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REVIEW

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Immunogenicity and safety of a quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenACYW-TT): A review of the evidence and expert opinion

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ABSTRACT

Introduction: Serogroups A, B, C, W, X, and Y of Neisseria meningitidis are responsible for almost all cases of invasive meningococcal disease. In Italy, vaccination against serogroup B is recommended at 3–13 months, C at 13–15 months, and A, C, Y and W in adolescents (12–18 years). Four quadrivalent meningococcal conjugate vaccines are available. This review describes the available data on a quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenACYW-TT; MenQuadfi®; Sanofi).

Areas covered: We identified articles on quadrivalent meningococcal conjugate vaccines indexed on PubMed since 2000. Of the 524 studies identified, 10 human studies investigating the immunogenicity and safety of MenACYW-TT in toddlers, children aged 2–9 years, and individuals 10–55 or ≥56 years are described in detail.

Expert opinion: In Italy, pediatric and public health groups recommend amending the current vaccination schedule to include a booster dose between 6 and 9 years and quadrivalent vaccine in young adults (≥19 years), targeting waning protection after childhood vaccination and the age cohort with the highest carrier prevalence (adolescents and young adults). MenACYW-TT is a suitable meningococcal vaccine for current and pending recommendations based on high seroprotection rates and a low incidence of adverse events in these age groups. Moreover, it does not require reconstitution.

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1. Introduction

Invasive meningococcal disease (IMD) has the main clinical presentations of meningitis and bacteremia and is caused by the obligate human bacterium *Neisseria meningitidis* [1]. IMD occurs in both endemic and epidemic forms and is associated with significant morbidity and mortality in all age groups, with young children and young adults more vulnerable to complications than more mature adults [1,2]. Indeed, if untreated, IMD is often rapidly fatal, with fatality rates of up to 15% even when treated. Survivors may also suffer from disabling sequelae (including amputations, hearing loss, and brain damage) that can have significant clinical, social, and economic impacts [3,4]. The risk of IMD is highest in infants and young children under 5 years of age, with peaks of incidence also seen in adolescents and adults ≥ 65 years of age [3,4]. Risk factors for IMD include congenital and acquired immunodeficiency, asplenia, autoimmune disorders, and severe chronic respiratory disorders [5].

Twelve serogroups of *N. meningitidis* have been identified, although serogroups A, B, C, W, X, and Y are responsible for almost all cases of IMD [6,7]. In Europe, serogroup C was the most prevalent until it was targeted by meningococcal C (MenC) vaccination campaigns, since which time serogroup B has generally predominated, although its incidence has decreased in recent years and the incidence of other serogroups has risen [8]. For example, the incidences of serogroups W and Y were once low but increased significantly from 2008 to 2017 [8]. It should also be kept in mind that *N. meningitidis* colonization of the upper airways can occur asymptomatically; asymptomatic carriers are an important part of the disease process [2,3].

Vaccines are available to protect against 5 of the 6 main disease-causing subgroups, and effective vaccination programs have led to a decline in IMD in many geographical areas [9]. Moreover, vaccination with conjugate vaccines also has the potential to influence the prevalence of carriage, further reducing transmission and achieving a herd effect [10]. However, waning of antibody titers has been observed 3–8 years after vaccination in childhood with some meningococcal conjugate vaccines [10], providing a rationale for targeting adolescents and young adults, the group with the highest prevalence of carrier status [6,11], as an important strategy for maintaining disease control. In many European countries, vaccination with a meningococcal B (MenB) or MenC vaccine (or both) is recommended in infants depending on local epidemiology,

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Article highlights

- This paper reviews the available data on the immunogenicity and safety of a quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenACYW-TT MenQuadfi®, Sanofi) and provides perspectives on its use for the prevention of invasive meningococcal disease.
- Overall, MenACYW-TT has shown high rates of seroprotection in all age groups (toddlers [12–24 months], children [2–9 years], ages 10–55 years, and ages ≥56 years), and no safety issues have been observed in clinical trials. In addition, MenACYW-TT demonstrates superior immune response against serogroup C versus existing monovalent and quadrivalent vaccines.
- A quadrivalent vaccine that does not require reconstitution, such as MenACYW-TT, and has the advantage of providing broad protection against multiple serogroups can help in meeting new vaccination targets.

while a quadrivalent meningococcal vaccine targeting serogroups A, C, W, and Y (MenACYW) is recommended in adolescents. In Italy, for example, MenB is recommended at 3, 4, 6, and 13 months and MenC at 13–15 months [12]. A quadrivalent meningococcal conjugate vaccine is recommended in adolescents aged 12–18 years. In this regard, quadrivalent meningococcal conjugate vaccines have been shown to be effective in preventing IMD caused by serogroups A, C, W, and Y [13].

Quadrivalent meningococcal vaccines are available in a number of formulations, including as conjugates with tetanus toxoid. The quadrivalent meningococcal tetanus toxoid-conjugate vaccine produced by Sanofi Pasteur has the brand name MenQuadfi®, while the one produced by Pfizer has the brand name Nimenrix®. To distinguish the two, MenQuadfi® is referred to in the literature as MenACYW-TT, while Nimenrix® is referred to as MenACWY-TT. To avoid potential confusion, in this article, we refer to MenQuadfi® as MenACYW-TT and to Nimenrix® as MCV4-TT. Furthermore, the quadrivalent meningococcal (targeting serogroups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (Menactra®; Sanofi) is referred to as MCV4-DT, the quadrivalent meningococcal (targeting serogroups A, C, Y, and W-135) oligosaccharide diphtheria CRM197 conjugate vaccine (Menveo®; GlaxoSmithKline) is referred to as MenACWY-CRM, and the unconjugated quadrivalent meningococcal (targeting serotypes A, C, Y, and W-135) polysaccharide vaccine (Menomune®; Sanofi) is referred to as MPSV4.

