Regional Inequity in 4CMenB Vaccination Coverage in Belgium: A Retrospective Ecological Study

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Keywords

Neisseria meningitidis ; invasive meningococcal disease ; vaccines ; Belgium.

Abstract

Invasive meningococcal disease is associated with a high mortality rate and severe long-term health issues. In Belgium, most serogroup-documented invasive meningococcal disease cases are caused by serogroup B. The four-component meningococcal serogroup B vaccine (4CMenB) is recommended in Belgium for certain age groups but is not a publicly funded vaccine. This analysis aimed to estimate 4CMenB coverage and the association between 4CMenB coverage, age and household income at a municipality level in Belgium. 4CMenB vaccinations between November 2022 and October 2023, as well as individuals' age, location and household income level were obtained. Individuals with two to three doses of 4CMenB and municipalities with ≥100 vaccinees were included in this analysis. Of the 16,816 individuals vaccinated, 71% were concentrated within 11% (65/593) of municipalities. 4CMenB coverage was highest amongst the <1 (16%) and 1–2 years (14%) age groups. There was a correlation observed between 4CMenB coverage and age, as well as 4CMenB coverage and household income at a municipality level. This interaction was observed in individuals up to 11 years, with the most statistically significant correlation occurring in age groups <1 and 1–2 years (both $p<0.001$). 4CMenB not being a publicly funded vaccine may contribute to inequity in vaccine access, potentially placing low-income populations in Belgium at increased risk of invasive meningococcal disease. Universal vaccine recommendations and inclusion of 4CMenB into Belgium's regional immunisation programs could reduce potential inequity in vaccine access.

At the end of the article you will find a graphical abstract that visually summarises the content of the article.

Introduction

Invasive meningococcal disease (IMD), caused by *Neisseria meningitidis*, is associated with a high mortality rate and long-term health implications (1, 2). There are twelve types, or serogroups, of this bacterium, six of which can cause epidemics (3). In Europe, the 2022 IMD notification rate rose to 0.3 cases per 100,000 population, after a decline in incidence in 2020 and 2021, potentially caused by COVID-19 pandemic quarantine measures. Incidence in 2022 was highest in infants aged <1 year, followed by those aged 1–4 and 15–24 years. Notably, meningitis caused by meningococcal serogroup B (MenB) accounted for 62% of IMD cases documented with a specific serogroup (4). Looking at 2022 Belgian data, incidence was highest in those aged 0–4 years (1.2 cases per 100,000 population) and <1 year (2.5 cases per 100,000 population) (5). Belgian IMD incidence in 2023 was 0.71 cases per 100,000 population and MenB accounted for 42% of cases (6).

MenB can be prevented through vaccination, with two MenB vaccines currently available in Belgium. The four-component MenB vaccine (4CMenB, Bexsero®; GSK), approved by the European Medicines Agency in 2013 for individuals aged ≥2 months, protects against MenB (7). In Belgium, 4CMenB can be administered to individuals aged ≥2 months on an individual basis, is preferentially recommended on this individual basis for children aged 2 months to 5 years as well as adolescents aged 15–19 years and is universally recommended for high risk groups, at a 2-dose vaccine schedule, followed by a booster dose for those aged <2 years or individuals at high risk (8, 9). 4CMenB is currently the only vaccine in Belgium recommended for infants and young children. The MenB-factor H-binding protein vaccine (MenB-FHbp, Trumenba®; Pfizer), approved by the European Medicines Agency in 2017 for individuals aged ≥10 years, also protects against MenB (10). MenB-FHbp was made available in Belgium in 2019. MenB-FHbp can be administered to individuals in Belgium aged ≥10 years on an individual basis, is preferentially recommended on this individual basis for adolescents aged 15–19 years and is universally recommended for high risk groups, at a 2-dose vaccine schedule, with a booster dose considered for individuals still at risk for IMD and high risk groups (8, 9).

