects with titers below this threshold were classified as non-responders, in accordance with WHO international standards.

### 2.4. Statistical Analysis

Data processing was carried out using Microsoft Excel and SPSS (version 21) software. The analysis relied on:
- Description of qualitative variables by absolute and relative frequencies.
- Use of the Chi-squared test for comparing variables and identifying associations.
- Fisher's exact test was preferred when expected counts were small, particularly for low-frequency variables.
- The threshold for statistical significance was set at $p < 0.05$. This methodological rigor ensures the robustness of the results, allowing a critical evaluation of pediatric immune coverage.

### 2.5. Ethical Considerations

Biological results were communicated to the participants by the pediatric department according to a predefined protocol. The parents of participating children provided informed consent prior to inclusion in the study, in accordance with the applicable ethical requirements.

## 3. RESULTS

In this series of 551 vaccinated children, we noted that anti-HBV vaccination conferred protective immunity in 89.84% (495 cases) of children, compared to 10.16% (56 cases) who were non-immunized (anti-HBs antibody levels < 10 IU/L). Among the immunized children, 57.35% (316 cases) were strongly immunized (anti-HBs antibody titer > 100 IU/L) and 32.49% (179 cases) of the children were moderately immunized (anti-HBs antibody titer between 10 and 100 IU/L).

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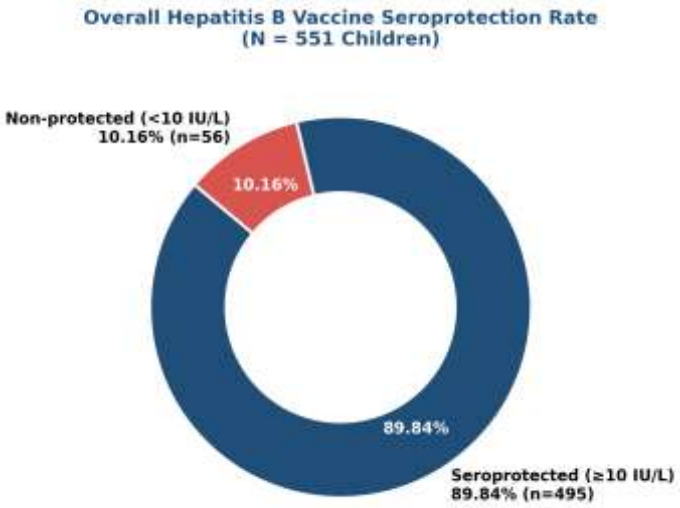


