Contact Dermatitis

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Prevalence of Contact Allergy to Neomycin in Dermatitis Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Neomycin, an aminoglycoside antibiotic frequently employed in topical formulations, is a recognised allergen that is part of many baseline series and can cause contact allergy (CA) in both adults and children. It is an allergen of interest as it has a widespread use in over-the-counter and prescription products globally, but geographical variations may exist. This study aimed to establish prevalence estimates of CA to neomycin in dermatitis patients and to investigate potential geographical variations. Three databases (PubMed, Embase, and Web of Science) were screened, revealing 70 included studies comprising 456 372 adults and 17 720 children who underwent patch testing. The pooled prevalence of CA to neomycin was found to be 3.2% (95% confidence interval [CI]: 2.6%–3.8%) in adults and 4.3% (95% CI: 2.65%–6.3%) in children. The highest prevalences were observed in North America (adults: 6.4%; children: 8.1%) and South Asia (adults: 4.9%), while Europe showed lower rates (adults: 2.5%; children: 0.8%). Studies after the year 2000 indicated a prevalence of 2.1% in adults and 5.1% in children across geographical regions. These findings highlight a public health concern, particularly in regions with high prevalence rates. The study underscores the need for more restrictive use of neomycin to reduce the incidence of neomycin-induced CA.

1 | Introduction

Neomycin is an aminoglycoside antibiotic commonly used in topical formulations. Although beneficial for infection control, neomycin is a recognised allergen, and exposure may cause contact allergy (CA) in both adults and children [1]. Neomycin can be administered orally, whereas topical formulations are available for localised use [2]. Neomycin is found in over-the-counter and prescription products worldwide, such as antibiotic ointments, eye drops, eardrops, and as an excipient in vaccines widely utilised for its antimicrobial properties [2–4]. Antibiotic resistance is often highlighted as an argument for restrictive antibiotic use; however, contact allergy to antibiotics is another issue that needs to be addressed. In the European baseline series, neomycin has been tested in 20% pet [5]. and neomycin is also part of the TRUE test system.

Little is known about the worldwide prevalence of CA to neomycin in adults and children. While individual studies have explored the prevalence of CA to neomycin [1, 6, 7], a comprehensive synthesis of this evidence is lacking. The aim of this study is to establish prevalence estimates of CA to neomycin in adults and children and investigate the prevalence in different geographical regions.

Mikkel Bak Jensen shared first authorship.

2 | Methods

A study protocol was conducted before initiating the study and registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024569404). The study was performed according to the Preferred Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [8].

2.1 | Literature Search

A comprehensive literature search was conducted using the databases PubMed, Embase and Web of Science with the following search strategies: *(neomycin) AND* ("allergic contact dermatitis" OR "contact allergy" OR "contact dermatitis" OR "allergic reaction" OR "hypersensitivity" OR "contact sensitization" OR "contact sensitivity"). The search was conducted on July 16th, 2024, and no restrictions were placed on publication date.

2.2 | Inclusion and Exclusion Criteria

Eligible studies were assessed by MBJ and DI. Inclusion criteria were: (I) Original studies (II) studies written in English (III) studies including ≥ 100 consecutively patch tested children and/or adults (≥ 18 years age) with dermatitis who were patch tested with neomycin of any concentration and vehicle. If different concentrations of neomycin were used for the same population, results would be presented separately if possible; otherwise, pooled data are provided. Exclusion criteria were: (I) studies specifically investigating dermatitis characterised by its anatomical location, such as hand dermatitis or scalp dermatitis, (II) studies examining samples from the general population, and (III) conference abstracts or letters to the editor. In the case of duplicate articles of the same population, the most comprehensive report was included. If inclusion criteria could not be determined based on title or abstract, the study was included for full-text screening.

2.3 | Data Extraction and Quality Assessment

Data were entered by MBJ and DI into a pre-defined table including data on the author, publication year, study period, study country, concentration, vehicle, number of positive patch tests (PPTs), sex distribution (female, %), age distribution (mean, standard deviation (SD)), history of atopic dermatitis (AD) (%), and clinical relevance (%). The quality of the included cross-sectional studies was assessed using the assessment tool for cross-sectional studies (AXIS) [9].