While MenB-FHbp is not included in any regional immunisation programs, 4CMenB is included in the National Immunisation Program of several European countries, including France, Luxembourg, Switzerland, Germany, Portugal, Czech Republic, United Kingdom, Italy, Ireland, Malta, Andora, San Marino and Lithuania (11-15). As 4CMenB is recommended on an individual basis in Belgium, it is not included in regional immunisation programs and is therefore not a publicly funded vaccine. Previous studies, conducted in Australia, France, Spain, United States and United Kingdom, have assessed the association between social deprivation and risk of meningococcal disease, hospitalisation for meningococcal disease or uptake of meningococcal vaccines. These studies show uptake of non-publicly funded vaccines correlates with income, suggesting inequity in access to vaccination, often leaving those most at risk, more vulnerable (16-18). Adding 4CMenB to regional immunisation programs in Belgium could increase vaccine access and immunisation coverage, thereby decreasing social inequity and protecting those at greatest risk of IMD (16).

The relationship between socioeconomic status and meningococcal vaccine coverage in Belgium is not clearly understood. This study aimed to

estimate 4CMenB coverage and evaluate associations between vaccine coverage, age and household income across Belgian municipalities.

Materials and methods

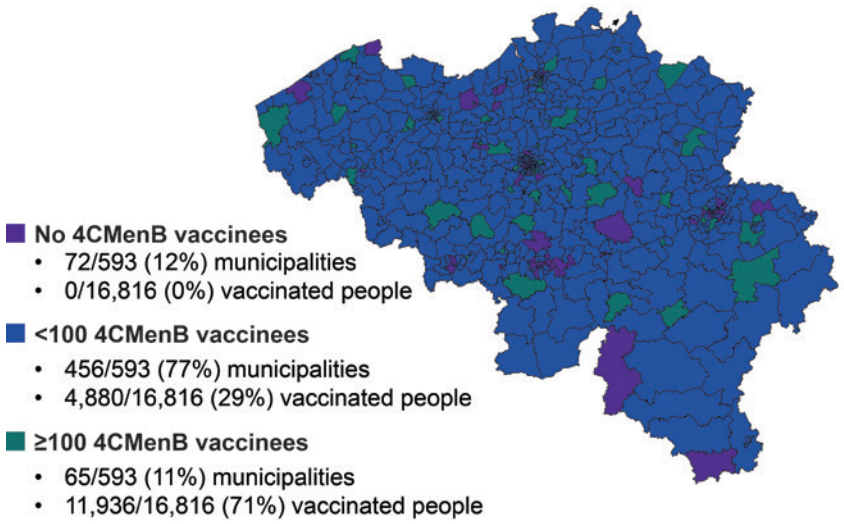
This retrospective, ecological study used data captured in longitudinal prescriptions and sociodemographic databases to obtain information on vaccine uptake, individual's age, location and household income level. Belgium is divided into three regions, 11 provinces (including Brussels) and 589 municipalities. All analyses were performed at a municipality level. Where municipalities are named, general description of municipalities may not align with the formal name due to the municipality granularity level used to map data to territories.

Longitudinal prescriptions data panel: Vaccine uptake, age and location

Vaccine uptake information, along with the age and location of vaccinees, were sourced from a national IQVIA sell-out database. This longitudinal prescriptions data panel contains patient-level information on what is dispensed by pharmacists to patients and collects information on approximately 30% of retail pharmacies (both chain and privately-owned pharmacies) in Belgium.

