4CMenB journey to the 10-year anniversary and beyond

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Invasive Meningococcal Disease (IMD) caused by *Neisseria meningitidis* is uncommon, unpredictable and life-threatening. It causes meningitis and septicemia, and can be associated with severe complications such as limb amputations, hearing loss, and neurologic damage. Most cases of IMD are caused by six serogroups (A, B, C, W, Y, and X).

Effective vaccines are available to prevent IMD: vaccines that target capsular meningococcal serogroups A, C, W, and Y (MenACWY) and protein-based vaccines against meningococcal serogroup B (MenB).

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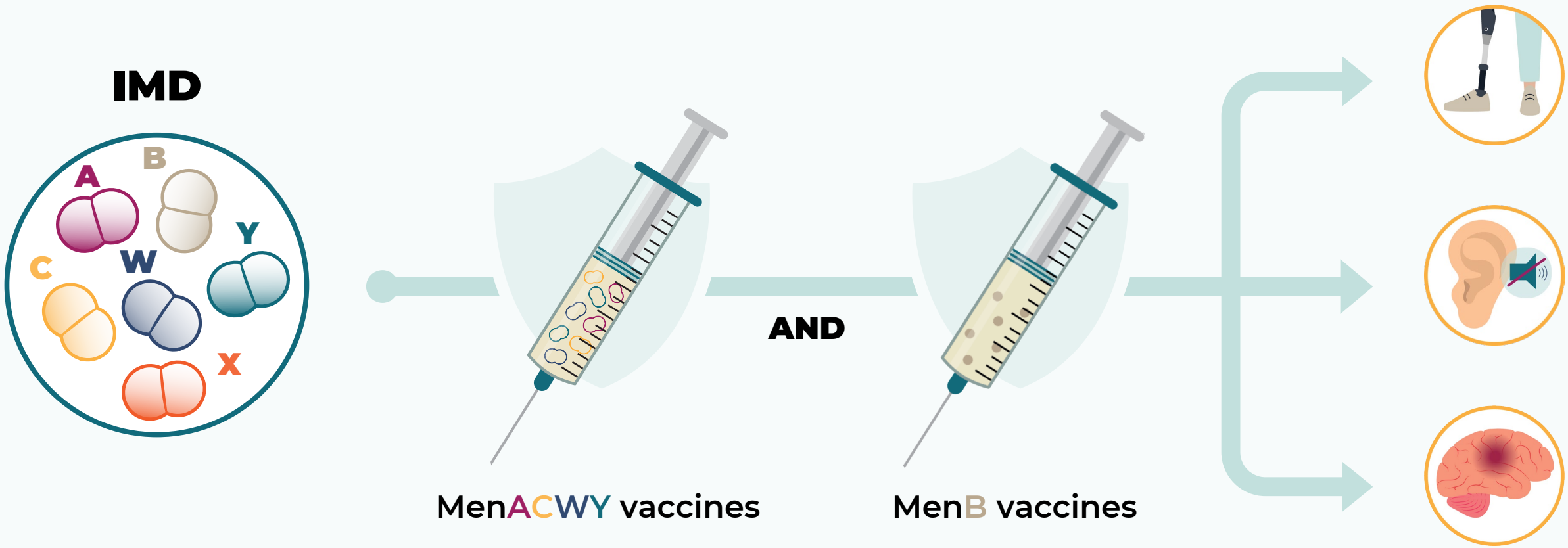

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From MenB vaccine to vaccination

1990s

Research and development

2013

EU approval for individuals aged ≥2 months

2015

US approval for individuals aged 10–25 years

2020

2+1 dose schedule from 2 months of age

2024

Approved in more than 50 countries

MenB: meningococcal serogroup B; US: United States.

After 20 years of research and development, the 4-component meningococcal serogroup B vaccine (4CMenB) was first licensed in the European Union (EU) in 2013 for individuals 2 months and above and in the US in 2015 for individuals 10-25 years. In 2020, the European registration was updated to include a two-dose series plus booster (2+1) from the age of 2 months. As of March 2024, 4CMenB is approved in more than 50 countries and recommended in national or regional immunization programs in infants and/or adolescents.