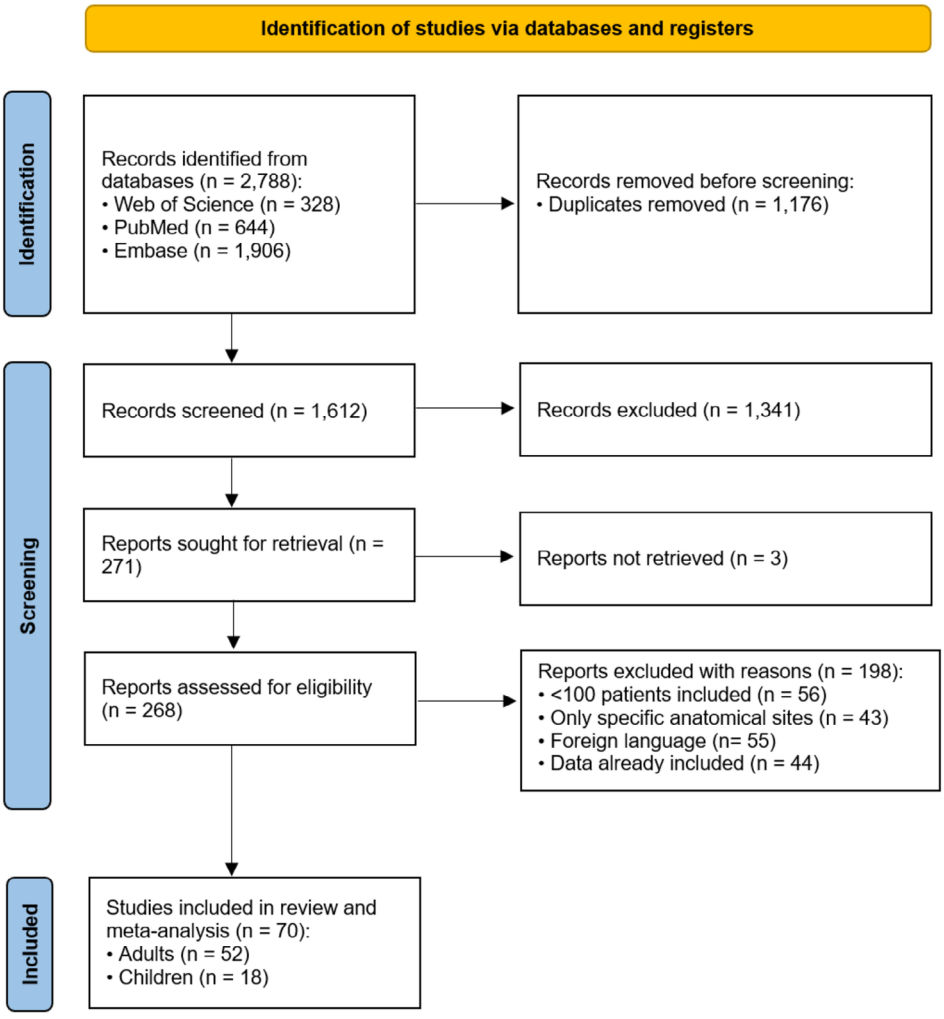

FIGURE 1 | Preferred items for systematic reviews and meta-analysis (PRISMA).

TABLE 1 | General characteristics of the included studies conducted on adults.

Label	Study period (year)	Study country	Total tested [*n*]	PPTs [*n*]	PPTs [%]	Female [*n* (%)]	Age [mean (SD)]	History of atopic dermatitis [%]	Clinical relevance [%]
Baer et al. (1973) [1]	1968–1970	United States	540	28	5.2	NA	NA	NA	NA
Hirano & Yoshikawa (1982) [2]	1976–1979	Japan	434	13	5.1	NA	NA	NA	NA
Hogan et al. (1988) [3]	1983–1987	Canada	542	31	5.7	330 (60.9)	39.4 (18.0)	30.1	NA
Gollhausen et al. (1988) [4]	1977–1983	Germany	11 962	419	3.5	7177 (60.0)	NA	NA	NA
Goh (1988) [5]	1984–1985	Singapore	2471	142	5.7	1160 (46.9)	32.0 (NA)	NA	NA
Goh (1989) [6]	1985–1986	Singapore	1685	132	7.8	838 (49.7)	31.8 (NA)	NA	NA
Leok et al. (1992) [7]	1986–1990	Singapore	5557	381	6.9	2923 (52.6)	NA	NA	NA
Bruckner-Tuderman et al. (1992) [8]	1989–1989	Switzerland	921	63	6.8	543 (59)	42.8 (NA)	NA	NA
el-Rab & al-Sheikh (1995) [9]	1993–1994	Saudi Arabia	240	26	11.0	131 (54.9)	NA	NA	NA
Holness et al. (1995) [10]	1985–1989	United States[a]	4055	292	7.2	2311 (57.0)	43.8 (NA)	NA	NA
Liu et al. (1997) [11]	1988–1996	China	1135	24	2.1	823 (72.5)	34.3 (NA)	NA	NA
Husajn (1997) [12]	1970–1973	Scotland	1312	55	4.2	709 (54.0)	NA	NA	NA
Sharma & Chakrabarti (1998) [13]	1996–1997	India	200	10	5	78 (39)	39.8 (NA)	NA	NA
Marinović-Kulisić et al. (2004) [14]	1998–2003	Croatia	4132	522	12.6	2940 (71.2)	40.0 (NA)	11.7	NA
Piaserico et al. (2004) [15]	1997–2001	Italy[c]	1444	37	2.4	980 (67.9)	72.5 (5.7)	7.1	NA
Machovcova et al. (2005) [16]	1997–2001	Czech Republic	12 058	234	1.9	7642 (63.4)	41.7 (12.6)	26.4	NA
Bruynzeel et al. (2005) [17]	1996–2000	Europa[d]	26 210	786	3.0	17 722 (67.6)	NA	NA	NA
Uter et al. (2005) [18]	2002–2003	Europa[b]	10 511	304	2.9	6611 (62.9)	NA	18.0	NA
Menezes de Padua et al. (2005) [19]	1998–2003	Germany	47 559	1208	2.5	29 386 (61.8)	NA	16.7	NA
Akyol et al. (2005) [20]	1992–2004	Turkey	1038	25	2.4	705 (67.9)	33.4 (13.7)	19.7	NA

(Continues)

TABLE 1 | (Continued)