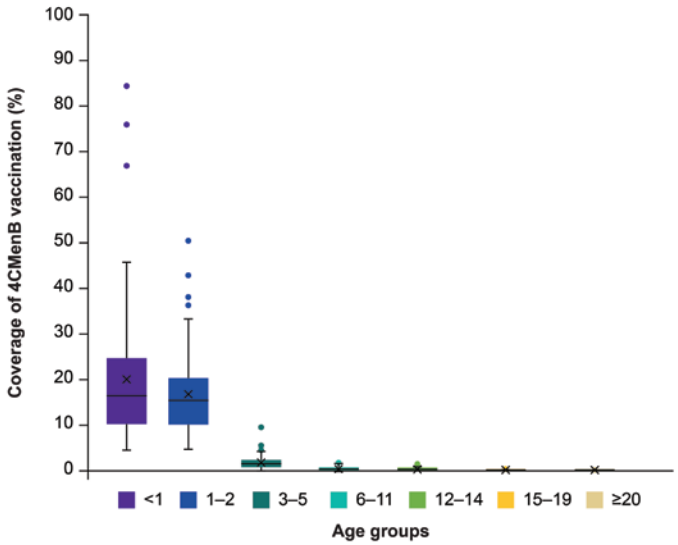
The panel contains metrics on the product, the patient and the prescriber, throughout time, as follows. Metrics on the product, i.e., what is dispensed by pharmacies, informed vaccine uptake data. The age of patients was not available from the database, but individuals' year of birth could be obtained. Posteriori analyses of patients' age range was obtained via a trusted third-party anonymisation process. At least 100 individuals per municipality were required for precise age determination. Age was aggregated to seven age classes based on age at first vaccination: <1 year, 1–2 years, 3–5 years, 6–11 years, 12–14 years, 15–19 years, ≥20 years. Age was rounded to the year (e.g., an individual aged 2.5 years would be classed as 2 years and belong to the 1–2 years age class). The municipality of the vaccination prescriber was used as a proxy to assign a municipality to the vaccinated individual, as an individual's municipality was not provided in the database to maintain data privacy. If an individual had more than one prescriber, the municipality of the first 4CMenB prescription was used.

Figure 1: Estimated 4CMenB coverage in Belgium between November 2022 and October 2023.



Municipalities with ≥100 4CMenB vaccinees were further analysed in this study.

Figure 2: Distribution of 4CMenB vaccinated population per municipality by age class.



Variation of vaccinated population per municipality, by age group; box plots show mean, median (interquartile range), minimum and maximum 4CMenB vaccination coverage

Sociodemographic database: Household income level

The sociodemographic database contains detailed information regarding the number of inhabitants and households, their distribution by age class and type of household (e.g, household size and property type). It also contains overall indicators (composite scores) of income, age (of the eldest member of a household) and type of housing. These sociodemographic data are obtained via a trusted third-party that aggregated data at a granular level. These aggregated data were then mapped to the Belgian municipality level. The indicator of income is a composite index and was calculated by aggregating wealth and income variables, normalised so that mean (standard deviation) at the municipality level was 100 (10). Income level ranged from 75 (lowest income indicator) to 140 (highest income indicator). The income indicator is a well-established proxy for the actual level of income, which is not directly available from the database.