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4CMenB

4CMenB: 4-component meningococcal serogroup B vaccine.

As of March 2024, 4CMenB is included in national immunization programs (NIPs) for infants in 16 countries: the UK, Andorra, Ireland, Italy, San Marino, Lithuania, Spain, Malta, Czechia, Portugal, France, New Zealand, Chile, Germany, Luxembourg, and Switzerland. Of these, only 4 countries recommend it in infants, adolescents and young adults (Czechia, Switzerland, New Zealand and France for adolescents who wish to be vaccinated), and regional programs in South Australia and in Italy (Sicily, Puglia, and Calabria). In addition, MenB vaccines are recommended in adolescents as shared clinical decision-making in the US and as regional program in adolescents in Canada.

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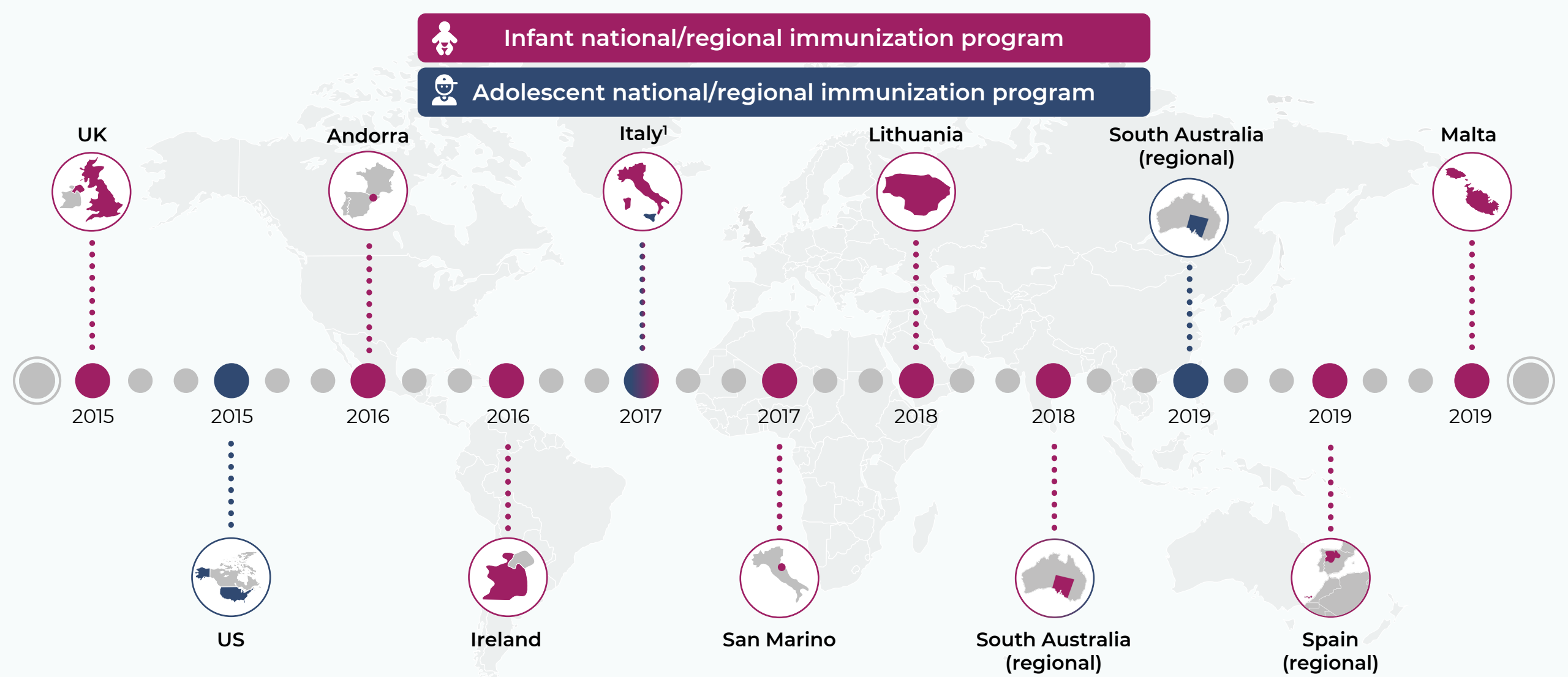

UK: United Kingdom; US: United States; 4CMenB: 4-component meningococcal serogroup B vaccine.