Label	Study period (year)	Study country	Total tested [*n*]	PPTs [*n*]	PPTs [%]	Female [*n* (%)]	Age [mean (SD)]	History of atopic dermatitis [%]	Clinical relevance [%]
Menezes de Pádua et al. (2006) [21]	1995–2005	Germany	80 867	2022	2.5	NA	NA	NA	NA
Lazarov (2006) [22]	1998–2004	Israel	2156	23	1.1	1462 (67.8)	45.5 (17.1)	21.9	68.4
Magen et al. (2006) [23]	2002–2005	Israel	864	4	0.5	547 (63.3)	NA	14.1	NA
Bajaj et al. (2007) [24]	1997–2006	India	1000	70	7.0	434 (43.4)	35.9 (NA)	NA	98.8
Lindberg et al. (2008) [25]	1992–2000	Sweden	7452	115	1.5	4780 (64.1)	NA	NA	NA
Carlsen et al. (2008) [26]	1985–2005	Denmark	14 998	420	2.8	9524 (63.5)	47.4 (NA)	NA	NA
Lam et al. (2008) [27]	1995–1999	Hong Kong	2585	126	4.9	1535 (59.4)	NA	NA	NA
Bilcha et al. (2010) [28]	2007–2008	Ethiopia	514	0	0	343 (66.7)	36.3 (12.1)	1.5	NA
Janach et al. (2010) [29]	2000–2004	Switzerland	4094	81	1.3	2388 (58.3)	45.4 (17.9)	10.6	NA
Yin et al. (2011) [30]	2004–2009	China	2758	17	0.6	1622 (58.8)	38.5 (12.4)	7.8	NA
Landeck et al. (2011) [31]	1990–2006	United States	1247	59	4.7	874 (70.1)	46.2 (15.2)	13.8	4.8
Rodrigues et al. (2012) [6]	2003–2010	Brazil	1406	88	6.3	955 (67.9)	42.0 (16)	34.1	NA
Uter et al. (2012) [32]	2007–2008	Europa[b]	25 181	161	0.6	16 421 (65.2)	NA	12.9	NA
Reduta et al. (2013) [33]	2007–2011	Poland	1532	69	4.4	1010 (65.9)	43.6 (15.5)	4.5	NA
Gilissen & Goossens (2016) [34]	1990–2014	Belgium	14 578	269	1.8	9.856 (66.1)	47 (NA)	22.2	NA
Uter et al. (2016) [35]	2009–2012	Europa[b]	28 569	371	1.3	NA	45.0 (NA)	NA	NA
Kot et al. (2016) [36]	2013–2014	Poland	126	2	1.6	80 (63.5)	50.4 (NA)	NA	NA
Linauskienė et al. (2017) [37]	2014–2015	Lithuania	297	7	2.4	257 (86.5)	NA	23.6	NA
Hassan et al. (2019) [38]	2011–2018	India	582	16	2.8	371 (63.8)	34.7 (11.3)	NA	75.0
Teo et al. (2019) [39]	1984–2014	United Kingdom	43 443	1557	3.6	27 061 (58.5)	41.0 (NA)	29.4	NA
Tagka et al. (2020) [40]	2014–2016	Greece	1978	57	2.9	1359 (68.7)	45.9 (18.6)	35.0	NA
Uter et al. (2021) [41]	2008–2011	Germany	515	1	0.3	283 (54.9)	NA	4.1	NA
Silverberg et al. (2021) [42]	2001–2016	United States[a]	36 896	3261	8.8	NA	NA	22.5	NA
Uter et al. (2022) [43]	2019–2020	Europa[b]	11 737	97	0.8	NA	NA	NA	NA

(Continues)

TABLE 1 | (Continued)

Label	Study period (year)	Study country	Total tested [*n*]	PPTs [*n*]	PPTs [%]	Female [*n* (%)]	Age [mean (SD)]	History of atopic dermatitis [%]	Clinical relevance [%]
Wee et al. (2022) [44]	2007–2017	Singapore	4903	127	5.1	2860 (58.3)	40.1 (16.3)	51.6	NA
Bizjak et al. (2022) [3]	2019–2021	Slovenia	748	21	2.8	550 (73.5)	45.0 (NA)	NA	NA
Ünal (2022) [45]	2012–2022	Turkey	1012	2	0.3	579 (57.2)	38.0 (NA)	33.2	NA
Scherrer et al. (2023) [46]	2009–2018	Brazil	1162	71	6.0	755 (65.0)	53.5 (NA)	24.0	14
Boonchai et al. (2023) [47]	2001–2021	Thailand	5010	224	4.5	3844 (76.73)	41.9 (15.3)	43.1	NA
Dekoven et al. (2023) [48]	2019–2020	United States[a]	4221	259	6.3	3142 (73.8)	47.7 (NA)	31.8	33.2
Larsen et al. (2024) [49]	2000–2023	Denmark	17849	255	1.4	12022 (67.35)	48.6 (16.9)	17.8	18.5
Slodownik et al. (2024) [49]	2019–2022	Israel	2086	6	0.3	1401 (67.0)	NA	19.0	17

Abbreviations: NA, not available; PPTs, positive patch tests; SD, standard deviation.
[a]NACDG.
[b]ESSCA.
[c]NEICDG.
[d]EECDRG.

2.4 | Statistical Analysis

Statistical analyses were performed using StatsDirect version 3.1.4 (StatsDirect Ltd., Wirral, UK). Pooled proportions for the total population were calculated using random-effects models with 95% confidence intervals (CI). In addition, stratified analysis was done for adults only, children only, and according to geographical areas and publication years. Heterogeneity between studies was assessed using the Cochran Q test and the I [2] statistic. Given the expected high heterogeneity among the included studies, pooled proportion analyses were performed using the DerSimonian-Laird method with random-effects models [10]. Forest plots were constructed, and the Egger's test and funnel plots were performed to assess the risk of publication bias. To assess differences in PPTs for both adults and children [2], tests of independence were conducted. A significance level of $p < 0.05$ was used to determine statistical significance. Due to limited data across different geographic subgroups, analyses were restricted to overall comparisons by time period within each age group.

3 | Results

In total, 2878 studies were identified. After removing duplicates, 2142 unique studies remained for title and abstract screening. In total, 268 studies were included for full-text evaluation. Of these, 198 studies were excluded after full-text evaluation based on the predetermined criteria. No additional study was included after screening the reference lists of the included studies. Finally, 70 studies [1, 3, 6, 7, 11–75] were included in the analysis (Figure 1). Of these studies, 52 [1, 3, 6, 7, 11–57] and 18 [58–75] examined a population of adults and children, respectively. A tabular summary of the general characteristics of the included studies for adults and children is presented in Tables 1 and 2, respectively. Generally, studies had low or medium risk of bias based on the AXIS assessment (Tables S1 and S2).