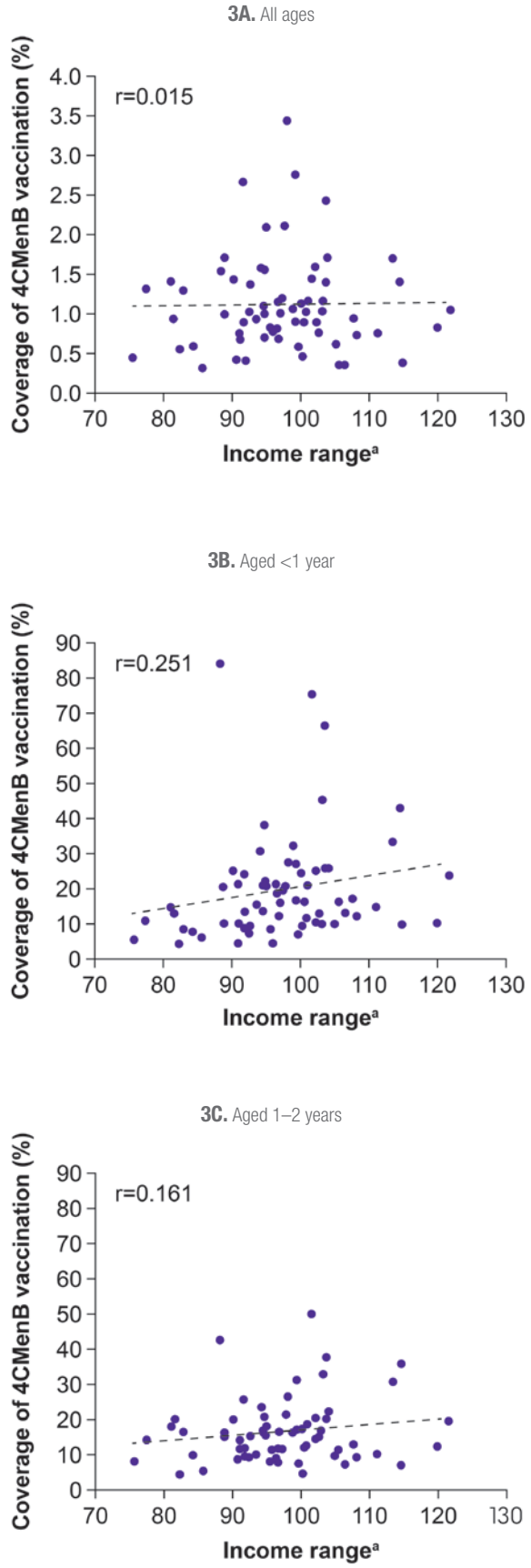
Patient population and municipality selection

Individuals with either only one or more than three doses of 4CMenB were excluded from this analysis. From November 2022 to October 2023, all individuals with two doses and those aged ≤2 years with three doses within a year were included in the vaccinated population. Due to anonymisation requirements only municipalities with at least 100 vaccinated individuals (two or three doses of 4CMenB) were analysed.

Descriptive and statistical analysis

4CMenB coverage at a municipality level was calculated as the percentage of 4CMenB vaccinated individuals out of the total municipality population. Coverage for a specific age class was calculated as the proportion of 4CMenB vaccinated individuals out of the total municipality population in the same age class. 4CMenB coverage per age class and per household income level was assessed via descriptive statistical analysis. A correlation analysis was performed to estimate the association between 4CMenB coverage and household income in the overall population and per age

Figure 3: Correlation analysis showing 4CMenB coverage versus household income for different age classes.



a: following aggregation at a municipality level, income level was rescaled to have a score of 100 on average, with 75 being the lowest income indicator and 140 being the highest income indicator.

class. A logistic regression modelling approach was implemented to assess the association between 4CMenB coverage by age and household income. Significant effects were measured using the likelihood-ratio test of significance of effects, with a 5% significance level.

Objective

The primary objective of this analysis was to estimate 4CMenB coverage at a municipality level in Belgium – overall, per age class and per income level. The secondary objective of this analysis was to estimate the association between 4CMenB coverage, age and household income level at a municipality level in Belgium.

Results

4CMenB coverage

Of the 16,816 individuals who had received two to three doses of 4CMenB and were therefore eligible for assessment, 71% (n=11,936) were concentrated within 11% (65/593) municipalities across Belgium. Most municipalities (77%) contained <100 vaccinated individuals and 12% of municipalities contained no individuals vaccinated with 4CMenB (Figure 1). These municipalities were not further analysed. The 65 municipalities further assessed in this study, each containing ≥100 vaccinated individuals, were assessed as representative of all Belgian municipalities according to distribution across Belgium, age and income level. Approximately 50% of analysed municipalities were in Flanders, 40% in Wallonia and 10% in Brussels, which aligns with the regional spread of all municipalities. Average national income level had a composite score of 100 and the analysed municipalities had a similar median composite score of roughly 95.

4CMenB coverage was highest in the two youngest age classes (<1 year: 16%; 1–2 years: 14%), with coverage decreasing significantly with age and reaching <0.5% in those aged ≥12 years. For those aged <1 year and 1–2 years, 4CMenB vaccination coverage varied significantly between the municipalities (Figure 2).