**Figure 1:** Overall vaccine seroprotection rate in the pediatric cohort (N = 551).

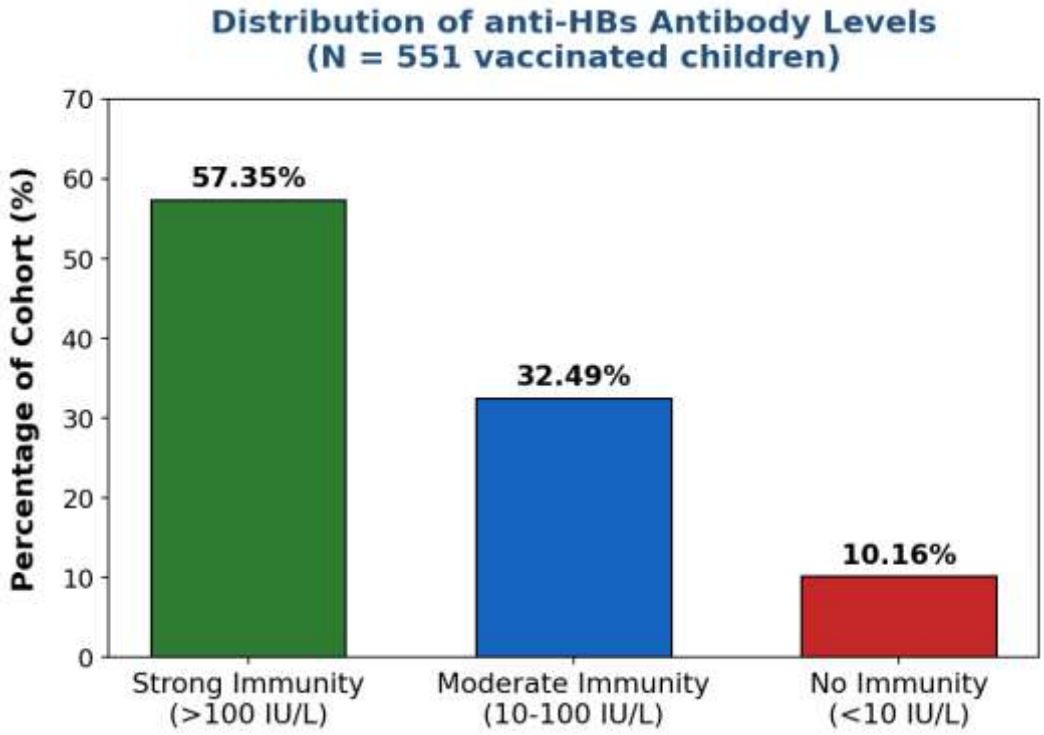


**Figure 2:** Distribution of anti-HBs antibody titers among vaccinated children (N = 551).

The bivariate statistical analysis revealed several highly significant predictors of vaccine non-response, including older age ($p < 0.001$), birth weight abnormalities ($p < 0.001$), non-compliance with the vaccination schedule ($p < 0.001$), maternal HBsAg positivity ($p < 0.001$), type 1 diabetes ($p < 0.001$), and biological anemia ($p < 0.001$ in v5, $p = 0.011$ in v4). A comprehensive summary of these variables is presented in the Consolidated Synthesis Table below.

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**Table 1.** Vaccine response according to sociodemographic and neonatal characteristics.

| Variable | Category | Non-Response <=10 IU/L, n (%) | Response >10 IU/L, n (%) | Total | p-value |
|---|---|---|---|---|---|
| Age | 14 months-3 years | 4 (4.3%) | 89 (95.7%) | 93 | <0.001 |
| | 4-7 years | 15 (10.6%) | 127 (89.4%) | 142 | |
| | 8-10 years | 17 (10.3%) | 148 (89.7%) | 165 | |
| | 11-15 years | 20 (13.2%) | 131 (86.8%) | 151 | |
| Sex | Male | 31 (13.0%) | 207 (87.0%) | 238 | 0.064 |
| | Female | 25 (8.0%) | 288 (92.0%) | 313 | |
| Geographical Origin | Constantine | 48 (10.5%) | 409 (89.5%) | 457 | 0.697 |
| | Guelma | 6 (9.2%) | 59 (90.8%) | 65 | |
| | Oum El Bouaghi | 2 (6.9%) | 27 (93.1%) | 29 | |
| Birth Weight | <2000 g | 12 (70.6%) | 5 (29.4%) | 17 | <0.001 |
| | 2000-4000 g | 37 (7.0%) | 489 (93.0%) | 526 | |
| | >4000 g | 7 (87.5%) | 1 (12.5%) | 8 | |
| Maternal HBsAg Status | Positive | 8 (72.7%) | 3 (27.3%) | 11 | <0.001 |
| | Negative | 48 (8.9%) | 492 (91.1%) | 540 | |
| Breastfeeding Type | Maternal | 21 (13.5%) | 134 (86.5%) | 155 | 0.258 |
| | Artificial | 17 (8.9%) | 174 (91.1%) | 191 | |
| | Mixed | 18 (8.8%) | 187 (91.2%) | 205 | |

**Table 2.** Vaccine response according to chronic pathologies.

| Chronic Pathology | Status | Non-Response <=10 IU/L, n (%) | Response >10 IU/L, n (%) | Total | p-value |
|---|---|---|---|---|---|
| Type 1 Diabetes | Yes | 15 (88.2%) | 2 (11.8%) | 17 (3.09%) | <0.001 |
| | No | 41 (7.7%) | 493 (92.3%) | 534 | |
| Anemia | Yes | 6 (66.7%) | 3 (33.3%) | 9 (1.63%) | <0.001 |
| | No | 50 (9.2%) | 492 (90.8%) | 542 | |

