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Role of Real-World Evidence in 4CMenB Regulatory Journey Against Invasive Meningococcal Disease

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Declaration of possible conflict of interest

Ilaria Bartalesi is an employee of the GSK group of companies and holds shares as part of her employee remuneration.

Introduction

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Serogroup B invasive meningococcal disease (MenB IMD) is **rare but can be life-threatening**. It develops rapidly in previously healthy people, with high morbidity **and a case fatality rate of 10–15%.**
10% to 20% of survivors have long-term sequelae (neurologic disability, limb or digit loss, or hearing loss).
Incidence is highest in infants under 1 year, with a second peak at 16–20 years [1].

4CMenB is a broadly protective vaccine against MenB IMD, currently registered worldwide.
Due to **the low incidence of MenB IMD**, conducting phase 3 randomized **clinical trials to assess vaccine efficacy** prior to licensure is not feasible.

As a result, **4CMenB was approved** by all Health authorities based on safety and immunogenicity data, using a recognized surrogate of protection combined with prediction of strain coverage using MATS (Meningococcal Antigen Typing System) [2].

Following licensure authorization, **post authorization commitments** were established to generate real-world evidence (RWE) on vaccine effectiveness: Canada, Europe (including UK), Hong Kong, Switzerland.

1. Centers for Disease Control and Prevention (CDC), 2025.
2. Borrow et al, Vaccine. 2005 Mar 18;23(17-18):2222-7. DOI: 10.1016/j.vaccine.2005.01.051

EMA Journey

Regulatory Journey

EMA

Licensure based on:
- Safety and immunogenicity data
- MATS-based coverage prediction

OF NOTE: commitment to perform post-licensure observational effectiveness study

13 January 2013

September 2015

Post approval commitment (V72_38OB:)[1-2] :
- Protocol discussed with EMA prior to study start.
- Study carried out in the context of the infants NIP * in the UK (first country introducing 4CMenB in its NIP in 2015.)
- Conducted by UKHSA**.

August 2018

*National Immunisation Program
** UK Health Security Agency

March 2020

- The vaccine effect was demonstrated by RWE data (V72_38OB)[1-2]
- EMA approved an updated label including vaccine impact.

Widespread use of 4CMenB worldwide → extensive RWE demonstrating reduction of MenB IMD and vaccine effectiveness across geographies[3].

These findings have contributed to amend the product information (PI)

September 2022

RWE consistently confirms the benefit of the 4CMenB vaccine [3]

1. https://catalogues.ema.europa.eu/node/2192/administrative-details
2. Ladhani et al. *NEJM* 2020 DOI: 10.1056/NEJMoa1901229
3. Ciconze et al, Vaccine 2023 https://doi.org/10.1016/j.vaccine.2023.05.025

Post-licensure observational study

V72_38OB – variation 2020

3-years report[1-2]:

- UK NIP 4CMenB administered at 2, 4, 12 months of age.
- Approx 2 million infants received the vaccine.
- Vaccine effectiveness (VE): 59.1% statistically not significant.
  (high vaccine uptake together with the low incidence of the disease).
- Vaccine impact (VI): 75% statistically significant
  - Reduction of 277 MenB cases was observed among children below 1 year of age.

SmPC changes:

Posology

Update of the 3-dose schedule posology to recommend the start of the vaccination series at 2 months of age instead of starting at 3 months of age.

Pharmacodynamic properties:

The addition of the 3-year vaccine impact real-world evidence data.

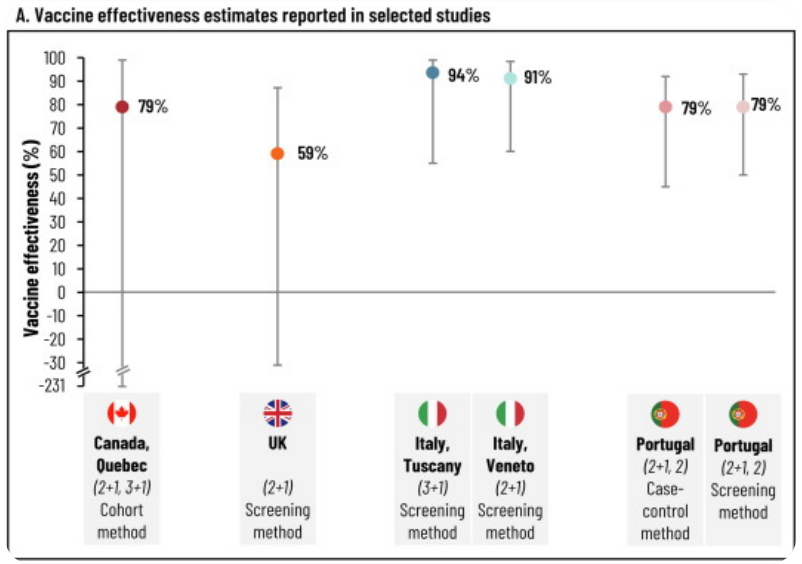
Country	Setting	Outcome
UK	NIP (infant)	75% MenB disease reduction