Association between 4CMenB coverage, age and household income

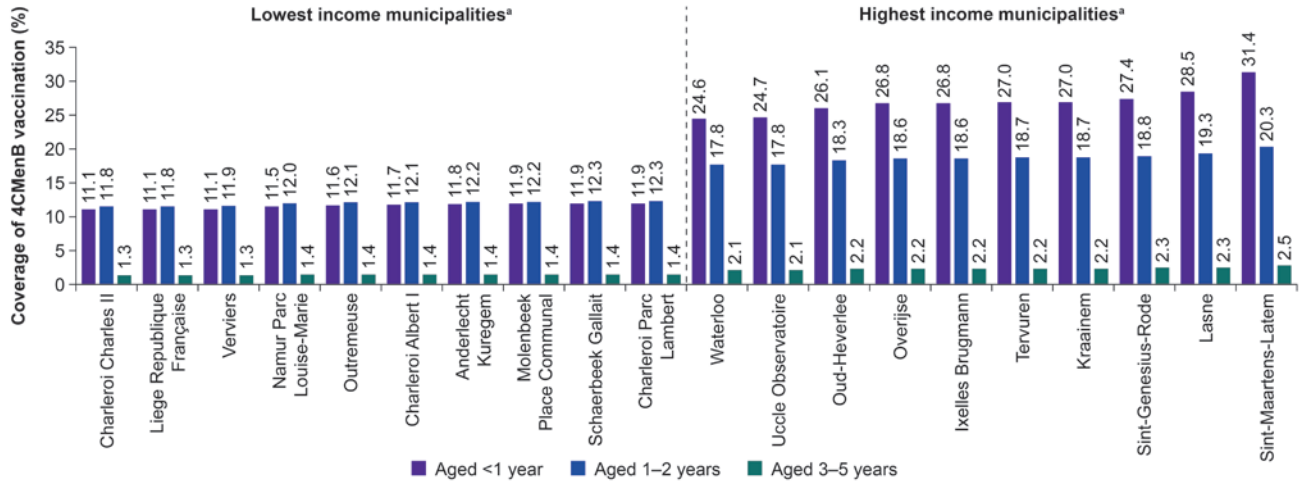
No overall correlation was observed between household income and Belgian 4CMenB coverage across municipalities (r=0.015, 95% CI: -0.230–0.258 for selected municipalities; Figure 3A). However, when analysing the specific age classes, there was a mild positive correlation between 4CMenB coverage and household income for those aged <1 year (r=0.251, 95% CI: 0.008–0.466, p<0.001) and 1–2 years (r=0.161, 95% CI: -0.088–0.388, p<0.001; Figure 3B and 3C) in analysed municipalities. For higher age groups, 4CMenB coverage was not correlated with household income level (r=0.156, 95% CI: -0.092–0.385, p=0.005 for the 3–5 years age class), partially due to low sample size.

When using the logistic regression model within the 65 individual municipalities, both age and income level had a statistically significant effect on 4CMenB coverage (p<0.001). There was also a significant relationship between age (across 0–11 years) and household income, with strong statistical confidence in this result (p=0.002); this association was particularly pronounced in the <1 year and 1–2 years age groups (p<0.001).

Furthermore, vaccine coverage in the 10 lowest income municipalities and the 10 highest income municipalities was estimated. The logistic regression model estimated that 4CMenB coverage for individuals aged <1 year was 11.1–11.9% in the lowest income municipalities and 24.6–31.4% in the highest income municipalities (Figure 4).