**Table 3.** Vaccine response according to serological markers.

| Serological Marker | Status | Non-Response <=10 IU/L, n (%) | Response >10 IU/L, n (%) | Total | p-value |
|---|---|---|---|---|---|
| HCV | Positive | 2 (40.0%) | 3 (60.0%) | 5 | 0.083 |
| | Negative | 54 (9.9%) | 492 (90.1%) | 546 | |
| HBsAg | Positive | 7 (100.0%) | 0 (0.0%) | 7 | <0.001 |
| | Negative | 49 (9.0%) | 495 (91.0%) | 544 | |
| Anti-HBc | Positive | 7 (58.3%) | 5 (41.7%) | 12 | <0.001 |
| | Negative | 49 (9.1%) | 490 (90.9%) | 539 | |
| HBeAg | Positive | 5 (100.0%) | 0 (0.0%) | 5 | <0.001 |
| | Negative | 51 (9.3%) | 495 (90.7%) | 546 | |
| Anti-HBe | Positive | 2 (100.0%) | 0 (0.0%) | 2 | 0.010 |
| | Negative | 54 (9.8%) | 495 (90.2%) | 549 | |

**Table 4.** Vaccine response according to ALT levels.

| ALT Level | Non-Response <=10 IU/L, n (%) | Response >10 IU/L, n (%) | Total | p-value (Fisher) |
|---|---|---|---|---|
| Elevated | 3 (60.0%) | 2 (40.0%) | 5 (0.91%) | 0.009 |
| Normal | 53 (9.7%) | 493 (90.3%) | 546 | |

**Table 5.** Vaccine response according to vaccination characteristics.

| Variable | Category | Non-Response <=10 IU/L, n (%) | Response >10 IU/L, n (%) | Total | p-value |
|---|---|---|---|---|---|
| Respect of Schedule | No | 41 (63.1%) | 24 (36.9%) | 65 | <0.001 |
| | Yes | 15 (3.1%) | 471 (96.9%) | 486 | |
| Time Since Vaccination | 2 years | 2 (4.1%) | 47 (95.9%) | 49 | <0.004 |
| | 5 years | 2 (6.3%) | 30 (93.8%) | 32 | |
| | 10 years | 3 (5.5%) | 52 (94.5%) | 55 | |
| | 15 years | 10 (24.4%) | 31 (75.6%) | 41 | |

## 4. DISCUSSION

### 4.1. Comparative Analysis of Overall Seroprotection Rates

Integrating vaccination against hepatitis B virus (HBV) into the Expanded Program on Immunization (EPI) in Algeria since the year 2000 represents a major milestone in public health. Twenty years after its implementation, the overall seroprotection rate stands as the pivotal indicator to validate the effectiveness of immunization strategies. In our cohort in Constantine, we report a seroprotection rate of 89.84%, a performance we describe as robust and aligned with WHO objectives for intermediate endemicity areas (prevalence 2%-8%) **[12]**. While encouraging, this result must be put into perspective with international dynamics to identify opportunities for optimization. This comparative analysis is synthesized globally in Figure 3, which places the seroprotection rates of our cohort in perspective with those described worldwide.