[1]Italy: infant **national** immunization program + adolescent **regional** immunization program (Sicily)

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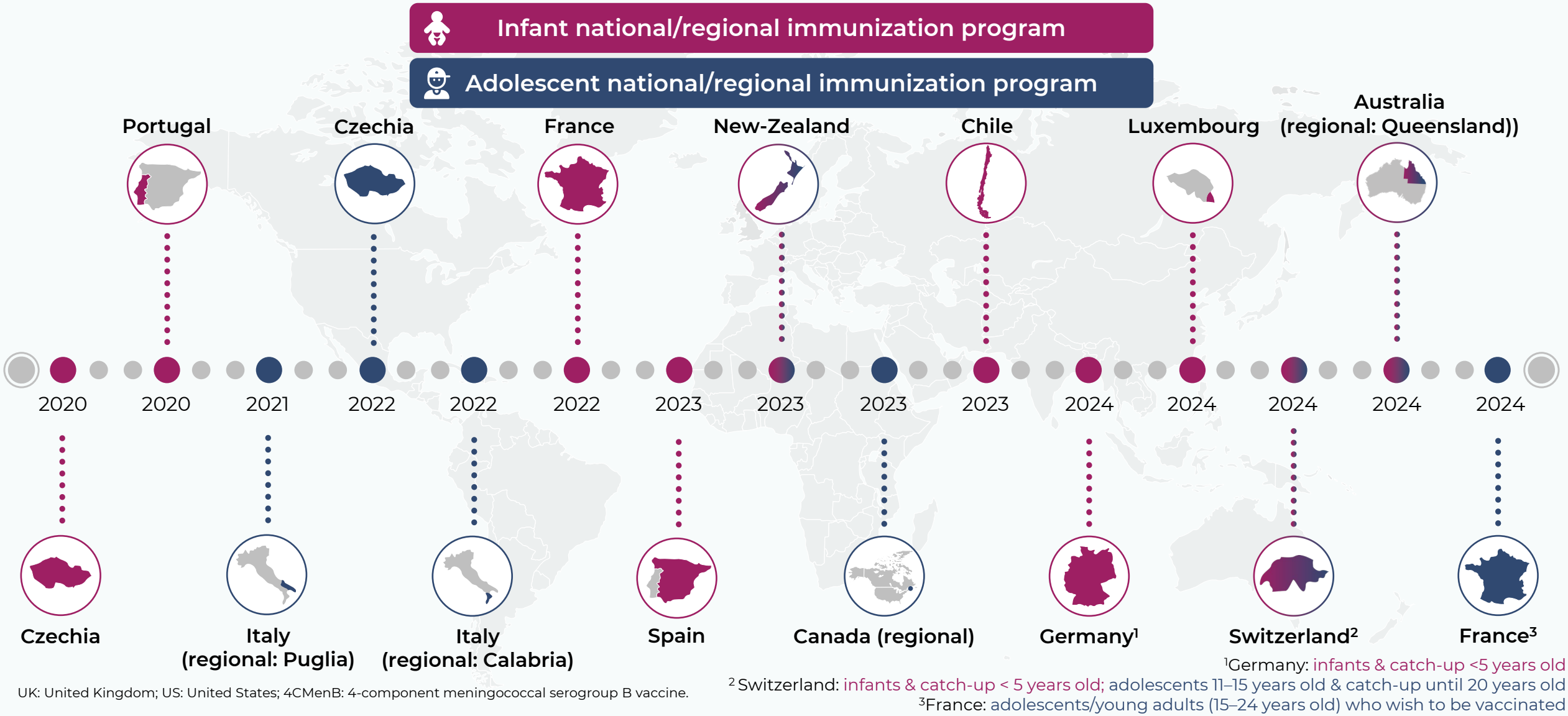

UK: United Kingdom; US: United States; 4CMenB: 4-component meningococcal serogroup B vaccine.