3.1 | Qualitative Assessment of the Included Studies

3.1.1 | Characteristics of Studies Conducted on Adults

Across 52 studies [1, 3, 6, 7, 11–57], the study periods ranged from 1968 to 2022. The percentage of females in the studies ranged from 39% to 86.5%, with a mean of 62.9% (SD: 10.5%), reported in 46 studies [1, 3, 6, 7, 11–35, 37, 39–43, 45–57]. The mean age of participants ranged from 25.3 to 72.5 years, with a mean of 43.4 years (SD: 8.4), reported in 33 studies. A history of atopic dermatitis was reported in 29 studies [3, 6, 7, 11, 13–16, 28, 30–33, 35, 37–40, 42, 45–51, 56, 57, 76], with values ranging from 1.5% to 51.6% and a mean of 21.0% (SD: 11.7%). The clinical relevance of neomycin contact allergy was reported in eight studies [6, 7, 31, 41, 48, 55, 57], ranging from 4.8% to 98.8% (Table 1).

Most studies originated from Europe ($n = 26$) [1, 3, 7, 12–16, 18, 21, 27, 34, 36, 37, 39, 40, 42–46, 50–53, 76] and North America ($n = 6$) [20, 28, 29, 31, 38, 48], followed by the Middle East ($n = 5$) [11, 30, 33, 56, 57], Southeast Asia ($n = 5$) [23–25, 32, 35], East

TABLE 2 | General characteristics of the included studies conducted in children.

Label	Study period (year)	Study country	Total tested [*n*]	PPTs [*n*]	PPTs [%]	Female [*n* (%)]	Age [mean (SD)]	History of atopic dermatitis [%]	Clinical relevance [%]
Manzini et al. (1998) [50]	1988–1994	Italy	670	24	3.9	NA	NA	75.5	NA
Giordano-Labadie et al. (1999) [51]	1998–1999	France	137	3	2.2	67 (48.9)	4.5 (NA)	100	NA
Roul et al. (1999) [52]	1995–1997	France	337	12	3.5	NA	NA	76.0	NA
Mortz et al. (2000) [53]	1995–1996	Denmark	1146	2	0.2	620 (54.1)	14.1 (NA)	21.3	0
Seidenari et al. (2005) [54]	1995–2001	Italy	1094	144	13.2	585 (53.5)	5.4 (3.1)	36.9	70.0
Goon & Goh (2006) [55]	1986–2003	Singapore	1063	43	4.0	583 (54.8)	NA	38.0	NA
Clayton et al. (2006) [56]	1995–2004	United Kingdom	500	4	0.8	310 (62.0)	12.0 (3.8)	61.0	100
Hogeling & Pratt (2008) [57]	1996–2006	United States	100	7	7.0	62 (50.8)	13.7 (3.4)	41.0	55.8
Fortina et al. (2011) [58]	2002–2008	Italy	320	16	5.0	177 (55.3)	2.3 (0.4)	7.3	31.25
Moustafa et al. (2011) [59]	2002–2008	United Kingdom	110	7	6.4	68 (62.0)	12.0 (NA)	51.0	59.1
Machovcova (2012) [60]	2005–2006	Czech Republic	218	25	11.5	104 (47.7)	12.6 (NA)	27.0	39.0
Simonsen et al. (2014) [61]	2003–2011	Denmark	2592	12	0.5	1709 (65.9)	NA	44.8	NA
Rodrigues & Goulart (2015) [62]	2003–2010	Brazil	125	8	6.4	96 (76.8)	14.3 (3.8)	44.8	45.6
Fortina et al. (2015) [63]	2002–2010	Europa[b]	6708	215	3.2	3965 (59.1)	NA	NA	NA
Yılmaz & Özkaya (2021) [64]	1996–2017	Turkey	146	4	1.3	109 (74.6)	14.0 (NA)	13.7	25.0
Bonamonte et al. (2022) [65]	2017–2018	Italy	432	8	1.9	232 (53.7)	10.4 (NA)	23.8	NA
Silverberg et al. (2022) [66]	2001–2018	United States[a]	1110	118	6.3	706 (63.6)	12.4 (3.9)	52.6	NA
Johnson et al. (2023) [67]	2018–2022	United States	912	56	6.1	561 (61.5)	11.3 (4.7)	67.4	NA

Abbreviations: NA, not available; PPTs, positive patch tests; SD, standard deviation.
[a]NACDG.
[b]ESSCA.

Asia ($n=4$) [19, 26, 49, 54], South Asia ($n=3$) [17, 41, 55], South America ($n=2$) [6, 47] and Western Asia ($n=1$) [22].

3.1.2 | Characteristics of Studies Conducted in Children

Across 18 studies [1, 3, 6, 7, 11–57], the study periods ranged from 1986 to 2022. The percentage of girls in the studies ranged from 47.7% to 76.8%, with a mean of 59.7% (SD: 8.2%), reported in 16 studies [58, 60, 62–75]. The mean age of participants ranged from 2.3 to 14.3 years, with a mean of 10.7 years (SD: 4.0), reported in 13 studies [60, 62–67, 70–75]. A history of atopic dermatitis was reported in 17 studies [58–68, 70–75], with values ranging from 7.3% to 100% and a mean of 46.6% (SD: 23.9%). A study by Giordano-Labadie et al. [60] from 1999 involved 137 children with atopic dermatitis. Of these, three exhibited PPTs yielding an estimate of CA to neomycin of 2.2%. The clinical relevance of neomycin CA was reported in 9 studies [62–67, 71, 72, 75], ranging from 0.0% to 100%, with a mean of 43.0% (SD: 30.2%) (Table 2).