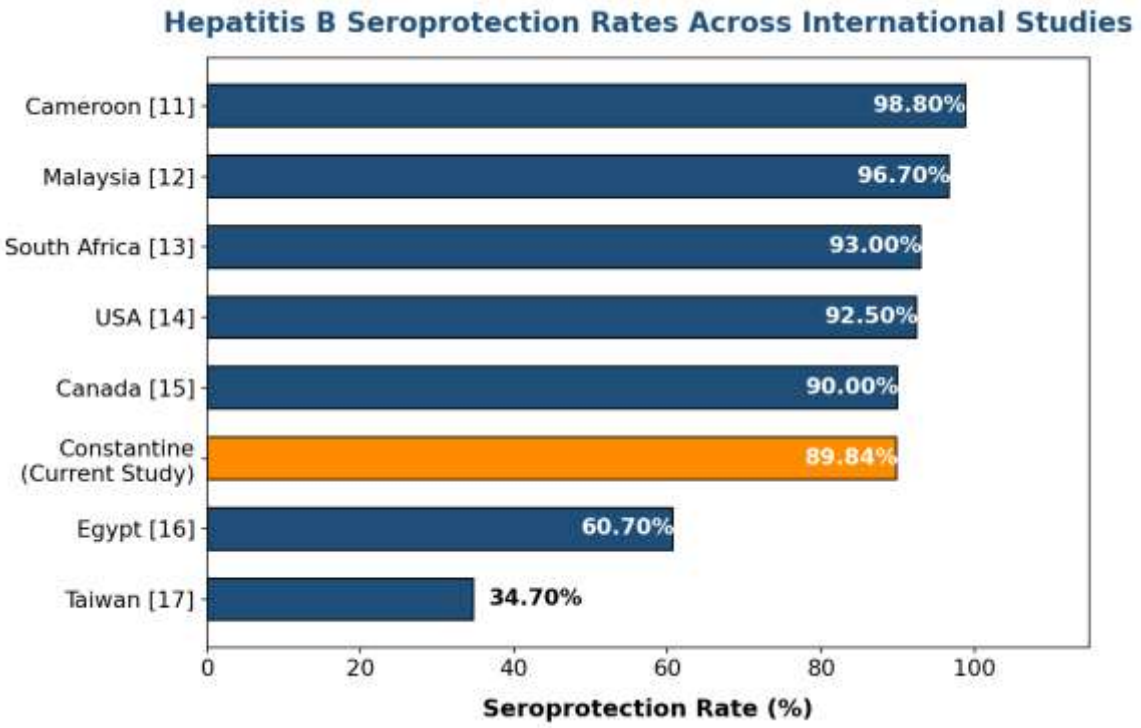


**Figure 3:** Comparison of pediatric overall hepatitis B vaccine seroprotection rates across international studies**.**

The comparative analysis reveals that Algeria significantly surpasses the rates reported in Taiwan **[17]** or Egypt **[16]**. This success reflects the efficacy of the Algerian EPI in controlling early horizontal transmission. Similar or comparable rates are observed in Canada (90%) **[15]**, the USA (92.5%) **[14]**, and South Africa (93%) **[13]**. However, the persistent gap with Malaysia (96.7%) **[12]** suggests 'missed opportunities', likely related to deficiencies in the logistics of the birth dose. While the overall rate is satisfactory for herd immunity, individual variability in the immune response warrants a rigorous analysis of circulating antibody kinetics.

**4.2. Antibody Kinetics and Robustness of Immunological Memory**

On a strategic level, understanding the persistence of long-term immunity is fundamental to avoiding unnecessary booster policies in the general population. Our data highlight a physiological decay in anti-HBs antibody titers, with the protection rate declining from 95.92% at 2 years of age to 75.61% at 15 years. This erosion is significantly correlated with the subject's age ($p = 0.001$) and the time since vaccination ($p = 0.004$). However, it is clinically imperative to specify that a decrease in serum titers does not mean a loss of protection. The robustness of immunity relies on a powerful anamnestic response mediated by specific memory T and B cells **[18]**. Upon exposure, these cells ensure a rapid surge in antibodies, neutralizing the virus before any hepatic damage occurs. For subjects presenting a titer below the 10 IU/L threshold, administering a 'challenge dose' constitutes a crucial diagnostic tool to confirm the presence of active immunological memory **[19]**. This approach justifies the absence of systematic boosters in initial responders, although certain host-related determinants can compromise this priming from the neonatal period **[20]**. Nevertheless, in an intermediate endemicity context, this decline invites vigilance as children enter adolescence, a period of increased risk for horizontal transmission.