In Italy, a change to the National Immunization Program recommendations is pending, whereby the quadrivalent vaccine will be recommended (instead of the monovalent MenC vaccine) for children aged 13–15 months. The quadrivalent vaccine is already used instead of monovalent MenC in this age group in some regions of Italy [11]. In the meningococcal vaccine-naïve toddler population, it has been observed that the MenACYW-TT vaccine (MenQuadfi®; Sanofi) gives rise to superior meningococcal C responses versus the existing monovalent MenC-TT vaccine or quadrivalent MCV4-TT vaccine (Nimenrix®; Pfizer) [14], supporting the potential switch from monovalent MenC to quadrivalent vaccination against all four serogroups. As well as providing MenC protection to children in this age group, such an approach would provide protection against other serogroups, although studies evaluating persistence of protection are ongoing to confirm the benefits of this switch. Protection against non-B and non-C serogroups is becoming increasingly important in Europe, as the number of IMD cases caused by serogroups Y and W has been increasing in recent decades, particularly in infants and children and older adults (≥65 years) [8].

The present paper reviews the available data on the immunogenicity and safety of the MenACYW-TT vaccine in the age groups who are eligible for this vaccine as part of the National Immunization Program in Italy, i.e. toddlers (12 to 24 months), adolescents (12–18 years), and adults>18 years, and to provide perspectives on its use. Research investigates the use of MenACYW-TT in infants and toddlers (NCT03547271 [EudraCT no. -2017–004731–36], NCT03630705, NCT03673462, NCT03537508, NCT03632720, NCT03547271, and NCT03691610 [EudraCT no. -2017–004520–30]), but the results of these ongoing studies are not yet available.

2. Search methodology

The PubMed database was searched on 6 July 2021 for papers published since 1 January 2000, using the following search terms: (MenQuadfi OR tetravalent OR quadrivalent) AND meningococ×. A total of 524 articles were identified. The titles and abstracts of these articles were manually reviewed to identify human studies with the MenACYW-TT vaccine. We excluded preclinical or non-human studies, reviews, case studies, epidemiological studies, and editorials, correspondence or comments. We also excluded studies of MCV4-TT (Nimenrix®), MCV4-CRM (Menveo®, GlaxoSmithKline) or MCV4-DT (Menactra®, Sanofi) that did not also include MenACYW-TT (MenQuadfi). Ten clinical trials with MenACYW-TT were identified and are discussed in detail below. Additional *ad hoc* searches were also conducted to provide support for the structural characteristics of MenACYW-TT compared with other quadrivalent meningococcal vaccines, and the Expert Opinion.

3. Structure and biochemistry

Table 1 summarizes the structural/biochemical differences in the quadrivalent meningococcal conjugate vaccines [15,16]. These vaccines differ in the types of carbohydrate antigens they contain (polysaccharide or oligosaccharide), carrier proteins, the type of chemical process used to conjugate the protein to the carbohydrate moiety, and whether linkers (or spacers) are used [16]. Linkers reduce the steric hindrance that can occur with large carbohydrate molecules, and their inclusion increases the efficiency of conjugation and may help to expose more antigenic epitopes on the surface of the conjugate [16]. The ability of the vaccine to evoke an immune response in specific age groups is influenced by several structural/biochemical factors, including the carrier protein, length of the saccharide chain, presence/absence of a linker, and the method used for conjugation [16]. MenQuadfi was developed to optimize the immune response across age groups, by altering various attributes (carrier protein, polysaccharide size,

Table 1. Biochemical and structural attributes of the four quadrivalent meningococcal conjugate vaccines.

	MenQuadfi® [15]	Nimenrix® [16]	Menveo® [16]	Menactra® [16]
Manufacturer	Sanofi Pasteur	Pfizer	GSK	Sanofi Pasteur
Type of A, C, Y, W antigen	Polysaccharide	Polysaccharide	Oligosaccharide	Polysaccharide
Type of carrier protein	Tetanus toxoid	Tetanus toxoid	*Corynebacterium diphtheriae* CRM_{197} protein	Diphtheria toxin
Linker/spacer				
A	ADH	ADH	6-Aminoadipic acid	None
C	None	ADH	6-Aminoadipic acid	None
W	None	None	6-Aminoadipic acid	None
Y	None	None	6-Aminoadipic acid	None
Chemical process				
A	Carbodiimide chemistry	Carbodiimide chemistry	Active ester	Reductive amination
C	Reductive amination	Carbodiimide chemistry	Active ester	Reductive amination
W	Reductive amination	Cyanylation	Active ester	Reductive amination
Y	Reductive amination	Cyanylation	Active ester	Reductive amination

Abbreviations: ADH, Adipic acid dihydrazide.

conjugation chemistry, linker vs no linker) in preclinical models until the optimal formulation was obtained to elicit a robust immune response in different age groups, specifically infants and older adults (≥50 years) [15]. This preclinical evaluation led to a formulation using tetanus toxoid as the carrier protein and polysaccharide chains exceeding 50 kDa. The formulation also used an adipic acid dihydrazide (ADH) linker and carbodiimide chemistry for serotype A polysaccharides, but used reductive amination and no linkers for conjugation of serotypes C, Y and W [15].

4. Clinical trials of MenACYW-TT

Rates of seroprotection in trials with MenACYW-TT and comparators in clinical trials that assessed the immunogenicity and safety of MenACYW-TT as a primary and/or booster dose in various patient groups are presented in Tables 2–5 [14,17–28].

For the purposes of international regulatory submission, antibody response was measured using human complement serum bactericidal assay (hSBA) and rabbit complement serum bactericidal assay (rSBA), which correlate with protection against meningococcal disease [29]. In most studies, seroresponse for each serogroup was defined as an hSBA antibody titer≥1:16 for those with a baseline titer of <1:8 or a ≥4-fold increase in post-vaccination titer for those with a baseline titer≥1:8 [14,18,19,21–25]. Three studies (one in children aged 12–24 months [17], one in children aged 10–17 years [24] and one in adults aged ≥56 years [20]) defined seroresponse as an hSBA antibody titer≥1:8 for those with a baseline titer of <1:8, or a ≥ 4-fold increase in post-vaccination titer for those with a baseline titer≥1:8. The criteria for seroresponse using rSBA were post-vaccination antibody titers≥1:32 if the baseline titer was<1.8 or a ≥ 4-fold increase in post-vaccination titer if the baseline titer was>1:8. Seroprotection against meningococcal disease can be defined as hSBA antibody titers≥1:4 or≥1:8, but the more conservative estimate was used in the MenACYW-TT clinical trial program. For rSBA assessments, seroprotection was defined as antibody titers 1:32 or 1:128.