Most studies originated from Europe ($n=12$) [59–70] and North America ($n=3$) [72–74], followed by the Middle East ($n=1$) [71], South America ($n=1$) [75] and Asia ($n=1$) [58].

3.2 | Quantitative Assessment

3.2.1 | CA To Neomycin in Adults

The prevalence of PPTs to neomycin in adults was reported in 52 studies [1, 3, 6, 7, 11–57] encompassing 456,372 patients with 14,590 PPTs yielding a pooled prevalence of 3.2% (95% CI, 2.6%–3.8%) (Figure 2, Table 3 and Figure S1).

3.2.2 | CA To Neomycin in Children

The prevalence of PPTs to neomycin in children was reported in 18 studies [58–75] encompassing 17720 patients with 708 PPTs, yielding a pooled prevalence of 4.3% (95% CI, 2.6%–6.3%) (Figure 3 and Table 3).

3.2.3 | Differences in CA to Neomycin According to Time Period in Adults and Children

In adults, PPTs showed a significant decrease when comparing data from before and after 2000 [χ [2] (1, $N=169209$) $=11.52$, $p<0.001$]. Conversely, in children, there was a significant increase in PPTs between the two periods [χ [2] (1, $N=13280$) $=20.46$, $p<0.001$].

3.2.4 | CA To Neomycin According to Geographical Regions

For adults, the highest pooled prevalences of CA to neomycin were 6.4% (95% CI, 5.0%–7.9%; $n=6$ studies [20, 28, 29, 31, 38, 48]) in North America, 6.2% (95% CI, 5.3%–7.2%; $n=2$ studies [6, 47]) in South America, 5.3% (95% CI, 3.6%–7.4%; $n=5$ studies [23–25, 32, 35]) in Southeast Asia, and 4.9% (95% CI, 2.3%–8.3%; $n=3$ studies [17, 41, 55]) in South Asia. The lowest prevalences of CA to neomycin were

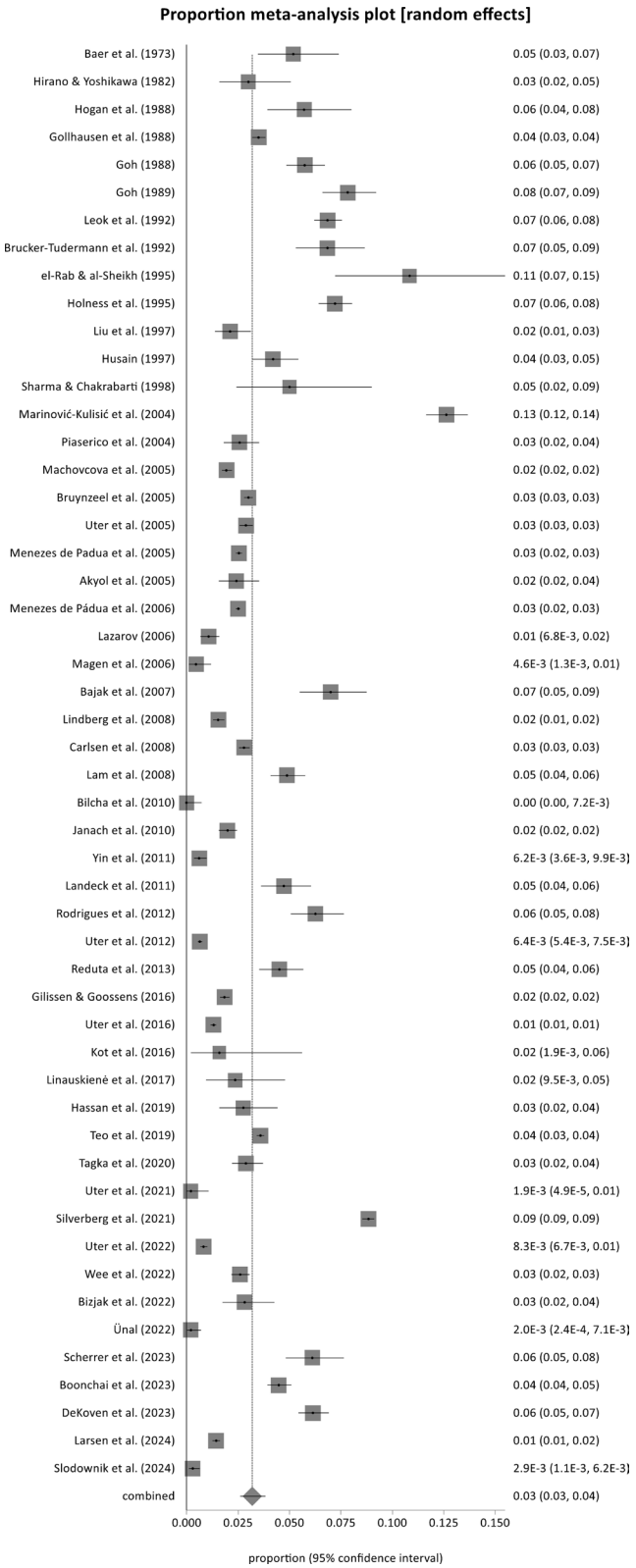

FIGURE 2 | Proportion meta-analysis plot with random effects for adults tested with neomycin. The figure displays the author, publication year, prevalence, confidence intervals, and the pooled prevalence for all studies.

TABLE 3 | Prevalences of positive patch tests to neomycin in adults and children.

