Sociedad Colombiana
de Medicina del Trabajo

¡JUNTOS CONSTRUYENDO EL MUNDO
DEL TRABAJO QUE SOÑAMOS



# 45 CONGRESO COLOMBIANO
## DE MEDICINA DEL TRABAJO Y SALUD OCUPACIONAL

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# A multi-center Study on Sensitization to Thimerosal in North-Eastern Italy, 1997-2023: Prevalence, Risk Factors, the Role of Occupation and the Impact of Vaccinations

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# Thimerosal in Human Vaccines and Medications

- Thimerosal (Methiolate) is a mercury derivative composed by ethyl mercury chloride (EtHgCl) and thiosalicylic acid (TSA), developed in 1927 as a preservative with anti-microbial properties

- Thimerosal has been employed since 1930ies as preservative in a range of medications, especially in childhood vaccines

# Removal of Thimerosal from medical

- Global scepticism on health (neurological) side effects of Thimerosal as an additive to medications started to spark from the early 80ies, leading to its removal from all vaccines in Denmark in 1992

- On July 7 1999, the US Public Health Service (USPHS) and the American Academy of Pediatrics (AAP) called for removal of Methiolate from all vaccines in the USA as soon as possible, leading to its progressive elimination from novel and existing vaccine formulations in Europe and North America, with the exceptions of multi-dose influenza vaccines and vaccines available in  developing countries

# An ongoing debate

- Some authors argued that Thimerosal is not an optimal preservative for vaccine at currently used dosage formulations, and higher concentrations would reduce vaccine efficacy as well as increasing the risk of side effects in recipients

- Official position of WHO:

*"It is important to note that concerns about the toxicity of Thiomersal are theoretical and that there is no compelling scientific evidence of a safety problem related to its use in vaccines, although public perception of risk has been reported in some countries*

# Thimerosal and Allergic Contact Dermatitis (ACD)

- Immune-mediated reactions to mercury-containing products are well documented in humans and in experimental animals, the most frequent being allergic contact dermatitis (ACD)

- Thimerosal appointed allergen of the year in 2002 by the American Contact Dermatitis Society, due to high prevalence of sensitization combined with low clinical relevance (<7.2%)

- As result of its removal from most vaccines, sensitization to Thimerosal has been progressively decreasing over time

- Most clinically relevant allergic reactions to Thimerosal occur following cosmetics use [19, 20, 21] or after contact with ophthalmic preparations, resulting mostly in facial dermatitis

# Study aim

Prevalence of sensitization to Thimerosal was investigated in 31,948 consecutive patients patch tested for suspected ACD during 1997-2023 (27 years) in four centers of Triveneto (North-Eastern Italy)- Trieste, Padua, Pordenone and Bolzano/Trento/Rovigo - to identify potential trends and associated factors

# METHODS

- Clinical pattern of patients assessed by MOAHLFA Index (percentage male of sex, occupational dermatitis, atopic dermatitis, hand dermatitis (HD), leg dermatitis (LD), face dermatitis (FD), age >40 years)

- Occupation classified using ISCO-88 codes and then summarized in groups with similar exposure.

- Occupational dermatitis assessed by a dermatologist or an occupational medicine consultant considering the clinical history, sites involved, occupational exposures and stop and go test.

# Patch testing

All patches applied on the upper part of patient back and removed after 48 hours. The area was examined upon removal of the patch and after 72/96 hours, according to guidelines of the International Contact Dermatitis Research Group.

- Reactions degree +, ++ and +++ were considered positive.

- Doubtful reactions (?+) were considered negative.