**4.3. Clinical Determinants and Impact of Comorbidities on Immunogenicity**

An infant's immune trajectory is early-on influenced by their physiological profile. Our work identifies high-risk groups for non-response that warrant increased surveillance:
- Birth weight and prematurity: We report a major correlation between birth weight and immunogenicity ($p < 0.001$). A statistical correction of our data reveals that low birth weight is a massive predictor of failure: within the hypotrophic child group (<2000 g), the non-response rate reaches approximately 70% (12 out of 17 children). These results agree with those of Schillie SF et al. **[21]**, whose review of 43 studies reports lower seroprotection in infants with birth weight < 2000 g than in those [more than or equal to] 2000 g, especially when vaccination is initiated within the first three days of life. This lower

immunogenicity is attributed to the immune immaturity of premature infants and is more pronounced as birth weight is lower. Nonetheless, prematurity and low birth weight do not constitute contraindications to birth-dose HBV vaccination **[21]**. In infants weighing < 2000 g, the dose administered at birth may induce an insufficient immune response and, according to adopted recommendations, may not be counted towards the primary series, thus requiring additional doses. Vaccine management must also take into account maternal HBsAg status. Finally, the impact of low birth weight/hypotrophy at birth ($p = 0.001$) confirms that the immature immune system of premature and low birth weight infants requires special attention. These subjects display sub-optimal lymphocyte activation, potentially justifying an adjustment of doses or the vaccination schedule.

- Vertical transmission: Mother-to-child transmission represents a major route of HBV transmission. In the absence of preventive measures, the risk of perinatal transmission is highly influenced by HBeAg status and, above all, by maternal viral load. Newborns infected with HBV have an approximately 90% risk of progressing to chronic infection **[22] [23]**. Prevention relies on the early administration of an anti-HBV vaccine dose at birth, associated with specific hepatitis B immunoglobulins (HBIG) in exposed newborns. This prophylaxis must be administered as early as possible, ideally within the first 24 hours of life **[24]**. In our cohort, the rate of insufficient vaccine response (<10 IU/L) was alarming among children born to HBsAg+ mothers, reaching 72.73%. This result underscores the importance of a complete immunoprophylaxis strategy in exposed newborns. Despite correctly performed prophylaxis, breakthrough infections can occur, particularly in newborns of mothers with high viral loads. Maternal viral load is indeed the main determinant of residual transmission risk. An HBV-DNA level [more than or equal to] 200,000 IU/mL is considered a threshold at which maternal antiviral prophylaxis with tenofovir may be indicated in addition to neonatal immunoprophylaxis **[22] [25]**. More rarely, vaccine escape variants can contribute to the occurrence of infection despite vaccination. These variants affect particularly the 'a' determinant of HBsAg, the main target of neutralizing antibodies induced by vaccination. The G145R mutation constitutes one of the best-characterized escape variants. However, their overall contribution to vaccine failure remains low and does not challenge the effectiveness of current vaccination programs **[26]**. The detection of HBsAg or HBV-DNA in umbilical cord blood can be associated with in utero infection, but these markers must be interpreted with caution in evaluating mother-to-child transmission. In our cohort, HBsAg seroprevalence was 1.27%, while anti-HBc reached 2.18%. This discordance may indicate prior exposure to HBV, suggesting persistent viral circulation and the possibility of previous or subclinical infections.

- Metabolic and hematological comorbidities: The response is significantly altered by type 1 diabetes ($p = 0.001$) and anemia ($p = 0.001$). Pathophysiologically, chronic hyperglycemia alters Natural Killer (NK) cell function. This dysfunction compromises the production of IFN-gamma necessary for the maturation of B lymphocytes into antibody-secreting plasma cells. Similarly, biological anemia limits protein synthesis, affecting the production of immunoglobulins.