In all studies, hSBA was measured in all vaccine recipients. In contrast, rSBA levels were measured in a subset of vaccinees in all the studies [17–25,28] except for a European Phase 3 comparative study in vaccine-naïve toddlers, which tested hSBA and rSBA levels in all vaccinees [14].

4.1. Studies in toddlers aged 12–24 months

Four studies have been carried out in toddlers, as summarized in Table 2. MET54 (ClinicalTrials.gov identifier: NCT03205358) was a Phase 2 study that compared the immunogenicity and safety of MenACYW-TT with MCV4-TT in meningococcal vaccine-naïve healthy toddlers aged 12–24 months [17]. A total of 188 participants were randomized 1:1 to receive a single vaccine dose of MenACYW-TT or MCV4-TT. Antibodies against each serogroup prior to vaccination and after 30 days were evaluated by serum bactericidal antibody assays using either hSBA or rSBA. For MenACYW-TT versus MCV4-TT, the seroprotection rates (post-vaccination hSBA titers of≥8) were as follows: serogroup A: 97.8% vs. 91.9%; serogroup C: 100% vs. 89.5%; serogroup W: 98.9% vs. 96.5%; serogroup Y: 98.9% vs. 100%.

The Phase 3 MET51 trial (NCT02955797) randomized healthy toddlers aged 12–23 months to MenACYW-TT or MCV4-TT [18]. Participants were either meningococcal vaccine-naïve [MenACYW-TT ($n = 306$) or MCV4-TT ($n = 306$)] or MenC conjugate (MCC) vaccine-primed (≥1 dose of MCC prior to 12 months of age) [MenACYW-TT ($n = 203$) or MCV4-TT ($n = 103$)]. The seroprotective response for all four serogroups was 83.6–99.3% for MenACYW-TT and 81.4–91.6% for MCV4-TT in vaccine-naïve toddlers and 84.9–99.2% and 84.0–91.6%, respectively, for the combined vaccine-naïve and MCC-primed population. The study concluded that MenACYW-TT was noninferior to MCV4-TT in MCC vaccine-primed and vaccine-naïve toddlers.

The Phase 3 MET57 study (NCT03205371) examined the immunogenicity of MenACYW-TT when co-administered with other pediatric vaccines (measles, mumps, and rubella [MMR]; varicella; 6-in-1 combination vaccine against diphtheria, tetanus, pertussis, polio, hepatitis B, and *Haemophilus influenzae* type b [DTaP-IPV-HepB-Hib]; and pneumococcal conjugate vaccine) in 1,183 meningococcal vaccine-naïve toddlers aged 12–23 months [19]. At day 30, the proportion of toddlers with seroprotection to each meningococcal serogroup was similar between MenACYW-TT alone and MenACYW-TT co-administered with each of the vaccines reported above. The response rates for the co-administered vaccine antigens at Day 30 were high and comparable between the vaccine groups. This indicates that co-administration of MenACYW-TT was safe and immunogenic when administered with other routine pediatric vaccines, thereby facilitating its incorporation into national immunization programs.

Table 2. Rates of seroprotection and seroresponse in trials with MenACYW-TT and comparators in toddlers aged 12–24 months [14,17–19,26,27].

Study	Seroprotection[a], % (95% CI)		Seroresponse[b], % (95% CI)	
MET54 [17] Children aged 12–24 months				
	MenACYW-TT (n = 91)	MCV4-TT (n = 86)	MenACYW-TT (n = 91)	MCV4-TT (n = 86)
A	97.8 (92.3–99.7)	91.9 (83.9–96.7)	96.7	91.9
C	100.0 (96.0–100.0)	89.5 (81.1–95.1)	100.0	86.0
Y	98.9 (94.0–100.0)	100 (95.8–100.0)	98.9	98.8
W	98.9 (94.0–100.0)	96.5 (90.1–99.3)	98.9	96.5
MET51 [18] Children aged 12–23 months				
	MenACYW-TT (n = 491)	MCV4-TT (n = 395)	MenACYW-TT (n = 491)	MCV4-TT (n = 395)
A (Naïve)	90.8 (86.9–93.8)	89.5 (85.4–92.7)	76.8 (71.5–81.5)	72.5 (67.1–77.6)
A (MCC-primed)	89.8 (84.8–93.7)	98.0 (92.9–99.8)	76.1 (69.6–81.9)	–
A (Naïve and primed)	90.4 (87.4–92.9)	91.6 (88.4–94.2)	76.5 (72.5–80.2)	77.1 (72.6–81.2)
C (Naïve)	99.3 (97.6–99.9)	81.4 (76.4–85.6)	98.3 (96.1–99.4)	71.5 (66.0–76.6)
C (MCC-primed)	99.0 (96.4–99.9)	98.0 (92.9–99.8)	95.4 (91.5–97.9)	–
C (Naïve and primed)	99.2 (97.9–99.8)	85.5 (81.7–88.9)	97.1 (95.2–98.4)	77.4 (72.9–81.4)
Y (Naïve)	93.2 (89.7–95.8)	91.6 (87.8–94.5)	81.9 (77.0–86.1)	79.1 (74.0–83.5)
Y (MCC-primed)	95.9 (92.2–98.2)	91.9 (84.7–96.4)	89.2 (84.0–93.2)	–
Y (Naïve and primed)	94.3 (91.8–96.2)	91.6 (88.5–94.2)	84.8 (81.3–87.9)	78.9 (74.6–82.9)
W (Naïve)	83.6 (78.9–87.7)	83.4 (78.7–87.5)	67.6 (61.9–72.9)	66.6 (60.9–71.9)
W (MCC-primed)	86.7 (81.2–91.1)	85.7 (77.2–92.0)	75.5 (68.9–81.4)	–
W (Naïve and primed)	84.9 (81.4–87.9)	84.0 (80.0–87.5)	70.8 (66.5–74.8)	68.4 (63.6–73.0)
MET57 [19] Children aged 12–23 months				
South Korea and Thailand	MenACYW-TT (n = 87)	MenACYW-TT + MMR + V (n = 177)	MenACYW-TT (n = 87)	MenACYW-TT + MMR + V (n = 177)
A	92.0 (84.1–96.7)	97.7 (94.3–99.4)	63.2	78.5
C	100.0 (95.8–100.0)	100.0 (97.9–100.0)	98.9	97.7
Y	95.4 (88.6–98.7)	99.4 (96.9–100.0)	93.2	88.5
W	92.0 (84.1–96.7)	96.0 (92.0–98.4)	83.9	86.4
Mexico	MenACYW-TT (n = 100)	MenACYW-TT + DTaP-IPV-HepB-Hib (n = 200)	MenACYW-TT (n = 100)	MenACYW-TT + DTaP-IPV-HepB-Hib (n = 200)
A	89.9 (81.0–95.5)	92.9 (87.7–96.4)	69.6	67.1
C	100.0 (95.4–100.0)	100.0 (97.6–100.0)	98.7	100.0
Y	98.7 (93.1–100.0)	98.7 (95.4–99.8)	87.3	92.3
W	92.4 (84.2–97.2)	90.3 (84.5–94.5)	82.3	82.6
Russia	MenACYW-TT (n = 100)	MenACYW-TT + PCV13 (n = 200)	MenACYW-TT (n = 100)	MenACYW-TT + PCV13 (n = 200)
A	90.6 (82.9–95.6)	83.7 (77.7–88.6)	71.9 (61.8–80.6)	56.1 (48.9–63.2)
C	99.0 (94.3–100.0)	93.9 (89.5–96.8)	91.7	90.8
Y	97.9 (92.7–99.7)	97.4 (94.1–99.2)	92.7	92.9
W	95.8 (89.7–98.9)	94.4 (90.2–97.2)	82.1	82.1
MEQ00065 [14] Children aged 12–23 months				
	MenACYW-TT (n = 227)	MCV4-TT (N = 228)	MenACYW-TT (n = 227)	MCV4-TT (N = 228)
C[c]	99.5 (97.4–100)	89.1 (84.1–93.0)	99.5 (97.4–100.0)	83.4 (77.7–88.2)
C[d]	100.0 (98.3–100)	–	99.5 (97.4–100.0)	92.9 (88.5–95.9)
		MenC-TT (n = 235)		MenC-TT (n = 235)
C[d]	–	100.0 (93.3–100)	–	99.5 (97.4–100.0)