When extrapolating data at a national level, the logistical regression model also predicted that 4CMenB coverage among those aged <1 year was lowest in Southern Belgium and in main city centers. 4CMenB coverage was highest in the areas surrounding Brussels, Ghent and Antwerp (Figure 5A), with higher vaccination coverage shown in Figure 5A mapping roughly onto areas of higher income indicator (Figure 5B). The distribution of 4CMenB coverage becomes increasingly uniform as

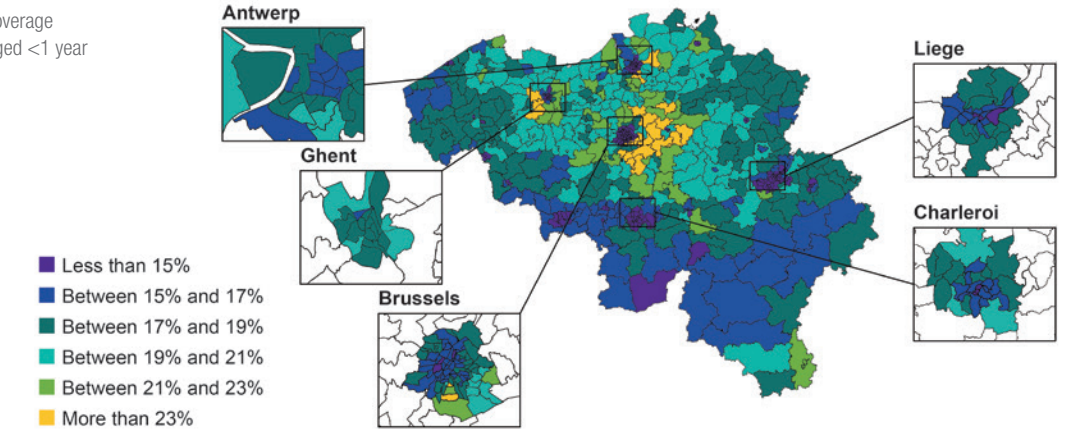
Figure 4: Logistical regression analysis estimating 4CMenB vaccination coverage across the 10 lowest and 10 highest income municipalities.



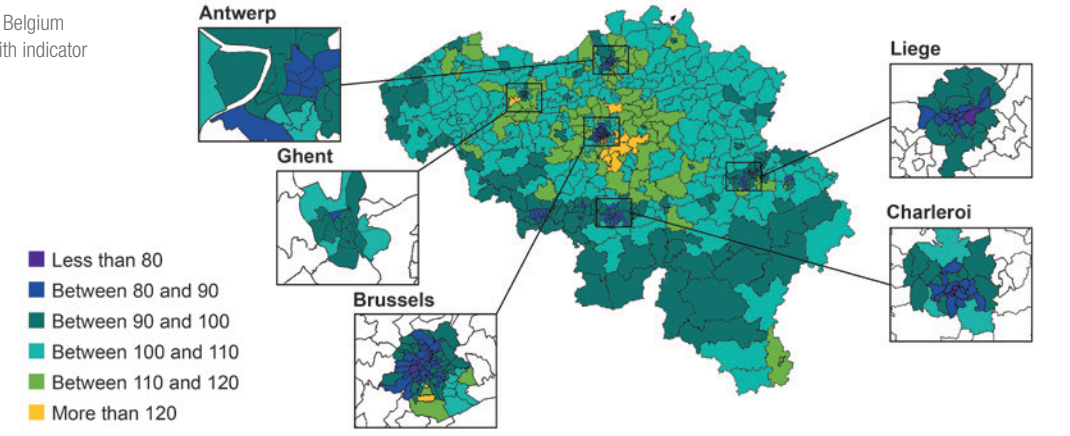
a: General descriptions of municipalities were based on a 593 granularity level, which may not align entirely with formal commune name.

Figure 5: Predicted 4CMenB vaccination coverage among those aged <1 year and indicator of income for municipalities.

5A: 4CMenB coverage among those aged <1 year



5B: Overview of Belgium municipalities with indicator of income



The indicator of income was calculated by aggregating wealth and income variables, normalised so mean (standard deviation) was 100 (10) at the municipality level. Income level ranges from 75 (lowest income indicator) to 140 (highest income indicator).

you move up the age classes, with the 3–5 years age class showing the most even distribution across assessed municipalities.