### 4.4. Influence of Compliance with the Vaccination Schedule and Birth Dose

Compliance with the vaccination schedule is an important determinant of vaccine effectiveness. In our cohort, non-compliance with the schedule was significantly associated with the absence of seroprotection ($p = 0.010$), with 73.21% of non-immunized children presenting an irregular vaccination history. Administering the birth dose of the anti-HBV vaccine within the first 24 hours of life is an essential measure to prevent perinatal transmission and early-life infections. Any delay in its administration can expose the newborn to a period of vulnerability before subsequent doses are completed, especially in intermediate endemicity contexts such as Algeria **[24]**.

### 4.5. Factors without Significant Influence on the Immune Response

In a perspective of refining predictive models, it is essential to identify variables that do not impact immunogenicity. Our analyses demonstrate the absence of a significant influence of sex ($p = 0.064$), type of breastfeeding ($p = 0.258$), and HCV co-infection ($p = 0.083$). These results highlight the universality of vaccine effectiveness within the Algerian pediatric population, independently of these parameters, thereby reinforcing the validity of a generalized vaccination strategy without distinction of gender or feeding mode.

### 4.6. Methodological Limitations and Future Perspectives

The intellectual honesty essential to validating our findings requires highlighting the limitations of this work. Opportunistic recruitment and the lack of traceability of vaccine brands limit the comparative scope across manufacturers. More crucially, the absence of serological data at month 1 to month 2 (one month after primary vaccination) constitutes a major gap. This limitation prevents us from differentiating primary vaccine failure (initial absence of seroconversion) from secondary vaccine

loss (antibody decay after an initial response). This distinction is vital to guide clinical decisions: a primary failure justifies the immediate administration of a fourth dose, whereas a secondary loss warrants simple monitoring of immunological memory. These limits shape the perspectives of future research, which should prioritize rigorous longitudinal follow-ups starting from birth.

## 5. CONCLUSION AND RECOMMENDATIONS

Evaluating post-vaccination immunity is an indispensable strategic tool to validate the operational efficiency of the Expanded Program on Immunization (EPI) in Algeria. Facing intermediate endemicity of the hepatitis B virus (HBV) on national territory—characterized by an HBsAg prevalence historically oscillating between 2% and 8%—serological characterization of pediatric cohorts allows for the quantification of seroprotection conferred by the standardized vaccine schedule and the identification of biological and operational determinants of non-immunization.

The cross-sectional study conducted in the Constantine region on a cohort of 551 vaccinated children demonstrated robust overall efficacy, with 89.84% of them (n = 495) presenting a protective anti-HBs antibody titer ([more than or equal to] 10 IU/L), while 10.16% (n = 56) remained below the seroprotection threshold. Bivariate analysis of statistical correlations reveals the determining influence of temporal, metabolic, and clinical variables on this immunization failure. Regarding immune kinetics, a progressive but highly significant erosion of humoral immunity is observed with increasing age ($p < 0.001$), with the 11-15 years age group concentrating a non-immunization rate of 35.71% (20 out of 56 non-immunized subjects); this decrease is closely correlated with the time since primary vaccination ($p < 0.001$), with the loss of protection reaching 24.39% (10 cases out of 41) after 15 years, suggesting a natural and physiological decline in circulating antibodies despite the probable persistence of specific T and B cell memory.

Among the major neonatal and metabolic predictors, birth weight stands out as a key variable ($p < 0.001$): while low birth weight (<2000 g) alters the response due to the immaturity of the neonatal immune system, showing a non-immunization rate of 70.59% (12 cases out of 17), macrosomia (>4000 g) exerts an even more deleterious impact with an 87.5% non-response rate (7 cases out of 8). Furthermore, exposure to vertical transmission constitutes a major factor in vaccine failure, as 72.73% (8 out of 11) of children born to HBsAg-positive mothers were found to be non-immunized ($p < 0.001$), emphasizing the limitations of standardized monovaccination without adequate seroprophylaxis using specific anti-HBs immunoglobulins.