a. Seroprotection was defined as post-vaccination hSBA titers of ≥8 (MET54) or ≥1:8 to each serogroup at Day 30 post-vaccination.

b. Seroresponse was defined in Study MET54 as Day 30 post-vaccination hSBA titers of ≥1:8 to each serogroup in individuals with a baseline titer of <1:8 or a ≥4-fold increase in GMT in individuals with a baseline titer of ≥1:8. In Studies MET51, MET57 and MEQ00065, seroresponse was defined as Day 30 post-vaccination hSBA titers of ≥1:16 to each serogroup in individuals with a baseline titer of <1:8 or a ≥4-fold increase in GMT in individuals with a baseline titer of ≥1:8. Where possible, 95% confidence intervals are reported, but where data were presented graphically in the reported studies, exact 95% confidence interval data were not available.

c. Assessed by serum bactericidal assays with human complement.

d. Assessed by serum bactericidal assays with rabbit complement.

Abbreviations: 95% CI, 95% confidence interval; DTaP-IPV-HepB-Hib, diphtheria, tetanus, pertussis, polio, hepatitis B and *Haemophilus influenzae* type b combination vaccine; GMT, geometric mean titer; hSBA, human serum bactericidal antibody assay; MCC, meningococcal C conjugate; MCV4-TT, quadrivalent meningococcal and tetanus conjugate vaccine (Nimenrix®; Pfizer Europe); MenC-TT, monovalent meningococcal C vaccine; MenACYW-TT, quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenQuadfi®, Sanofi); MMR, measles, mumps and rubella vaccine; PCV13, pneumococcal polyvalent vaccine; V, varicella vaccine.

Most recently, Knuf and colleagues compared the meningococcal serogroup C immune response elicited by MenACYW-TT with a quadrivalent or monovalent meningococcal vaccine in meningococcal vaccine-naïve toddlers aged 12–23 months [14]. In this Phase 3 study (MEQ00065; NCT03890367), 701 individuals received a single dose of MenACYW-TT (n = 227), MCV4-TT (n = 228) or MenC-TT (n = 235). At day 30, the serogroup C immune response to MenACYW-TT was significantly superior to MCV4-TT both in terms of seroprotection assessed using hSBA (99.5% vs. 89.1%, respectively [95% confidence interval (CI) 5.68–16.20]) and geometric mean titers (GMT) (ratio 16.3 [95% CI 12.7–21.0]). Compared with MenC-TT, MenACYW-TT induced a superior GMT response to serogroup C (ratio 1.32 [95% CI 1.06–1.64]); when evaluated using rSBA, both MenACYW-TT and MenC-TT showed seroprotection rates of 100%.

Table 3. Rates of seroprotection and seroresponse in trials with MenACYW-TT and comparators in children aged 2–9 years [23,28].

Study	Seroprotection[a], % (95% CI)		Seroresponse[b], % (95% CI)	
MET35 [23] Children aged 2–9 years				
	MenACYW-TT (n = 499)	MenACWY-CRM (n = 501)	MenACYW-TT (n = 458)	MenACWY-CRM (n = 460)
A	86.4 (82.9–89.4)	79.3 (75.3–82.9)	55.4 (50.7–60.0)	47.8 (43.2–52.5)
C	97.8 (96.0–98.9)	67.1 (62.6–71.4)	95.2 (92.8–97.0)	47.8 (43.2–52.5)
Y	98.5 (96.9–99.4)	90.8 (87.8–93.3)	91.5 (88.5–93.9)	79.3 (75.3–82.9)
W	94.8 (92.3–96.9)	86.3 (82.8–89.3)	78.8 (74.8–82.5)	64.1 (59.5–68.4)
MET62 [28] Children aged 4–5 years				
	MenACYW-TT Primed (n = 40)	MCV4-TT Primed (n = 44)	MenACYW-TT Primed (n = 40)	MCV4-TT Primed (n = 44)
A	100.0 (91.2–100.0)	100.0 (92.0–100.0)	100.0 (91.2–100.0)	95.5 (84.5–99.4)
C	100.0 (91.2–100.0)	100.0 (92.0–100.0)	95.0 (83.1–99.4)	100.0 (92.0–100.0)
Y	97.5 (86.8–99.9)	100.0 (92.0–100.0)	100.0 (91.2–100.0)	100.0 (92.0–100.0)
W	100.0 (91.2–100.0)	100.0 (92.0–100.0)	97.5 (86.8–99.9)	100.0 (92.0–100.0)

a. Seroprotection was defined as post-vaccination hSBA titers of ≥1:8 to each serogroup at Day 30 post-vaccination.

b. Seroresponse in Study MET35 was defined as Day 30 post-vaccination hSBA titers of ≥1:16 to each serogroup in individuals with a baseline titer of <1:8 or a ≥4-fold increase in GMT in individuals with a baseline titer of ≥1:8. Seroresponse in Study MET62 was defined as Day 30 post-vaccination hSBA titers to each serogroup of ≥1:8 in individuals with a baseline titer of <1:8 or a ≥4-fold increase in GMT in individuals with a baseline titer of ≥1:8.