[1]Germany: infants & catch-up <5 years old

[2] Switzerland: infants & catch-up < 5 years old; adolescents 11–15 years old & catch-up until 20 years old

[3]France: adolescents/young adults (15–24 years old) who wish to be vaccinated

As of March 2024, 4CMenB is included in national immunization programs (NIPs) for infants in 16 countries: the UK, Andorra, Ireland, Italy, San Marino, Lithuania, Spain, Malta, Czechia, Portugal, France, New Zealand, Chile, Germany, Luxembourg, and Switzerland. Of these, only 4 countries recommend it in infants, adolescents and young adults (Czechia, Switzerland, New Zealand and France for adolescents who wish to be vaccinated), and regional programs in South Australia and in Italy (Sicily, Puglia, and Calabria). In addition, MenB vaccines are recommended in adolescents as shared clinical decision-making in the US and as regional program in adolescents in Canada.

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4CMenB

Evidence of real-world effectiveness and impact against MenB disease

MenB: meningococcal serogroup B; 4CMenB: 4-component MenB vaccine.

Post-licensure data accumulated over the last 10 years from four European countries (the UK, Italy, Spain, and Portugal), Canada, the US, and South Australia provide evidence of the real-world effectiveness and impact of 4CMenB against MenB disease.

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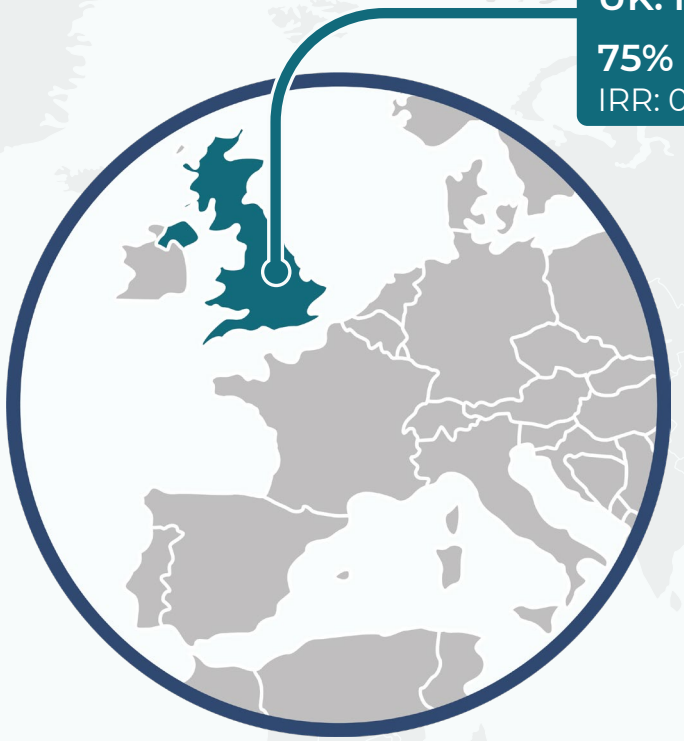
4CMenB

VE

Vaccine Effectiveness

I

Impact



UK: NIP

75% decrease in MenB disease
IRR: 0.25 (95% CI: 0.19–0.36)

CI: confidence interval; IRR: incidence rate ratio; MenB: meningococcal serogroup B; NIP: national immunization program; UK: United Kingdom; 4CMenB: 4-component MenB vaccine.

After introduction of 4CMenB in the infant NIP first in the UK in September 2015, incidence of MenB disease decreased by 75%. Over a 3-year period, it was estimated that one case of MenB IMD was avoided every 4 days. Outcome data are available up to 5 years after implementation of two-dose priming in infancy and a booster dose at 12 months of age.

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4CMenB

VE

Vaccine Effectiveness

I

Impact

4CMenB: 4-component meningococcal serogroup B vaccine.

Italy, Portugal and Spain have evaluated impact and effectiveness of 4CMenB in infants, children and adolescents.

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4CMenB

VE

Vaccine Effectiveness

I

Impact

Italy: NIP

- **Tuscany: 94% VE** (95% CI: 55–99%)
- **Veneto: 91% VE** (95% CI: 60–98%)
- **Tuscany, Veneto, Piedmont: 95% VE** (95% CI: 83-99%)
- **Tuscany, Veneto, Piedmont, Apulia, Liguria, Sicily: 92% VE** (95% CI: 24-99%)

CI: confidence interval; NIP: national immunization program; 4CMenB: 4-component meningococcal serogroup B vaccine.