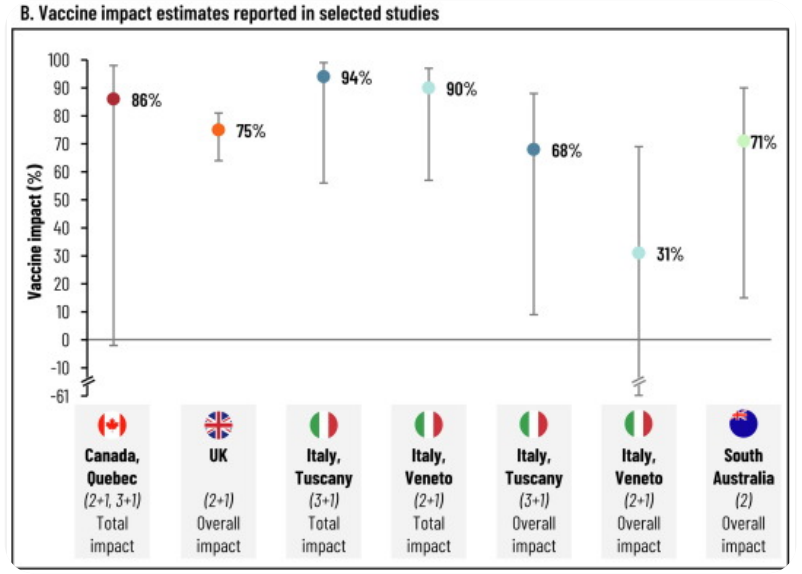
1. https://catalogues.ema.europa.eu/node/2192/administrative-details
2. Ladhani et al. *NEJM* 2020 DOI: 10.1056/NEJMoa1901229

4CMenB real-world experience across multiple settings

Product Information update 2022

- A systematic literature review was performed of all real-world studies on 4CMenB vaccine effects on meningococcal serogroup B disease, since its licensure in 2013 (from January 2014 until July 2021).
- Five studies presenting estimates on 4CMenB vaccine effectiveness and impact were retrieved.
- These studies showed great diversity in population, vaccination schedule and analysis methods mainly due to diversity in vaccine strategies and recommendations in the study settings.
- Directed by this diversity, no quantitative pooling methods to synthesize findings could be applied; instead, we descriptively assessed study methods.
- VE estimates ranged from 59% to 94% and VI estimates ranged from 31% to 75%, representing diverse age groups, vaccination schedules and analysis methods. [1-6]
- EMA approved the addition of VI of McMillan study in the label (South Australia in adolescents) [6].





Figures A and B reproduced from Reference 1: Cicanze et al 2023, without modification

1. Ciconze et al, Vaccine 2023 https://doi.org/10.1016/j.vaccine.2023.05.025
2. Deceuninck G, et al. *Vaccine 2019* DOI: 10.1016/j.vaccine.2019.06.021
3. Ladhani et al. *NEJM* 2020 DOI: 10.1056/NEJMoa1901229
4. Azzari C, et al. *Vaccine 2020* https://doi.org/10.3390/vaccines8030469
5. Rodrigues FMP, et al. *JAMA 2020* DOI: 10.1001/jama.2020.20449
6. McMillan M, et al. *Clin. Inf. Dis. 2021*, 10.1093/cid/ciaa1636