Triveneto patch test series (22 haptens) tested in the overall study period (all in pet when not otherwise specified)

| | |
|---|---|
| 1 | 4-ter-Butylphenol- formaldehyde resin 1% |
| 2 | Carba mix 3% |
| 3 | Cobalt chloride hexahydrate 1% |
| 4 | Colophonium 20% |
| 5 | Disperse blu 35 1% |
| 6 | Disperse yellow 3 1% |
| 7 | Epoxy resin 1% |
| 8 | Formaldehyde 1% aq |
| 9 | Fragrance mix-I 8% |
| 10 | Methyl-chloro-isothiazolinon/methyl-isothiazolinon (Kathon) 0.02 aq. |
| 11 | Lanolin alcohol 30%, |
| 12 | Mercaptobenzothiazole 2% |
| 13 | Mercaptobenzothiazole mix 2% |
| 14 | Neomycin sulfate 20% |
| 15 | Nickel sulphate 5% |
| 16 | N-Isopropy-N-phenyl-4-phenylendiamine 0.1% |
| 17 | Parabens mix 16% |
| 18 | Peru balsam 25% |
| 19 | Potassium bichromate 0.5% |
| 20 | p-Phenylenediamine 1% |
| 21 | Quaternium-15 1% |
| 22 | Thiuram mix 1% |

# Study periods

Since Trento-Bolzano-Rovigo contributed only until 2004 and in Trieste the formulation used for patch-test was tenfold diluted (0.1% pet.) compared to other centers during 1997-2009, prevalence of sensitization to Thimerosal by explanatory variables was assessed in these 3 time periods:

- Years 1997-2004 in all 4 research centres;

- Across the entire study period (1997-2023), excluding Trento-Bolzano-Rovigo;

- Years 2010-2023, hence Trento-Bolzano-Rovigo inevitably excluded.

# The impact of childhood vaccinations

The year of birth of patients patch tested was split into categories in order to take into account the effect of various vaccinations policies enforced in Italy over time

- **1904-1938**: when only vaccination against small pox had been mandatory in Italy since 1888.
- **1939-1965**: diphtheria vaccination mandatorily introduced in 1939
- **1966-1980:** polio enforced in 1966 and tetanus in 1968
- **1981-1990**: small pox immunization abolished in 1981
- **1991-1998:** HBV vaccination made mandatory for all newborn in 1991
- **1999 -** : year when a call for removal of thimerosal from all new vaccine formulations was launched.