Population	Studies [*n*]	Patients [*n*]	PPTs [*n*]	Proportion of positive reactions [%]	95% CI	*p*-value for Q test	I^2 (95% CI) [%]	Egger's bias (95% CI)	Egger's bias *p*-value
Adults	52	456 372	14 590	3.2	2.6–3.8	< 0.0001	99.2 (99.2–99.2)	5.6 (1.5–9.7)	0.0084
Children	18	17 720	708	4.3	2.6–6.3	< 0.0001	96.9 (96.3–97.4)	4.7 (1.9–7.5)	0.0025

Abbreviations: CI, confidence interval; PPTs, positive patch tests.

2.5% (95% CI, 2.0%–3.0%; *n* = 26 studies [3, 7, 12–16, 18, 21, 27, 34, 36, 37, 39, 40, 42–46, 50–53, 76]) in Europe, 2.4% (95% CI, 0.6%–5.3%; *n* = 4 studies [19, 26, 49, 54]) in East Asia, and 0.8% (95% CI, 0.2%–1.5%; *n* = 5 studies [11, 30, 33, 56, 57]) in the Middle East (Figure 4a and Table 4).

For children, the pooled prevalence of CA to neomycin was 0.8% (95% CI, 0.4%–1.5%; *n* = 12 studies [59–70]) in Europe, and 8.1% (95% CI, 4.9%–11.9%; *n* = 3 studies [72–74]) in North America. Pooled prevalences of CA to neomycin in children in the Middle East, South America, East Asia, South Asia, and Southeast Asia could not be calculated due to a limited number of studies (Figure 4b and Table 4).

3.2.5 | CA To Neomycin According to Publication Year and/or Region in Adults and Children

For adults, the prevalence of CA to neomycin in studies with study periods before the year 2000 was 5.2% (95% CI, 4.2%–6.4%; *n* = 15 studies [17–29, 53, 54]). For studies after the year 2000, the prevalence was 2.1% (95% CI, 1.1%–3.3%; *n* = 24 studies [6, 7, 13, 30–39, 41–47, 49–51, 56]). European studies after the year 2000 (*n* = 13 studies [7, 13, 34, 36, 37, 39, 42–46, 50, 51]) revealed a prevalence of CA to neomycin of 1.6 (95% CI, 1.1%–2.1%), while high prevalences were found in North America (7.4%, 95% CI: 5.0%–10.3%; *n* = 2 studies [31, 38]) after the year 2000 (Table 5).

For children, the prevalence before year 2000 was 2.0% (95% CI; 1.3%–6.1%; *n* = 3 studies [59, 61, 62]) and after year 2000 was 5.1% (95% CI: 2.7%–8.2%; *n* = 9 studies [65–70, 73–75]). In Europe, the prevalence before year 2000 was 2.0% (95% CI, 1.3%–6.1%; *n* = 3 studies [59, 61, 62]) and after year 2000 was 3.9% (95% CI, 1.7%–6.9%; *n* = 6 studies [65–70]). For North America, the prevalence of CA to neomycin after year 2000 was 8.3% ((95% CI, 4.5%–13.2%); *n* = 2 studies [73, 74]) (Table 5).

4 | Discussion

In this systematic review and meta-analysis of 70 studies encompassing 456 372 adults and 17 720 children undergoing patch testing, the overall prevalence of CA to neomycin was 3.2% in adults and 4.3% in children across all included studies. Based on geographical regions, the highest prevalences of CA to neomycin were found in North America (Adults: 6.4%, children: 8.1%) and South Asia (Adults: 4.9%), while European data showed lower prevalences of 2.5% and 0.8% in adults and children, respectively. Based on newer studies after the year 2000, the overall prevalence was 2.1% in adults and 5.1% in children. These high rates of CA to neomycin emphasise the important role of neomycin as a sensitiser, particularly in comparison to more well-known allergens. For example, prevalences of CA have been reported to be 2.0%–2.7% for rubber accelerators [77, 78], 7% for fragrance mix I and 3.7% for fragrance mix II [78, 79], and 5.0% for preservatives like methylisothiazolinone (MI) [36, 80], which often have comparable prevalence rates. The prevalence of CA to neomycin in this study was even higher in North America and South Asia, highlighting an overlooked problem in these regions.

For children, the estimate found in this study is slightly higher than that of a recent systematic review and meta-analysis on CA in children from 2010 to 2024 revealing an overall prevalence of 3.2% [81]. The differences in these findings may rely on the methodology of the two studies, as the current study did not have any restrictions on the publication year. Further, the discrepancies may be attributed to the fact that the present study encompasses a diverse range of geographical regions, each with distinct policies governing the utilisation of neomycin and varying degrees of leniency in antibiotic prescription.

The presence of neomycin as an excipient in vaccines may contribute to the development of contact allergy, particularly in younger individuals. A previous study demonstrated notable age-related differences in CA to both neomycin and thimerosal among children and teenagers with eczema [82]. The prevalence of CA to neomycin was 4.9% in 7–8-year-olds, whereas no cases were observed among 16–17-year-olds [82]. This contrast aligns with differences in vaccine exposure: the older cohort received multiple thiomersal-containing vaccines, while the younger cohort had fewer thiomersal-containing vaccines but increased exposure to vaccines with trace amounts of neomycin. These findings highlight the importance of considering vaccine composition as a potential factor influencing variations in neomycin allergy prevalence across age groups and geographical locations [83–85]. Since aminoglycosides such as neomycin are used as preservatives in certain vaccines, repeated exposure during early childhood may induce sensitisation in susceptible individuals [84, 85]. Future studies should investigate the relationship between