Two regions in Italy introduced 4CMenB: Tuscany, where vaccination was implemented in 2014 using a 3 + 1 schedule starting at 2 months, and Veneto in 2015 with a 2 + 1 schedule starting at 7 months.
Vaccine effectiveness against MenB disease was 94% and 91% in Tuscany and Veneto respectively, which shows the importance of early vaccination with 4CMenB.

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4CMenB

VE
Vaccine Effectiveness

I
Impact

Portugal:
79% VE
OR: 0.21 (95% CI: 0.08–0.55)

Spain:
71% VE (95% CI: 45–85%)

Italy: NIP
- **Tuscany: 94% VE** (95% CI: 55–99%)
- **Veneto: 91% VE** (95% CI: 60–98%)
- **Tuscany, Veneto, Piedmont: 95% VE** (95% CI: 83-99%)
- **Tuscany, Veneto, Piedmont, Apulia, Liguria, Sicily: 92% VE** (95% CI: 24-99%)

CI: confidence interval; NIP: national immunization program; OR: odds ratio; US: United States; 4CMenB: 4-component meningococcal serogroup B vaccine.

Portugal and Spain provide further real-world evidence of 4CMenB.
In Portugal, a matched case-control study demonstrated 79% vaccine effectiveness in individuals 2 months to 18 years.
In Spain, a nationwide case-control study showed 71% vaccine effectiveness in infants and children younger than 5 years old.

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4CMenB

VE

Vaccine Effectiveness

I

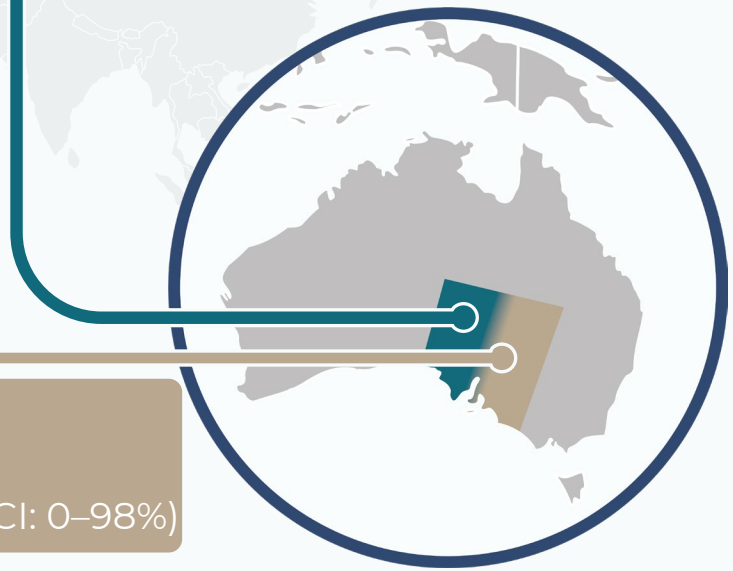
Impact

Canada (SLSJ region): MenB outbreak

96% decrease in MenB disease in those aged 2 months to 20 years. Incidence from 11.4 to 0.4 per 100,000 person-years.

South Australia: regional program

63% decrease in MenB disease in infants (95% CI: 29–81%)
79% decrease in MenB disease in adolescents (95% CI: 33–93%)



US: university MenB outbreak

No cases in vaccinated individuals

South Australia: regional program

- **91% VE** in children (95% CI: 7–99%)
- **84% VE** in adolescents and young adults (95% CI: 0–98%)

CI: confidence interval; MenB: meningococcal serogroup B; SLSJ: Saguenay-Lac-Saint-Jean; US: United States; 4CMenB: 4-component MenB vaccine.

In other countries and different settings, 4CMenB has demonstrated consistent results, with 91% vaccine effectiveness in children and 84% in adolescents and young adults in South Australia.
In the context of outbreaks, no cases of MenB occurred after vaccination of university students in the US and 96% reduction of IMD in individuals <20 years old in the Saguenay-Lac-Saint-Jean region in Canada.