Abbreviations: 95% CI, 95% confidence interval; GMT, geometric mean titer; hSBA, human serum bactericidal antibody assay; MCV4-TT, quadrivalent meningococcal and tetanus conjugate vaccine (Nimenrix®; Pfizer Europe); MenACWY-CRM, quadrivalent meningococcal and diphtheria conjugate vaccine (Menveo®; GlaxoSmithKline); MenACYW-TT, quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenQuadfi®; Sanofi).

4.2. Studies in children aged 2–9 years

Two studies have been carried out in this age group: MET62 and MET35 (Table 3). The Phase 3 open-label MET62 trial (NCT03476135) [28] assessed the immunogenicity of a booster dose of MenACYW-TT in children 4–5 years old who were primed 3 years earlier in the MET54 study [17] with MenACYW-TT (n = 40) or MCV4-TT (n = 44). In both groups, titers of hSBA increased from day 0 to day 30. Of note, GMTs for serogroup C were higher in those primed with MenACYW-TT at both day 0 and day 30 (106 and 5,894 IU/mL, respectively) compared with those primed with MCV4-TT (11.7 and 1,592 IU/mL, respectively). In addition, almost all children achieved≥1:8 hSBA titers at day 30 that were higher or similar to those seen after the primary dose, indicating that immunogenicity is persistent and that MenACYW-TT elicits a robust booster response.

The Phase 3 MET35 study (NCT03077438) compared the immunogenicity of MenACYW-TT with a quadrivalent meningococcal vaccine conjugated with diphtheria protein CRM197 (MenACWY-CRM) [23]. Healthy meningococcal vaccine-naïve children, 2–9 years of age, were randomized to receive either MenACYW-TT (n = 499) or MenACWY-CRM (n = 501). At day 30, the proportion of participants who achieved seroprotection (hSBA titers≥1:8) with MenACYW-TT versus MenACWY-CRM was serogroup A: 86.4% vs. 79.3%; C: 97.8% vs. 67.1%; Y: 94.8% vs. 86.3%; and W: 98.5% vs. 90.8%, respectively. Moreover, GMTs were higher with MenACYW-TT compared with MenACWY-CRM for serogroups C, W, and Y. Noninferiority between the vaccines, measured by comparing seroresponse rates (defined as Day 30 titers≥1:16 for a participant with prevaccination titers of<1:8, or ≥4-fold increase in titers if the prevaccination titers were≥1:8) showed that MenACYW-TT was noninferior to MenACWY-CRM (A: 55.4% vs. 47.8%; C: 95.2% vs. 47.8%; Y: 91.5% vs. 79.3%; and W: 78.8% vs. 64.1%, respectively).

4.3. Studies in individuals aged 10–55 years

Studies on individuals aged 10–55 years are summarized in Table 4. The Phase 2 MET50 noninferiority trial (NCT02199691) compared immunogenicity of MenACYW-TT to MenACWY-CRM and also when co-administered with tetanus, diphtheria, acellular pertussis (Tdap), and human papillomavirus type 4 (HPV4) vaccines, in 1,715 healthy meningococcal vaccine-naïve adolescents aged 10–17 years [24]. In this trial, noninferiority was established for MenACYW-TT versus MenACWY-CRM and for MenACYW-TT when co-administered with Tdap and HPV4 compared with MenACYW-TT alone. For each serogroup, the seroprotection rates were higher with MenACYW-TT compared with MenACWY-CRM: A: 93.5% vs. 82.8%; C: 98.5% vs. 76.0%; Y: 97.2% vs. 83.2%; and W: 99.1% vs. 90.7%, respectively.

MET43 (NCT02842853) was a Phase 3 study that randomized (3:3:3:2) 3,344 meningococcal vaccine-naïve participants aged 10–55 years to receive one of three lots of MenACYW-TT or MCV4-DT [25]. First, the study demonstrated that consistency was seen for all three lots of MenACYW-TT, with GMT ratios that ranged from 0.87 to 1.1. Moreover, more participants achieved seroprotection with MenACYW-TT than with MCV4-DT (A: 94.7% vs. 88.5%; C: 95.7% vs. 76.2%; Y: 98.8% vs. 87.9%; and W: 95.9% vs. 87.0%, respectively). MenACYW-TT was considered noninferior to MCV4-DT in adolescents and adults.

The Phase 3 MET56 trial (NCT02752906) compared MenACYW-TT (n = 403) with MCV4-DT (n = 810) as a single booster in MCV4-primed participants ≥ 15 years of age [22]. The authors reported seroprotection rates with MenACYW-TT versus MCV4-DT as follows: serogroup A: 100% vs. 99%; C: 99.5% vs. 99.0%; W: 100% vs. 99.7%; and Y: 99.7% vs. 99.5%. In terms of seroresponse (defined as above) at Day 30, noninferiority criteria for the MenACYW-TT versus MCV4-DT were met for all four serogroups (A: 92.2% vs. 87.1%; C: 97.1% vs. 91.8%; W: 98.2% vs. 90.7%; and Y: 97.4% vs. 95.6%). The study also assessed the rapidity of the booster response at day 6: seroprotection rates

Table 4. Rates of seroprotection and seroresponse in trials with MenACYW-TT and comparators in individuals aged 10–55 years [22,24–27].