Similarly, chronic comorbidities deeply alter humoral immunogenicity: type 1 diabetes appears as a critical comorbidity with a non-protection rate of 88.24% (15 cases out of 17, $p < 0.001$), potentially related to a functional alteration and under-representation of Natural Killer (NK) cells involved in the regulation of the antibody response. Personalised management of these vulnerable populations and children suffering from metabolic or hematological comorbidities is essential to optimize the overall efficiency of this national program.

### 5.2. Perspectives and Public Health Recommendations

Eradicating HBV in Algeria requires this shift toward targeted serological surveillance and personalization of vaccination protocols. We advocate the following recommendations:

- Birth dose: Mandatory universal implementation of the monovalent dose within <24 hours of life to block vertical transmission.
- Newborns <2000 g: Systematic implementation of a reinforced four-dose schedule (M0, M1, M2, M6).
- HBsAg+ mamas/mothers: Strict application of immunoprophylaxis (vaccine + HBIG) at birth.
- Interrupted schedule: Adopt a catch-up philosophy without restarting the series from zero, regardless of the duration of the delay.
- Surveillance and 'Challenge Dose': Evaluate non-responding subjects with a booster dose to confirm the existence of cellular memory before classifying them as vaccine failures.

### 5.3. Future Research Directions

Long-term epidemiological surveillance is crucial. It is recommended to implement large-scale longitudinal studies to monitor the kinetics of immunity over several decades. A priority research area should concern the microbiological monitoring of

escape mutants (S gene mutations) to evaluate their potential circulation within the vaccinated population and adjust, if necessary, the composition of future recombinant vaccines.

**Declaration of Interest & Contribution Statement**

**Declaration of Interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**REFERENCES**

[1] World Health Organization. Hepatitis B: key facts and global prevalence data. Geneva: World Health Organization; 2019.

[2] Li H, Yan L, Shi Y, Lv D, Shang J, Bai L, Tang H. Hepatitis B virus infection: overview. In: Tang H, editor. Hepatitis B Virus Infection: Molecular Virology to Antiviral Drugs. Singapore: Springer Singapore; 2020. p. 1–16.

[3] Denis F. Hepatitis B vaccination: evolution of hepatitis B vaccine coverage, public health impact, efficiency limits, new vaccines. Bull Acad Natl Med. 2016;200(1):33–45. doi:10.1016/S0001-4079(19)30799-X.

[4] Hodgens A, Marathi R. Hepatitis B vaccine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.

[5] Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H, editors. Hepatology: a clinical textbook. 10th ed. Hamburg: Medizin Fokus Verlag; 2020.

[6] Zhao H, Zhou X, Zhou YH. Hepatitis B vaccine development and implementation. Hum Vaccin Immunother. 2020;16(7):1533–1544. doi:10.1080/21645515.2020.1732166.

[7] Boumansour N, Midoun N, Mallem L, Hakem S. Profil épidémiologique de l'hépatite virale B à l'ouest Algérien, 2010–2012. Rev Epidemiol Sante Publique. 2016;64:S207. doi:10.1016/j.respe.2016.06.100.

[8] Ministère de la Santé, de la Population et de la Réforme Hospitalière. Arrêté du 28 octobre 2000 fixant le calendrier de vaccination obligatoire contre certaines maladies transmissibles. Alger: Ministère de la Santé, de la Population et de la Réforme Hospitalière; 2000.

[9] Denis F, Roingeard P. Vaccination contre l'hépatite B. EMC - Hépatologie. 2017;12(4):1–14. Article 7-015-B-32.

[10] Gomes LC, Sanson MCG, Brainin P, de Melo MCV, de Souza RM, Mazaro J, et al. Levels of hepatitis B antibody titers are affected by age and doses gap time in children from a high endemic area of the western Amazon. PLoS One. 2021;16(7):e0253752. doi:10.1371/journal.pone.0253752.

[11] Anutebeh EN, Tatah L, Feteh VF, Aroke D, Assob JCN, Choukem SP. Immune response to hepatitis B vaccine following complete immunization of children attending two regional hospitals in the Southwest region of Cameroon: a cross-sectional study. BMC Infect Dis. 2021;21(1):1205. doi:10.1186/s12879-021-06913-y.