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4CMenB

VE

Vaccine Effectiveness

I

Impact

4CMenB: 4-component meningococcal serogroup B vaccine.

Altogether, real-world evidence from various countries demonstrate consistent 4CMenB effectiveness (71–95%) and impact (63–96%) in different age groups, infants, children and adolescents and settings.

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4CMenB

Evidence of **4CMenB safety profile** (from clinical development to RWE)

Outbreak settings

Post-marketing surveillance

NIP

State-wide study in adolescents

NIP: national immunization program; RWE: real world evidence; 4CMenB: 4-component meningococcal serogroup B vaccine.

In the clinical development program, involving more than 6000 participants, 4CMenB had an acceptable safety and tolerability profile in infants, toddlers, children, adolescents, and adults.
4CMenB safety profile has been demonstrated across many countries through Real World Evidence and results are consistent with those seen in the clinical program with no unexpected safety concern.

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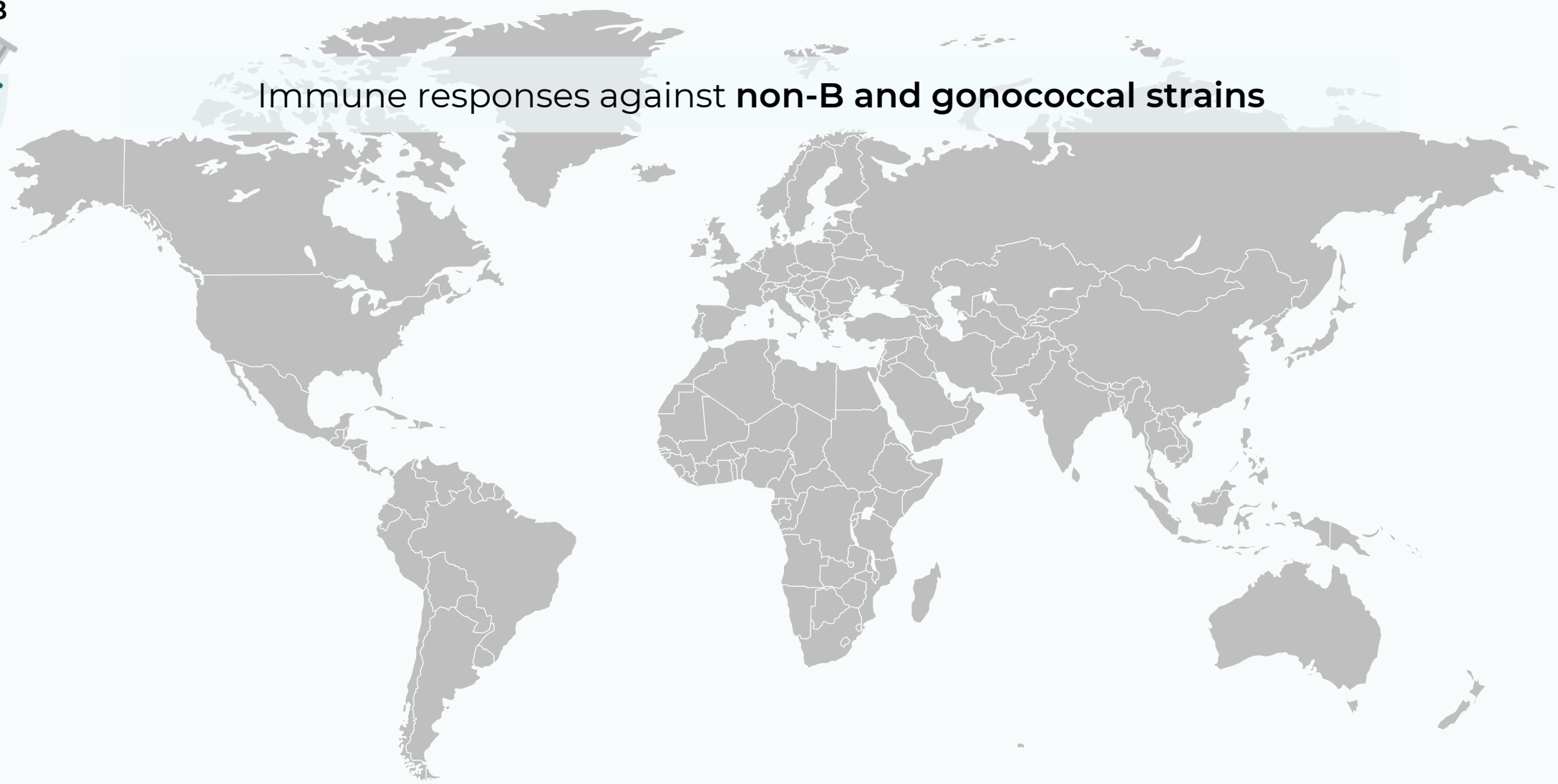
4CMenB