Study	Seroprotection[a], % (95% CI)		Seroresponse[b], % (95% CI)	
MET50 [24] Children aged 10–17 years				
	MenACYW-TT (n = 463)	MenACWY-CRM (n = 464)	MenACYW-TT (n = 463)	MenACWY-CRM (n = 464)
A	93.5 (90.9–95.6)	82.8 (79.0–86.1)	75.6 (71.4–79.4)	66.4 (61.9–70.7)
C	98.5 (96.9–99.4)	76.0 (71.9–79.8)	97.2 (95.2–98.5)	72.6 (68.3–76.6)
Y	97.2 (95.2–98.5)	83.2 (79.5–86.5)	97.0 (95.0–98.3)	80.8 (76.9–84.3)
W	99.1 (97.8–99.8)	90.7 (87.7–93.2)	86.2 (82.7–89.2)	66.6 (62.1–70.9)
MET43 [25] Children, adolescents and adults aged 10–55 years				
	MenACYW-TT (n = 2508) (3 pooled lots)	MCV4-DT (n = 593)	MenACYW-TT (n = 2508) (3 pooled lots)	MCV4-DT (n = 593)
A	94.7 (93.7–95.5)	88.5 (85.7–91.0)	73.8 (72.0–75.5)	54.6
C	95.7 (94.8–96.4)	76.2 (72.6–79.6)	88.8 (87.5–90.0)	47.9
Y	98.8 (98.3–99.2)	87.9 (84.0–89.6)	91.4 (90.3–92.5)	73.4
W	95.9 (95.3–96.9)	87.0 (85.0–90.4)	80.3 (78.7–81.8)	61.2
MET56 [22] Subjects aged ≥15 years				
	MenACYW-TT (n = 394)	MCV4-DT (n = 389)	MenACYW-TT (n = 394)	MCV4-DT (n = 389)
A	100.0 (99.0–100.0)	99.0 (97.4–99.7)	92.2 (89.0–97.7)	87.1 (83.4–90.3)
C	99.5 (98.1–99.9)	99.0 (97.4–99.7)	97.1 (94.9–98.6)	91.8 (88.6–94.3)
Y	99.7 (98.6–100.0)	99.5 (98.6–100.0)	97.4 (95.3–98.7)	95.6 (93.1–97.4)
W	100.0 (99.0–100.0)	99.7 (98.2–99.9)	98.2 (96.3–99.3)	90.7 (87.4–93.4)

a. Seroprotection was defined as post-vaccination hSBA titers ≥1:8 to each serogroup at Day 30 post-vaccination.
b. Seroresponse was defined in Study MET50 as Day 30 post-vaccination hSBA titers of ≥1:8 to each serogroup in individuals with a baseline titer of <1:8 or a ≥4-fold increase in GMT in individuals with a baseline titer of ≥1:8. In studies MET43 and MET56, it was defined as Day 30 post-vaccination hSBA titers of ≥1:16 to each serogroup in individuals with a baseline titer of <1:8 or a ≥4-fold increase in GMT in individuals with a baseline titer of ≥1:8. Where possible, 95% confidence intervals are reported, but where data were presented graphically in the reported studies, exact 95% confidence interval data were not available.
Abbreviations: 95% CI, 95% confidence interval; GMT, geometric mean titer; hSBA, human serum bactericidal antibody assay; MenACWY-CRM, quadrivalent meningococcal and diphtheria conjugate vaccine (Menveo®; GlaxoSmithKline); MenACYW-TT, quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenQuadfi®; Sanofi); MCV4-DT, quadrivalent meningococcal and diphtheria conjugate vaccine (Menactra®; Sanofi).

were similar for the MenACYW-TT and MCV4-DT vaccines (A: 96.4% vs. 96.8%; C: 96.4% vs. 96.8%; W: 98.2% vs. 98.4%; and Y: 98.2% vs. 96.8%), suggesting a rapid booster response at Day 6 in addition to the noninferiority of the immune response observed following priming with either MenACYW-TT or MCV4-DT.

The Phase 3b MET59 trial (NCT04084769) evaluated immune response to a single booster dose of MenACYW-TT (with or without concomitant MenB vaccination) in adults and adolescents primed 3–6 years earlier with MenACYW-TT or MCV4-CRM [30]. Preliminary data from this study indicated persistence of immune response at 3–6 years after the primary vaccination and robust booster response at Day 30 for serogroups A, C, Y, and W.

4.4. Studies in individuals≥56 years

Two studies have been carried out in individuals aged ≥56 years (Table 5). The Phase 2 MET44 trial (NCT01732627) compared the immunogenicity of MenACYW-TT with that of a quadrivalent

Table 5. Rates of seroprotection and seroresponse in trials with MenACYW-TT and comparators in individuals aged ≥ 56 years [20,21,26,27].

Study	Seroprotection[a], % (95% CI)		Seroresponse[b], % (95% CI)	
MET44 [20] Adults aged ≥56 years				
	MenACYW-TT (n = 195)	MPSV4 (n = 94)	MenACYW-TT (n = 195)	MPSV4 (n = 94)
A	93.8 (89.5–96.8)	85.1 (76.3–91.6)	65.1	46.8
C	74.9 (68.2–80.8)	62.8 (52.2–72.5)	70.8	59.6
Y	80.5 (74.2–85.8)	59.6 (49.0–69.6)	75.4	48.9
W	79.5 (73.1–84.9)	60.6 (50.0–70.6)	74.4	55.3
MET49 [21] Adults aged ≥56 years				
	MenACYW-TT (n = 433)	MPSV4 (n = 431)	MenACYW-TT (n = 433)	MPSV4 (n = 431)
A	89.4 (86.1–92.1)	84.2 (80.4–87.5)	58.2 (53.4–62.9)	42.5 (37.7–47.3)
C	90.1 (86.9–92.7)	71.0 (66.5–75.2)	77.1 (72.9–81.0)	49.7 (44.8–54.5)
Y	91.7 (88.7–94.1)	67.7 (63.1–72.1)	74.4 (70.0–78.4)	44.8 (40.0–49.6)
W	77.4 (73.1–81.2)	63.1 (58.4–67.7)	62.6 (57.8–67.2)	44.8 (40.0–49.6)

a. Seroprotection was defined as post-vaccination hSBA titers ≥1:8 to each serogroup at Day 30 post-vaccination.
b. Seroresponse was defined in Study MET44 as Day 30 post-vaccination hSBA titers of ≥1:8 to each serogroup in individuals with a baseline titer of <1:8 or a ≥4-fold increase in GMT in individuals with a baseline titer of ≥1:8. In Study MET49, seroresponse was defined as Day 30 post-vaccination hSBA titers of ≥1:16 to each serogroup in individuals with a baseline titer of <1:8 or a ≥4-fold increase in GMT in individuals with a baseline titer of ≥1:8. Where possible, 95% confidence intervals are reported, but where data were presented graphically in the reported studies, exact 95% confidence interval data were not available.
Abbreviations: 95% CI, 95% confidence interval; GMT, geometric mean titer; hSBA, human serum bactericidal antibody assay; MenACYW-TT, quadrivalent meningococcal tetanus toxoid-conjugate vaccine (MenQuadfi®; Sanofi); MPSV4, quadrivalent meningococcal polysaccharide vaccine (Menomune®; Sanofi).