Discussion

This is the first study to analyse the correlation between 4CMenB coverage, age and household income level at a municipality level in Belgium. 4CMenB coverage was highest in those aged <1 year and 1–2 years and a statistically significant, positive correlation between 4CMenB coverage and household income was observed for individuals of these ages. This suggests potential inequity in vaccine access at a municipality level in Belgium for those aged <1 year and 1–2 years.

This analysis shows that over 70% of vaccinated individuals are concentrated in just 11% of Belgian municipalities; these municipalities include large cities and so are likely to have higher populations and more vaccinated individuals than other, potentially smaller, municipalities.

In Belgium, the socioeconomic status of families may impact the decision to vaccinate children, particularly with non-publicly funded vaccinations. The positive correlation between MenB coverage and household income observed in this study at a municipality level has also been seen at a provincial level. A study of 2020 vaccination coverage in Flanders showed that children aged 18–24 months from families with an income lower than €3,000 per month were more often incompletely vaccinated against MenB compared with children from families with an income greater than €3,000 (19). A similar trend was also seen with the publicly funded COVID-19 vaccine, with lower uptake of the first dose observed in socioeconomically disadvantaged adults in Belgium (20). Parallels can be seen when looking at the risk of IMD. In France, individuals with a low income are at an increased risk of hospitalisation due to IMD compared with high income individuals, reinforcing the importance of MenB vaccination in populations with a lower income (18).

The higher levels of 4CMenB coverage for the two youngest age classes (<1 year and 1–2 years) compared with the older age classes confirm that paediatricians and general practitioners follow the recommendations of the Belgian Superior Health Council. These recommendations stipulate the best vaccination schedule against MenB is at 8 and 16 weeks, with the third booster dose given between 11 and 14 months, as a high percentage of cases occur before 6 months (8). Despite the recommendations in Belgium, 4CMenB coverage among individuals aged 15–19 years included in this analysis was less than 0.5%. Vaccine uptake and hesitancy in the adolescent population is a known issue and is likely due to a number of reasons, such as adolescents having fewer preventative healthcare visits than infants (21). This holds especially true in non-reimbursed settings and where infrastructure to vaccinate adolescents is lacking. The European Program of Work 2020–2025 of the World Health Organization, which details health priorities for the next five years, has been criticised by the European Academy of Pediatrics for lacking strategies that specifically improve the health of children and adolescents (22, 23). Given adolescent vaccination levels are lower than infant levels and adolescents appear to be overlooked in some policies, universally recommended freely-available vaccination could be key to increasing vaccination coverage and improving the health of all ages. This may also explain why no overall correlation between 4CMenB coverage and household income level was observed. Nearly 80% of individuals in the 65 selected municipalities were aged ≥20 years and 4CMenB coverage in this age group was less than 0.5%. Therefore, the lack of association observed between 4CMenB coverage and household income for older ages is potentially limited by a smaller sample size of vaccinated individuals in these age groups.

Despite the 2019 MenB notification rate in Belgium being similar to or higher than countries where MenB vaccination is publicly funded (United Kingdom and Italy), MenB is not included in any regional immunisation programs in Belgium (24-26). Having 4CMenB as a universally recommended, publicly funded vaccine could reduce inequity in access to 4CMenB and therefore reduce the incidence of MenB in Belgium.

This analysis was associated with some limitations. Firstly, the data panel used for vaccine uptake information represents approximately 30% of Belgian pharmacies and so not all 4CMenB vaccinations were captured. This analysis is also significantly limited by selection bias. Due to anonymisation requirements, only municipalities with ≥100 4CMenB vaccinees were analysed. However, the sample of municipalities used in this study was assessed as representative of the general Belgian population according to distribution across Belgium, age and income level. Thirdly, this analysis only looks at household income as an indicator for socioeconomic status. Factors shown to influence vaccine uptake, such as education and literacy level, were not investigated (20). Additionally, the type and quality of pre-vaccination information provided by healthcare workers, a known key determinant of vaccine uptake, was not assessed. Furthermore, communication regarding vaccine recommendations differs between Belgian regions, which may have independently impacted vaccine coverage. Differences observed between correlation analysis and logistic regression analysis when assessing coverage and age/income level (e.g., effects in older age groups) were caused by the regression analysis testing effects simultaneously, instead of independently. Finally, the location of the prescribing healthcare professional is used as a proxy for patient location, meaning patients may be wrongly allocated to the municipality of their prescriber, while living elsewhere. However, checks prior to this study have shown that such bias is somewhat limited and compensates for each other (i.e., incorrect patient allocation is symmetrical for two municipalities).