Immune responses against **non-B and gonococcal strains**



4CMenB: 4-component meningococcal serogroup B vaccine.

Antigenic components of 4CMenB can also be expressed in non-B meningococcal strains and in other pathogenic *Neisseria* species, including *Neisseria gonorrhoeae* strains. 4CMenB has been shown to elicit immune responses against both non-B and gonococcal strains, demonstrating the potential for additional protection beyond MenB disease.

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4CMenB

The potential effect of **4CMenB against non-B and *N. gonorrhoeae***

***N. gonorrhoeae* VE**

US: VE against *N. gonorrhoeae* in adolescents:

- **40%** (95% CI: 23–53%) in individuals **16-23 years old**
- **46%** lower gonorrhea rates **among recipients of 4CMenB vs MenACWY**
- **47%** (95% CI: 13–68%) in individuals **18-29 years old**

France: Phase 3 RCT (discontinued):

VE against *N. gonorrhoeae* in 556 MSM on HIV PrEP with STI history:

- **22%** (95% CI: -1–40%)

Australia: VE against *N. gonorrhoeae* in adolescents:

- **34.9%** (95% CI: 15.0–50.1%) **6–36 months after vaccination**
- **33.2%** (95% CI: 15.9–47.0%) **>6 months after vaccination**
- **23.2%** (95% CI: 0–47.5%) **>36 months after vaccination**

CI: confidence interval; MenACWY: meningococcal serogroups ACWY vaccine; MSM: men who have sex with men; PrEP: pre-exposure prophylaxis; RCT: randomized controlled trial; STI: sexually transmitted infection; US: United States; VE: vaccine effectiveness; 4CMenB: 4-component meningococcal serogroup B vaccine.

Encouraging vaccine effectiveness results against *Neisseria gonorrhoeae* have been reported after vaccination with 4CMenB in adolescents and young adults during the outbreak controls in the Saguenay-Lac-Saint-Jean region in Canada, the US, and in South Australia. In this Australian State, following a two-doses vaccination in adolescents and young adults, vaccine effectiveness against *Neisseria gonorrhoeae* was 33.2%.
Recently, efficacy results of a randomized controlled trial showed inconclusive results in France.

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4CMenB

The potential effect of **4CMenB against non-B and *N. gonorrhoeae***

UK: NIP

69% decrease in MenW disease
aIRR 0.31 (95% CI: 0.20–0.67)

***N. gonorrhoeae* VE**

Non-B VE

MenW results

Spain:

- **76% VE** against any serogroup (95% CI: 57-87%)
- **92% VE** against non-B disease (95% CI: 28-99%)

aIRR: adjusted incidence rate ratio; CI: confidence interval; MenW: meningococcal serogroup W; NIP: national immunization program; UK: United Kingdom; VE: vaccine effectiveness; 4CMenB: 4-component meningococcal serogroup B vaccine.

The first real-world evidence of 4CMenB protection against MenW disease came from England. Following implementation of the 4CMenB infant immunization program, 69% decrease in MenW disease was observed.
Further evidence of an effect against non-B serogroups comes from other countries such as Spain where vaccine effectiveness of two 4CMenB doses resulted in 76% against IMD caused by any serogroup and 92% against non-B disease.