meningococcal polysaccharide vaccine (MPSV4; Menomune®, Sanofi) in 301 healthy meningococcal vaccine-naïve participants aged ≥56 years [20]. The proportion of adults with seroprotective titers after receiving MenACYW-TT was similar to that seen for the MPSV4 vaccine for serogroups A (93.8% vs. 85.1%, respectively) and C (74.9% vs. 62.8%, respectively) and clearly greater than for MPSV4 for serogroups W (79.5% vs. 60.6%, respectively) and Y (80.5% vs. 59.6%, respectively).

Lastly, MET49 (NCT02842866) also compared the immunogenicity of MenACYW-TT ($n = 451$) with that of MPSV4 ($n = 455$) in meningococcal vaccine-naïve adults ≥56 years of age [21]. Seroresponse (defined as above) to MenACYW-TT at Day 30 was noninferior to that of MPSV4 for all serogroups (A: 58.2% vs. 42.5%; C: 77.1% vs. 49.7%; Y: 74.4% vs. 43.4%; and W: 62.6% vs. 44.8%, respectively). Seroprotection rates (MenACYW-TT vs MPSV4) are as follows: A: 89.4% vs. 84.2%; C: 90.1% vs. 71.0%; Y: 91.7% vs. 67.7%; and W: 77.4% vs. 63.1%, respectively.

Six to 7 years after vaccination, GMTs for serotype A were similar in the groups receiving MPSV4 and MenACYW-TT, while GMTs for serotypes C, W, and Y tended to be higher in the group that had received MenACYW-TT [31]. Bactericidal antibody levels remained above prevaccination levels for all serotypes in both groups, indicating a persistent immune response [31]. A robust anamnestic response was seen when a single booster dose of MenACWY-TT was given 3 years or 6–7 years after the primary vaccination [31].

This indicates that MenACYW-TT has the potential to fill an unmet need in areas where there are only polysaccharide vaccines or where no meningococcal vaccines are currently available for older adults.

5. Summary of immunogenicity

In clinical trials, the immunogenicity of MenACYW-TT has been assessed in several age groups. Notably, immunological noninferiority of MenACYW-TT was demonstrated for all four serogroups and all meningococcal vaccine comparators, including MCV4-DT, MPSV4, MenACWY-CRM, and MCV4-TT vaccines. In toddlers>12 months, MenACYW-TT provided high rates of immunogenicity that were similar to that conferred by MCV4-TT across all serogroups [17,18] and also demonstrates superiority against serogroup C versus existing monovalent MenC-TT and quadrivalent MCV4-TT vaccines [14]. High rates of seroresponse were also seen when co-administered with other common pediatric vaccines [19]. In children aged 2–9 years, high rates of seroresponse were observed with MenACYW-TT compared with both MCV4-TT and MenACWY-CRM [23,24]; notably, higher rates of seroprotection were seen for serogroup C 3 years after the primary vaccination [23,28]. For example, 3 years after the primary course of vaccination, 100% of children who received MenACWY-TT had hSBA titers≥1:8 for serogroup C compared with 57.1% of children who received MCV4-TT [28]. In individuals 10–55 years of age, rates of seroresponse with MenACYW-TT were also higher than those observed with either MenACWY-CRM or MCV4-DT [24,25]. As a single booster, MenACYW-TT was noninferior to MCV4-DT, providing robust immunogenicity on Day 6 [22]. Furthermore, in two studies in individuals≥56 years of age, MenACYW-TT seemingly provided greater immunogenicity than MPSV4 across all four serogroups [20,21], with persistent immune responses lasting up to 7 years [31]. Finally, MenACYW-TT provided similar immunogenicity alone or when co-administered with other routine pediatric vaccines [19].

6. Summary of safety

In addition to immunogenicity, all of the studies described above evaluated the safety of both MenACYW-TT and comparators. None of these studies raised any safety concerns or issues of vaccine-related serious adverse events. When administered as a single dose, MenACYW-TT was well tolerated in all age groups alone or together with licensed pediatric vaccines. In toddlers, the safety profile of MenACYW-TT was similar to that of the comparator, with no immediate unsolicited adverse events or reactions after vaccination in either vaccine group and no serious adverse reactions [17–19]. Similar safety results were seen in individuals 2–9 years of age with MenACYW-TT and comparators, and there were no discontinuations due to adverse events or reactions [23,28]. Moreover, the safety profiles of MenACYW-TT, MenACWY-CRM, and Tdap and HPV4 vaccines, administered with or without MenACYW-TT, were all comparable in meningococcal vaccine-naïve adolescents [24]. Near identical safety profiles of MenACYW-TT and comparators were also seen in adolescents and adults [22,25]. In adults≥56 years of age, there were likewise no safety concerns, and most unsolicited adverse events were Grade 1 or 2 in intensity and similar to the comparator [20,21]. In MET49, but not MET44, a higher rate of injection site reactions, most commonly Grade 1 or 2 pain, was reported in the MenACYW-TT compared with the MPSV4 group (26.6% vs. 9.5%) [21]. However, there was no increase in pain severity, with Grade 3 pain reported by 0.7% of each group.