[12] Wong HT, Ho SC, Chew KS, Lee WS. Immune response in infants after universal hepatitis B vaccination: a community-based study in Malaysia. Singapore Med J. 2013;54(4):224–226. doi:10.11622/smedj.2013078.

[13] Simani OE, Leroux-Roels G, François G, Burnett RJ, Meheus A, Mphahlele MJ. Reduced detection and levels of protective antibodies to hepatitis B vaccine in under 2-year-old HIV-positive South African children at a paediatric outpatient clinic. Vaccine. 2009;27(1):146–151. doi:10.1016/j.vaccine.2008.10.004.

[14] Le MH, Yeo YH, So S, Gane E, Cheung RC, Nguyen MH. Prevalence of hepatitis B vaccination coverage and serologic evidence of immunity among US-born children and adolescents from 1999 to 2016. JAMA Netw Open. 2020;3(11):e2022388. doi:10.1001/jamanetworkopen.2020.22388.

[15] Gilca V, De Serres G, Boulianne N, Murphy D, De Wals P, Ouakki M, et al. Antibody persistence and the effect of a booster dose given 5, 10 or 15 years after vaccinating preadolescents with a recombinant hepatitis B vaccine. Vaccine. 2013;31(3):448–451. doi:10.1016/j.vaccine.2012.11.037.

[16] Salama II, Sami SM, Elserougy SM, Emam HM, Salama SI, Elhariri HM, et al. Humoral immune memory to hepatitis B vaccine after primary vaccination of children and adolescents in Assiut, Egypt. Oman Med J. 2020;35(5):e175. doi:10.5001/omj.2020.117.

[17] Ni YH, Chang MH, Wu JF, Hsu HY, Chen HL, Chen DS. Minimization of hepatitis B infection by a 25-year universal vaccination program. J Hepatol. 2012;57(4):730–735. doi:10.1016/j.jhep.2012.05.021.

[18] AlAteeq MA, AlEnazi LM, AlShammari MS, AlAnazi EE, Al-Hababi FH, Alateeq AM. Long-term immunity against hepatitis B virus after routine immunization among adults visiting primary care centers in Riyadh, Saudi Arabia. Cureus. 2022;14(1):e21266. doi:10.7759/cureus.21266.

[19] Van Damme P, Dionne M, Leroux-Roels G, Van Der Meeren O, Di Paolo E, Salaun B, et al. Persistence of HBsAg-specific antibodies and immune memory two to three decades after hepatitis B vaccination in adults. J Viral Hepat. 2019;26(9):1066–1075. doi:10.1111/jvh.13125.

[20] Ma JC, Wu ZW, Zhou HS, Gao Z, Hao ZY, Jin F, et al. Long-term protection at 20–31 years after primary vaccination with plasma-derived hepatitis B vaccine in a Chinese rural community. Hum Vaccin Immunother. 2020;16(1):16–20. doi:10.1080/21645515.2019.1646575.

[21] Schillie SF, Murphy TV. Seroprotection after recombinant hepatitis B vaccination among newborn infants: a review. Vaccine. 2013;31(21):2506–2516. doi:10.1016/j.vaccine.2012.12.012.

[22] World Health Organization. Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy. Geneva: World Health Organization; 2020. ISBN: 978-92-4-000270-8.

[23] World Health Organization. Hepatitis: preventing mother-to-child transmission of the hepatitis B virus [Internet]. Geneva: World Health Organization; 2020.

[24] Ministère de la Santé, Direction Générale de la Prévention et de la Promotion de la Santé. Guide pratique de mise en œuvre du calendrier national de vaccination [Internet]. Alger: Ministère de la Santé; 2023.

[25] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of liver diseases in pregnancy. J Hepatol. 2023;79(3):768–828. doi:10.1016/j.jhep.2023.03.006.

[26] Sheldon J, Rodes B. Hepatitis B vaccination: are escape mutant viruses a matter of concern? J Viral Hepat. 2008;15(10):673–679.