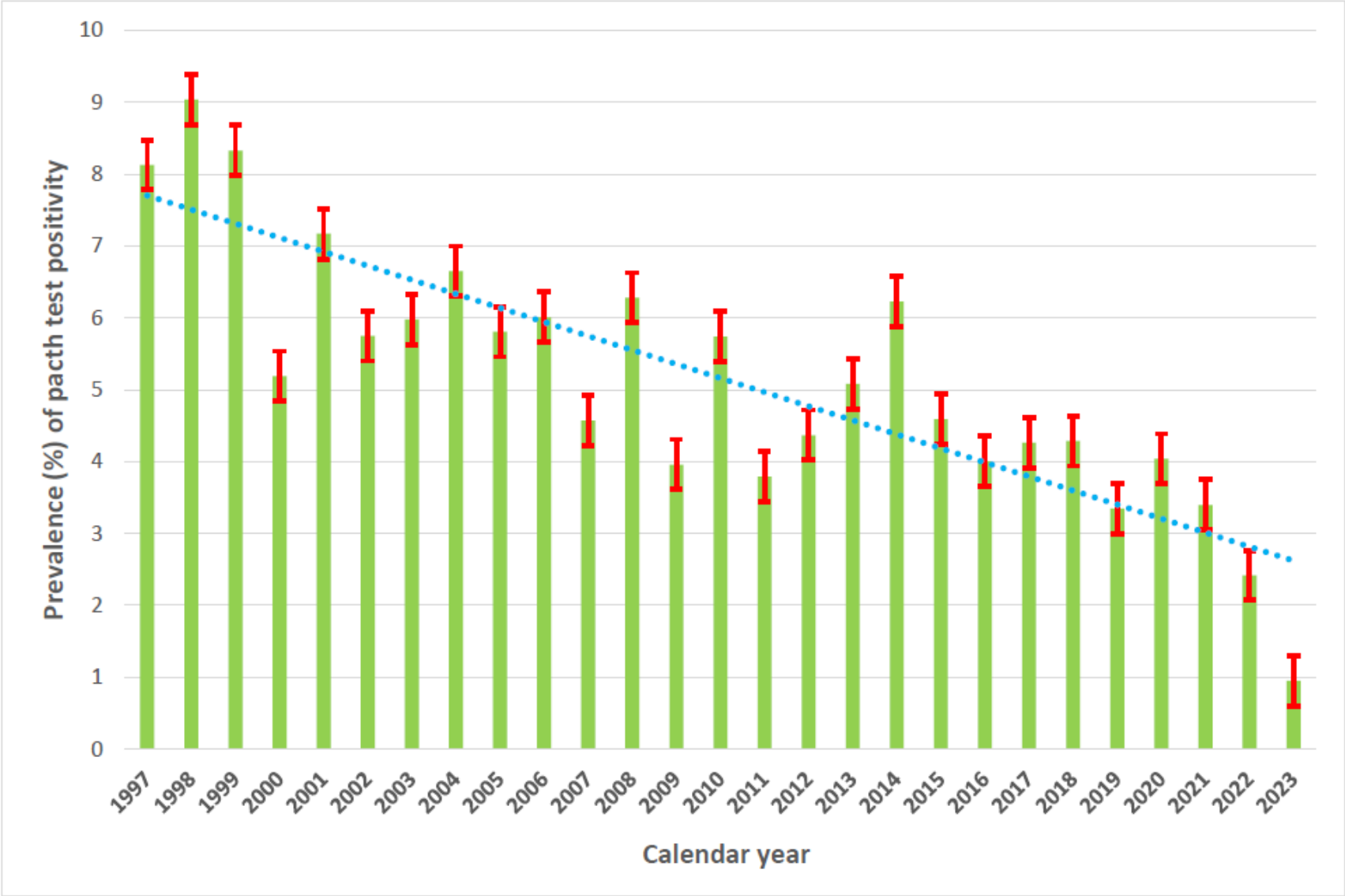



**Figure 1.** Prevalence (%) of patch test positivity to Thimerosal in all centres combined, 1997-2023.

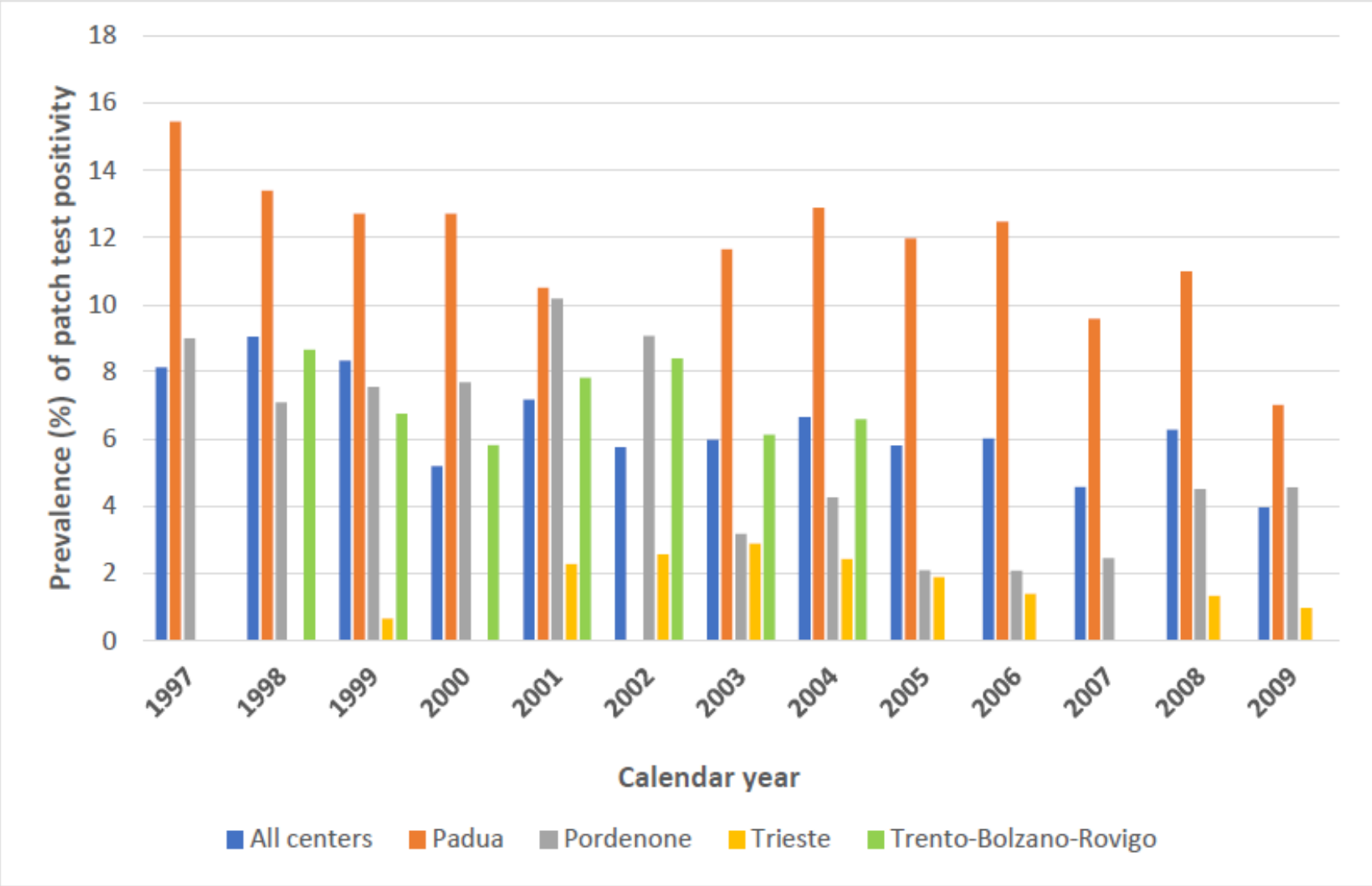



**Figure 2.** Prevalence (%) of patch test positivity to Thimerosal by center, 1997-2009.

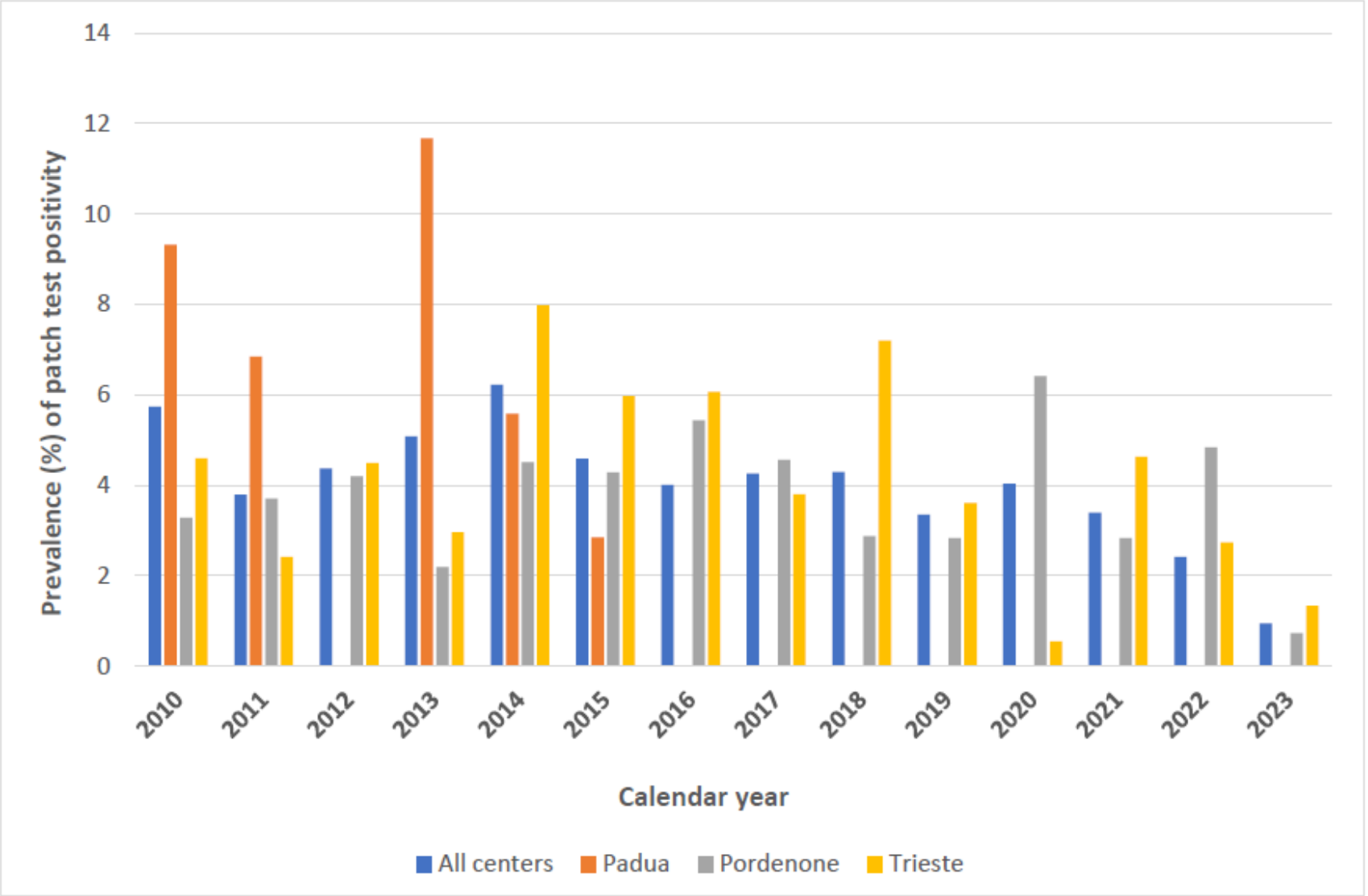



**Figure 3.** Prevalence (%) of patch test positivity to Thimerosal by center, 2010-2023.

**Frequency distribution of patients patch tested for contact dermatitis and rates of positivity against para-tertiary-butylphenol-formaldehyde resin (PTBP-FR), by calendar year (1997-2021) and research centre. Number (N) and row percentage (%)**

| CALENDAR YEAR | ENTIRE COHORT | | RESEARCH CENTRE | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Padua | | Pordenone | | Trieste | | Trento/Bolzano/Rovigo | |
| | N. tests | Thimerosal + | N. tests | Thimerosal + | N. tests | Thimerosal + | N. tests | Thimerosal + | N. tests | Thimerosal + |
| **1997-2009** | 20,958 | 1,402 (6.69) | 7,224 | 828 (11.46) | 4,058 | 226 (5.57) | 6,043 | 79 (1.31) | 3,633 | 269 (7.40) |
| **2010-2023** | 10,957 | 434 (4.25) | 2,629 | 102 (5.26) | 3,700 | 140 (3.78) | 4,628 | 193 (4.19) | NA | NA |

| STUDY PERIOD | TERMS | | aOR (95%CI) | p- value | BH p value |
|---|---|---|---|---|---|
| Years 1997-2004 (15,307 obs.) | | | | | p<0.0140 |
| | Center | Trieste | reference | | |
| | | Padua | 8.55 (6.51; 11.23) | <0.001 | 0.0020 |
| | | Pordedone | 5.01 (3.70; 6.80) | <0.001 | 0.0040 |
| | | Trento-Bolzano-Rovigo | 5.02 (3.77; 6.69) | <0.001 | 0.0060 |
| | Sex | Females | reference | | |
| | | Males | 0.93 (0.81; 1.08) | 0.365 | - |
| | Birth year | 1904-1938 | reference | | |
| | | 1939-1965 | 2.51 (1.75; 3.61) | <0.001 | 0.0080 |
| | | 1966-1980 | 2.83 (1.93; 4.15) | <0.001 | 0.0100 |
| | | 1981-1990 | 7.81 (5.14; 11.88) | <0.001 | 0.0140 |
| | | 1991-1998 | omitted | | NS |
| | | 1999-2015 | omitted | | NS |
| | Occupation | Clerks | reference | | |
| | | HCWs | 1.51 (1.24; 1.83) | <0.001 | 0.0014 |
| | | Housewives | 0.74 (0.58; 0.96) | 0.021 | NS |
| | Calendar year (1997-2004) - linear term | | 0.98 (0.94; 1.01) | 0.181 | NS |