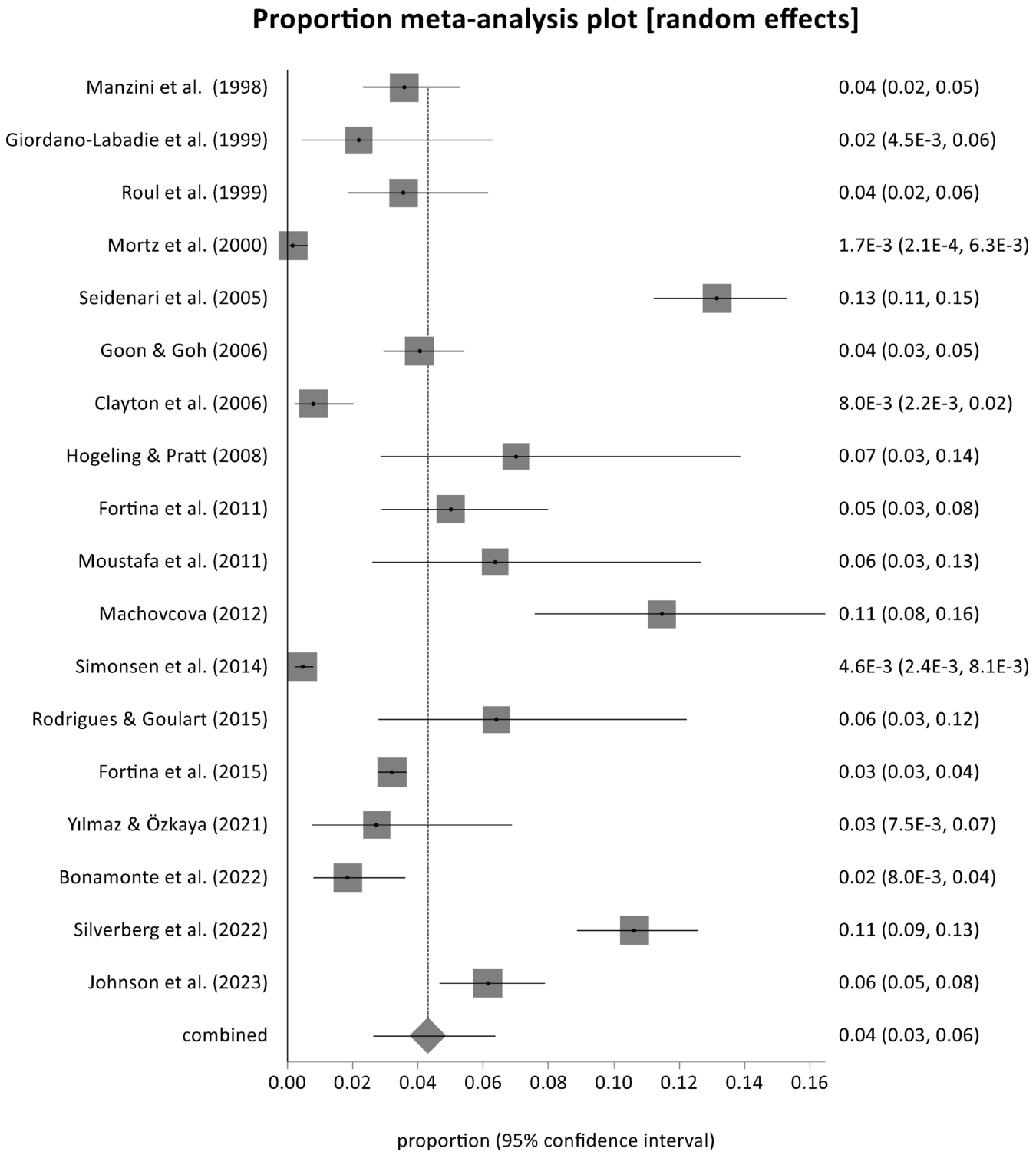

FIGURE 3 | Proportion meta-analysis plot with random effects for children tested with neomycin. The figure displays the author, publication year, prevalence, confidence intervals, and the pooled prevalence for all studies.

vaccine-related exposure and neomycin sensitisation and assess whether changes in vaccine formulations over time affect trends in contact allergy prevalence.

Differences in geographical variation of CA to neomycin were exploited in sub-analyses. The high prevalence of contact allergy in especially southeast Asia and north America compared to Europe may be explained by less regulation on neomycin medication in these first mentioned regions. For example, over-the-counter preparations are widely available in the USA and many Asian countries, unlike Europe. In Denmark, neomycin was withdrawn as a medical product in October 2009. In a cross-sectional study by Kursawe Larsen et al., it was shown that this action significantly decreased CA to neomycin in Denmark

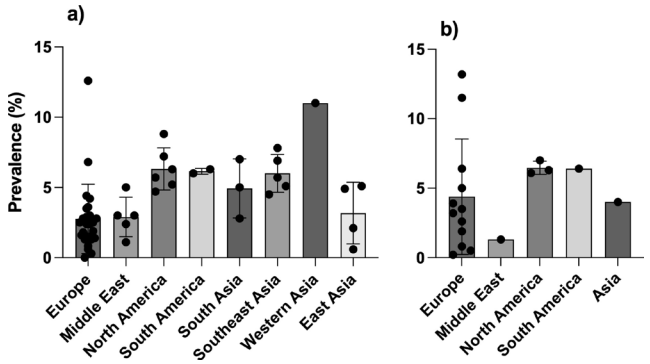

FIGURE 4 | Prevalence estimates of contact allergy to neomycin according to geographical regions in adults (a) and children (b). Each bullet represents one study. Standard deviation (SD) was calculated for regions where two or more studies were included. There was only one study on children in Asia, and thus it could not be made more region-specific.

from 1.8% in the period from 2000 to 2009 to 1.2% in the period from 2010 to 2023 ($p < 0.005$) [7].