Conclusion

Only a small number of Belgian municipalities contained ≥100 vaccinated individuals and 4CMenB coverage in these municipalities was highest in individuals aged <1 and 1–2 years. For individuals aged 0–11 years, higher household income correlated with higher 4CMenB coverage when looking at the individual municipality level, with a more pronounced effect in the <1 year and 1–2 years age groups. Indeed, in the highest income municipalities analysed, individuals aged <1 year, 1–2 years and 3–5 years were approximately two times more likely to be vaccinated than in the lowest income municipalities. The availability of 4CMenB only in the private sector may contribute to inequity in vaccination access, potentially placing low-income populations in Belgium at an increased risk of IMD. A universal vaccine recommendation, high quality pre-vaccine information from healthcare professionals and inclusion of 4CMenB into Belgium's regional immunisation programs to make the vaccine free of charge could decrease the current inequity in 4CMenB coverage observed in children <2 years of age in Belgium. Although the results of this study indicate inequity in access to 4CMenB vaccination in Belgium, the study has limitations and additional analyses are required to confirm results, such as those investigating additional parameters impacting vaccination uptake. Moreover, conducting a precise cost-effectiveness analysis of the 4CMenB vaccine is crucial to reflect the disease's lifetime impact.

Data sharing statement

Data used for this publication was generated by IQVIA. For access to anonymised subject level data, please contact IQVIA.

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Conflicts of interest

GN, AGA, AM and FS: employees of and hold financial equities in GSK; KB: employee of GSK; DM and CV: employees of IQVIA; BB: received consultancy fee for the present study; WM: received a research grant from GSK and Pfizer for vaccine coverage of meningococcal B strains; MR: no conflicts of interest reported.

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In Belgium, meningococcal serogroup B is the most common form of invasive meningoccocal disease

The 4CMenB vaccine, which protects against meningitis B (MenB), is recommended for children aged 2 months to 5 years, adolescents aged 15 years to 19 years and high-risk groups in Belgium

Despite these national recommendations, the 4CMenB vaccine is not a publicly funded vaccine in Belgium

This study aimed to answer:

- **How 4CMenB vaccination coverage is distributed across Belgian municipalities**
- **What the relationship is between 4CMenB vaccine coverage, age and household income**

Information was sourced from two databases:

Sociodemographic database	Longitudinal prescriptions database
Level of household income	4CMenB doses; Year of birth; Municipality (Database granularity level meant data were mapped to 593 municipalities)

Individuals with 2 to 3 doses of 4CMenB vaccine were included

The following was observed from the 16,816 4CMenB vaccinees identified:

Vaccine coverage

71% of vaccinees were concentrated within **65 Belgian municipalities** (11%)

These 65 municipalities were further analysed

Vaccine coverage and age

4CMenB vaccine coverage was **highest** in those aged

<1 year	1–2 years
16%	**14%**

Vaccine coverage and household income

4CMenB vaccine coverage **correlated with household income** only for those aged **less than 1 year and 1–2 years**

Municipalities with the **lowest average household income** had **lower 4CMenB vaccine coverage** rates than municipalities with the **highest average household income**

<1 year	1–2 years
12%	**12%**
27%	**19%**

4CMenB not being a publicly funded vaccine in Belgium may contribute to inequity in vaccine access

The potential inclusion of the 4CMenB vaccine in Belgian regional immunisation programs could help reduce this inequity

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