4CMenB real-world experience across multiple settings

Summary

IDENTIFIED PUBLICATIONS[1]	COUNTRY (STUDY PERIOD) CONTEXT	SCHEDULE POPULATION AGE	EMA approved
Deceuninck G, et al. [2019] [2]	• Canada Quebec (2014) • Regional targeted campaign	• Either 2-1 or 3+1 doses • 2 months to 20 years	
Ladhani SN, et al. [2020a] [3]	• United Kingdom (2015/18) • National Immunisation Program	• 2+1 doses • 2 months to 12/13 months	75% MenB disease reduction
Azzari C, et al. [2020] [4]	• Italy (2014/19) • Regional Program	• Either 2+1 or 3+1 doses • 2 months to 15 months	
Rodrigues FMP, et al. [2020] [5]	• Portugal (2014/19) • Private Market	• 2 doses • 2 months to 18 years	
McMillan M, et al. [2021] [6]	• South Australia (2017/19) • State-wide clinical trial	• 2 doses • 16 to 19 years	71% MenB disease reduction

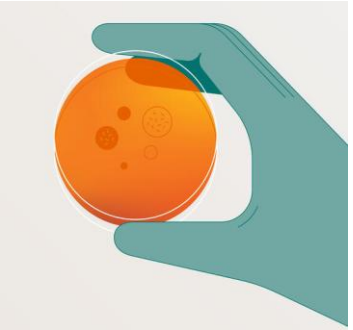
EUPI currently reports Ladhani (2020) and McMillan (2022), both studies:

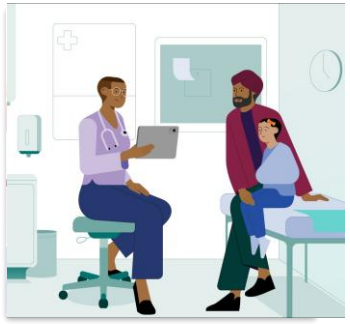
- are large studies in which vaccination was offered through the NIP
- involve infants and adolescents, the two peak age groups for MenB disease.

1. Ciconze et al, Vaccine 2023 https://doi.org/10.1016/j.vaccine.2023.05.025
2. Deceuninck G, et al. *Vaccine 2019* DOI: 10.1016/j.vaccine.2019.06.021
3. Ladhani et al. *NEJM* 2020 DOI: 10.1056/NEJMoa1901229
4. Azzari C, et al. *Vaccine 2020* **https://doi.org/10.3390/vaccines8030469**
5. Rodrigues FMP, et al. *JAMA 2020* DOI: 10.1001/jama.2020.20449
6. McMillan M, et al. *Clin. Inf. Dis. 2021,* 10.1093/cid/ciaa1636

Journey outside Europe (EMA)

US Experience





Company proposals

- Use of RWE from V72_38OB (UK) to demonstrate effectiveness of 4CMenB in infants.

- McMillan study (Australia) selected for inclusion in the USPI as the most appropriate study for the US-approved age range (10–25 years of age).

CBER's feedback

- the differences in meningococcal strains between countries affect the applicability of foreign study results to the U.S. population.

- the schedule is not completely aligned with the US schedule.

Ex-US and ex-EU countries

Ladhani et al. NEJM 2020
DOI: 10.1056/NEJMoa1901229

Countries	Status	Publications included in the label
All country except South Korea	Approved	• Ladhani et al. NEJM 2020 (V72_38OB)

Ciconze et al, Vaccine 2023
https://doi.org/10.1016/j.vaccine.2023.05.025

Countries	Status	Publications included in the label
Hong Kong, Egypt, Israel, Turkey	Approved	• McMillan M, *et al.* (VI) -Aligned with EMA
Saudi Arabia, Unted Arab Emirates, Dominican Republic, El Salvador, Panama, Argentina, Brazil, Chile, Mexico, Philippines, Russia, South Africa, Thailand, Uruguay	Approved	• McMillan M, *et al.* (VI) • Rodrigues, *et al.* (VE)
South Korea, Switzerland, Taiwan, UK	Not approved	None

Conclusions

RWE is increasingly recognized by Health Authorities as critical for demonstrating vaccine effectiveness, which are key for rare diseases like MenB IMD.

Post-Licensure Studies: Observational studies, such as V72_38OB conducted in the UK, have demonstrated significant reductions in MenB IMD cases, leading to updates in product information.

While many Health Authorities have approved RWE for inclusion in the 4CMenB label, acceptance varies significantly across regions due to differing regulatory requirements.

- acceptance is higher when RWE studies are discussed/approved with the Health Authority prior the study start (V72_38OB case for EU).

The lack of alignment among health authorities on RWE acceptance underscores the need for guidelines to enable standardized assessment of vaccine performance.

The 4CMenB journey shows the crucial role of RWE in informing global immunization policy, reinforcing vaccine confidence, and supporting adaptive disease-control strategies.