With sensitization rates for children in this study exceeding 8% in North America, and for adults being 6.4% in North America, 5.3% in Southeast Asia, and 4.9% in South Asia, there is an immediacy call for better regulation on neomycin medical products in these regions. Redundant use of antibiotics is increasingly problematic, not only due to the well-documented issue of antibiotic resistance [86], but also because of its role in CA. We propose that neomycin should be withdrawn as a medical product in countries still using it, or at least legislation requiring a prescription to buy neomycin-containing medicine should be implemented.

Cross-reactivity between neomycin and other aminoglycosides, including framycetin, paromomycin, gentamycin, and tobramycin, exists primarily due to their similarities in chemical structure [87]. Thus, cross-reactivity is an important factor to consider when interpreting rates of PPTs. Aminoglycosides are frequently used in topical formulations, both as prescription and over-the-counter products, and prior exposure to these structurally related compounds may contribute to sensitisation and PPTs [83]. Therefore, it may be likely that this phenomenon influences the reported prevalence of CA to neomycin and should be recognised as a potential confounder. Further, clinicians prescribing neomycin should be aware of this when prescribing topical aminoglycosides and when diagnosing and treating patients with known CA to neomycin.

The strengths of this study are (I) the comprehensive literature review including 70 studies encompassing 456,372 adults and 17,720 children, (II) the concentration or vehicle for neomycin has not changed during the study period, and (III) sub-analyses were conducted based on geographical regions to reveal differences and trends based on local regulations to further strengthen the estimates presented in our study. However, when interpreting the results of the current study, some limitations should be noted. While we report the prevalence of CA to neomycin, only a few studies report clinically relevant PPTs leading to allergic contact dermatitis. Further, estimates on prevalences of CA to neomycin in various regions relied on few studies and should be interpreted with caution.

TABLE 4 | Prevalences of positive patch tests to neomycin according to geographical regions in adults and children.

	Europe		Middle East		North America		South America		East Asia		South Asia		Southeast Asia	
Population	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]
Adults	26	2.5 (2.0–3.0)	5	0.8 (0.2–1.5)	6	6.4 (5.0–7.9)	2	6.2 (5.3–7.2)	4	2.4 (0.6–5.3)	3	4.9 (2.3–8.3)	5	5.3 (3.6–7.4)
Children	12	0.8 (0.4–1.5)	NA	NA	3	8.1 (4.9–11.9)	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: CI, confidence interval; NA, not applicable; PPTs, positive patch tests.

TABLE 5 | Prevalence of positive patch tests to neomycin across geographical regions in adults and children, categorised by study periods before and after the year 2000. Studies overlapping 2000 were excluded from the analysis. Pooled meta-analyses with random effects were conducted for groups with two or more studies. Single-study data are indicated with ([a]).

	Study period	All countries		Europe		Middle East		North America	
	Year	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]
Adults	< 2000	15	5.2 [4.2–6.4]	4	0.4 [0.3–0.5]	NA	NA	3	6.4 [5.0–7.7]
	> 2000	24	2.1 [1.1–3.3]	13	1.6 [1.1–2.1]	3	0.3 [0.1–0.5]	2	7.4 [5.0–10.3]
Children	< 2000	3	2.0 [1.3–6.1]	3	2.0 [1.3–6.1]	NA	NA	NA	NA
	> 2000	9	5.1 [2.7–8.2]	6	3.9 [1.7–6.9]	NA	NA	2	8.3 [4.5–13.2]

	South America		East Asia		South Asia		Southeast Asia		Western Asia	
	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]	Studies [*n*]	Proportion of PPTs (95% CI) [%]
Adults	NA	NA	3	3.3 [1.7–5.5]	1[a]	5.0	3	6.8 [5.8–7.8]	1[a]	10.4
	NA	NA	1[a]	0.6	1[a]	2.7	2	3.5 [1.8–5.5]	NA	NA
Children	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	1a	6.4	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: CI, confidence interval; NA, not applicable; PPTs, positive patch tests.
[a]One study.

5 | Gaps in Knowledge

While this meta-analysis consolidates available data on the prevalence of CA to neomycin in dermatitis patients, several knowledge gaps limit our understanding of the allergen's epidemiology, diagnosis, and management. These gaps highlight areas where further research could provide valuable insights and enhance clinical practice. Firstly, longitudinal studies including clinical relevance are highly needed. While PPTs confirm sensitization to neomycin, the clinical relevance is not well understood, though understanding these factors could provide valuable insights into disease severity, chronicity, and quality of life in dermatitis patients. Further, more knowledge is needed on the cross-reactivity between neomycin and other aminoglycosides [87, 88].

6 | Conclusion

CA to neomycin is frequent in both adults and children throughout the study period. However, the prevalence varies significantly according to geographical regions. We recommend a withdrawal of neomycin in regions still utilising it or limiting over-the-counter sale with legislation requiring a prescription to buy neomycin medication.

Author Contributions

Mikkel Bak Jensen: investigation, validation, visualization, software, formal analysis, supervision, writing – review and editing, writing – original draft, conceptualization, project administration, methodology. **Daniel Isufi:** investigation, validation, writing – original draft, writing – review and editing, project administration, methodology. **Christoffer Kursawe Larsen:** investigation, writing – original draft, writing – review and editing, supervision, conceptualization. **Jakob Ferløv Baselius Schwensen:** writing – original draft, writing – review and editing, validation, project administration, supervision. **Farzad Alinaghi:** supervision, project administration, conceptualization, investigation, validation. **Jeanne Duus Johansen:** writing – original draft, writing – review and editing, project administration, supervision, validation.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.