7. Conclusion

This narrative review summarizes the available literature relating to the quadrivalent meningococcal vaccine, MenACYW-TT, and comparators in clinical trials that assessed the immunogenicity and safety of MenACYW-TT as a primary and/or booster dose in various patient groups. Our review has several limitations. This is not a systematic review, and the sample size for individual age groups is limited in some studies. However, the studies referenced report comparable study designs and immunological end points, and the findings provide an overview of the safety and immunogenicity noninferiority of MenACYW-TT across a range of age groups from various countries and superiority against serogroup C in toddlers.

8. Expert opinion

One drawback of most quadrivalent vaccines is that they require reconstitution prior to use, with the potential to introduce errors and consequently reduce immunization and/or safety issues. To overcome this shortcoming, a novel

quadrivalent meningococcal conjugate vaccine with tetanus toxoid carrier, MenACYW-TT, that does not require reconstitution, was approved as a single-dose vaccine for active immunization in the USA in April 2020 (individuals aged≥24 months) and in Europe in November 2020 (individuals aged≥12 months). It has since been approved in several countries globally, including Australia, Brazil, and Canada. The characteristics of MenACYW-TT highlight its potential to serve as a new option for the prevention of IMD, and the clinical development program reviewed herein demonstrates its noninferior immunogenicity against all four meningococcal serogroups with a well-tolerated safety profile that is similar to comparators. Most recently, MenACYW-TT also demonstrated superiority against serogroup C versus existing meningococcal monovalent MenC-TT and quadrivalent MCV4-TT vaccines in toddlers. The immunogenicity observed in older adults is also of relevance, given the hitherto marginal role of meningococcal vaccination in adults.

In light of the ongoing COVID-19 pandemic, there is also the need to strengthen coverage and adherence to meningococcal vaccination, which has likely decreased in many regions [32,33]. There is a need to ensure adequate coverage overall and, specifically, timed booster dosing to allow coverage of vaccination in individuals who could benefit from vaccination. Among these individuals are the immunocompromised [5,11], the elderly [34], and special populations [11]. MenACYW-TT also achieved high rates of immunogenicity in all age groups assessed in clinical trials and across all meningococcal serogroups, appeared to provide higher immune responses for serogroup C than MCV4-DT and MenACWY-CRM in adolescents and adults [24,25], and induced superior serogroup C immune responses compared with the quadrivalent MCV4-TT vaccine and the monovalent MenC-TT vaccine in toddlers [14]. The confirmation of these promising data in immunocompromised individuals and the elderly would make the MenACYW-TT vaccine even more relevant for these special populations.

Moreover, the immunogenicity and safety of MenACYW-TT used as a booster was shown in children primed with MenACYW-TT or MCV4-TT, and in adolescents and adults primed with MenACWY-CRM or MCV4-DT. As a booster, a rapid immune response seen by Day 6 is notable (data not shown). Primary vaccination with MenACYW-TT achieves high rates of seroresponse when co-administered with other pediatric vaccines, enabling its use as part of routine vaccination schedules. During the present pandemic, co-administering several vaccines can be viewed as a valid and efficient means of achieving vaccination objectives while responding to the need for families to reduce access to overwhelmed vaccination facilities. This has the potential to open up new settings for vaccine administration, considering that MenACYW-TT is a fully liquid formulation that does not require reconstitution and can be administered with other vaccines. Ready-to-use vaccines are associated with fewer errors, thereby improving safety, and require less preparation time compared with vaccines that need to be reconstituted [35].

Indeed, a vaccination strategy based on territorial vaccination centers and/or general practitioners is beneficial for the healthy population that takes advantage of routine visits to perform vaccinations. In the same way, it seems increasingly important to establish vaccine centers in hospitals for patients who need complex care. These patients often have frailties that make them more susceptible to meningococcal disease (e.g. HIV, asplenia, congenital immunodeficiency, and/or complement deficiency) and may not have received the recommended vaccines [36]. The importance of vaccination in-hospital originates from the opportunity to vaccinate high-risk individuals who, to date, have not been effectively vaccinated with traditional strategies. The availability of a single, easy-to-administer vaccine, co-administered with routine pediatric vaccines, may thus be an incentive for many primary care physicians to start vaccinating in the office, in addition to in-hospital vaccination.

In Italy, regional vaccination recommendations often differ slightly from the National Immunization Program recommendations. For example, many regions already use quadrivalent meningococcal vaccines rather than monovalent MenC vaccines in the 13- to 15-month age group [11], and Tuscany introduced a booster dose of MenC vaccine for children aged 6 to 9 years in 2017 after a meningococcal outbreak there [37]. A health technology assessment has recommended that additional cohorts are added to the current Italian vaccination schedule. In addition to a booster dose for all children between 6 and 9 years, vaccination with a quadrivalent meningococcal vaccine would be extended to young adults (≥19 years) [11]. This represents a new position on meningococcal vaccination and recognizes the age-related epidemiology of IMD and *N. meningitidis* carriage, as well as the waning of protection over time after childhood vaccination. There are two peaks in IMD incidence – one in children aged≤4 years and the other in adolescents and young adults (15 to 24 years) [38,39]. The adolescent and young adult age group is also the cohort with the highest prevalence of carrier status [40]. Moreover, immunity to the MenC vaccination administered to toddlers in Italy wanes after 5–6 years [41,42], supporting the need for a booster dose in children aged ~6 years. Based on available data, most children who receive MenACYW-TT retain seroprotection against all serogroups in the vaccine for at least 3 years after the primary course of vaccination, with 3-year seroprotection rates ranging from 66.7% against serogroup A to 100.0% against serogroup C [28]. The multicohort strategy for a quadrivalent meningococcal vaccine would now be at 13–15 months, 6 years, 12 years, and 19 years [11]. Lastly, a quadrivalent vaccine has the advantage of providing broad protection against multiple serogroups and addresses a public health need in terms of variable and unpredictable epidemiology.

For the reasons cited above, MenACYW-TT has the potential to be a valuable tool in achieving these new vaccination targets. Currently, the duration of immune persistence after childhood vaccination with MenACYW-TT is at least 3 years [28], but data for adults aged ≥59 years indicate that elevated

GMTs against all four serotypes in the vaccine persist for at least 6 to 7 years after primary vaccination [31].

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Author contributions

All listed authors made substantial contributions to the conception and design of the review, drafting the article and revising it critically for important intellectual content. All authors provided final approval of the version submitted. All authors attest that they meet the ICMJE criteria for authorship.

Data availability statement

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

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