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Different repertoire in **laboratory assays** to evaluate MenB strain coverage or immunological vaccine effectiveness (VE)

Traditional hSBA

Immunogenicity endpoints in pre-licensure clinical trials

Assessment of serum bactericidal antibody induction against each of the four indicator strains

MATS

Strain coverage

Strain coverage estimated through comparison of 4CMenB antigens with the equivalent antigens in circulating bacteria

gMATS

Strain coverage

Strain coverage estimated using genomic-based MATS, utilizing MenB strain genetic sequence information

Real world evidence

Increasing amount of post-licensure data on 4CMenB impact and VE supports these coverage estimation methods

hSBA: human serum bactericidal antibody assay; gMATS: genetic MATS; MATS: meningococcal antigen typing system; MenB: meningococcal serogroup B; VE: vaccine effectiveness; 4CMenB: 4-component MenB vaccine.

As IMD is uncommon, the efficacy of meningococcal vaccines could not be determined in clinical trials. In 4CMenB clinical development, the immune response was assessed using a traditional human serum bactericidal antibody assay (hSBA) in presence of external complement from seronegative donors against antigen-specific indicator strains. Later, the meningococcal antigen typing system (MATS) was developed to predict 4CMenB strain coverage on genetically diverse MenB strains and was complemented by genetic MATS (gMATS), based on the correlation between antigen genotypes and MATS outcome.

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Strain coverage estimated using genomic-based MATS, utilizing MenB strain genetic sequence information

Enc-hSBA

Immunological VE

Real world evidence

Increasing amount of post-licensure data on 4CMenB impact and VE supports these coverage estimation methods

enc-hSBA: endogenous complement hSBA; hSBA: human serum bactericidal antibody assay; gMATS: genetic MATS; MATS: meningococcal antigen typing system; MenB: meningococcal serogroup B; VE: vaccine effectiveness; 4CMenB: 4-component MenB vaccine.

An approach to evaluate the performance of meningococcal serogroup B-containing vaccines, including 4CMenB and the investigational MenABCWY vaccine, in the context of clinical trials has been developed, using a qualified assay in which the endogenous subject's own complement is preserved for hSBA assay (enc-hSBA).

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Different repertoire in **laboratory assays** to evaluate MenB strain coverage or immunological vaccine effectiveness (VE)

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Strain coverage estimated using genomic-based MATS, utilizing MenB strain genetic sequence information

Enc-hSBA

Immunological VE

A qualitative method to estimate VE against a broad panel of 110 randomly selected MenB strains representative of:

87% of European isolates

95% of US isolates

90% of Canadian isolates

97% of Australian isolates

Real world evidence

Increasing amount of post-licensure data on 4CMenB impact and VE supports these coverage estimation methods

enc-hSBA: endogenous complement hSBA; hSBA: human serum bactericidal antibody assay; gMATS: genetic MATS; MATS: meningococcal antigen typing system; MenB: meningococcal serogroup B; US: United States; VE: vaccine effectiveness; 4CMenB: 4-component MenB vaccine.

Endogenous complement hSBA should enable the assessment of the synergistic effects induced by multiple antigens. It estimates immunological vaccine effectiveness of MenB-containing vaccines on a broad panel of 110 MenB strains in clinical trial settings, in conditions as close as possible to real-world. The 110 strain panel is representative of 89% of serogroup B isolates globally, ranging from 87% for European, 90% for Canadian to 95% for US and 97% for Australian isolates.

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Together, RWE and immunological VE measured by **enc-hSBA** can provide a complete picture of **4CMenB vaccine performance**

RWE (VE, impact and safety) continues to provide reassurance of the benefits of vaccination against IMD.

enc-hSBA which uses a large panel of randomly selected circulating strains and subject's own complement is a relevant method to evaluate VE in clinical trial settings as a close surrogate to what is seen in the real world.

enc-hSBA: endogenous complement human serum bactericidal antibody assay; IMD: invasive meningococcal disease; RWE: real world evidence; VE: vaccine effectiveness; 4CMenB: 4-component meningococcal serogroup B vaccine.

Over the last 10 years, 4CMenB has provided growing real-word evidences (vaccine effectiveness, impact and safety) and the reassurance of its benefits against MenB IMD and beyond serogroup B.
enc-hSBA is a biologically relevant method to estimate immunological vaccine effectiveness of MenB containing vaccines on a broad representative panel of 110 MenB strains in clinical trials, in conditions as close surrogate to real-world settings.

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