**Years 1997-2023 (excluding Trento-Bolzano-Rovigo) (27,506 obs.)**

| | | | | p<0.0167 |
|---|---|---|---|---|
| **Center** | **Trieste** | reference | | |
| | **Padua** | 3.79 (3.27; 4.40) | <0.001 | 0.0033 |
| | **Pordenone** | 1.86 (1.58; 2.19) | <0.001 | 0.0050 |
| **Sex** | **Females** | reference | | |
| | **Males** | 0.90 (0.80; 1.02) | 0.105 | - |
| **Birth year** | **1904-1938** | reference | | |
| | **1939-1965** | 2.26 (1.64; 3.12) | <0.001 | 0.0067 |
| | **1966-1980** | 2.97 (2.12; 4.15) | <0.001 | 0.0083 |
| | **1981-1990** | 7.30 (5.14; 10.36) | <0.001 | 0.0100 |
| | **1991-1998** | 2.62 (1.61; 4.25) | <0.001 | 0.0112 |
| | **1999-2015** | 1.16 (0.43; 3.10) | 0.771 | - |
| **Occupation** | **Clerks** | reference | | |
| | **HCWs** | 1.63 (1.37; 1.94) | <0.001 | 0.0133 |
| | **General cleaners** | 0.32 (0.13; 0.79) | 0.014 | 0.0150 |
| | **Unemployed** | 0.54 (0.40; 0.74) | <0.001 | 0.0167 |
| **Calendar years (1997-2023) - linear term** | | 0.97 (0.96; 0.98) | <0.001 | 0.0017 |

**Years 2010-2023 (10,168 obs.)**

| | | | | p<0.0069 |
|---|---|---|---|---|
| **Center** | **Trieste** | reference | | |
| | **Padua** | 1.23 (0.95; 1.60) | 0.111 | - |
| | **Pordedone** | 0.95 (0.75; 1.20) | 0.680 | - |
| **Sex** | **Females** | reference | | |
| | **Males** | 0.77 (0.61; 0.99) | 0.038 | - |
| **Birth year** | **1904-1938** | reference | | |
| | **1939-1965** | 1.50 (0.53; 4.29) | 0.444 | - |
| | **1966-1980** | 2.68 (0.92; 7.82) | 0.070 | - |
| | **1981-1990** | 5.57 (1.91; 16.27) | 0.002 | 0.0052 |
| | **1991-1998** | 2.04 (0.66; 6.29) | 0.216 | - |
| | **1999-2015** | 0.90 (0.22; 3.74) | 0.887 | - |
| **Occupation** | **Clerks** | reference | | |
| | **HCWs** | 1.51 (1.10; 2.08) | 0.011 | NS |
| | **Restaurant workers** | 0.44 (0.25; 0.78) | 0.005 | 0.0069 |
| | **Unemployed** | 0.49 (0.26; 0.92) | 0.026 | NS |
| | **Retirees** | 0.34 (0.19; 0.62) | <0.001 | 0.0034 |
| **Calendar year (2010-2023) - linear term** | | 0.94 (0.92; 0.97) | <0.001 | 0.0017 |

| Calendar year of birth | Age (years) | | | |
|---|---|---|---|---|
| | <31 | 30-42 | 43-57 | 58+ |
| 1904-1938 | 0 | 0 | 0 | 3,401 (100) |
| 1939-1965 | 0 | 2,600 (19.76) | 6,291 (47.00) | 4,269 (32.44) |
| 1966-1980 | 4,110 (40.60) | 4,339 (42.87) | 1,673 (16.33) | 0 |
| 1981-1990 | 2,668 (77.85) | 759 (22.15) | 0 | 0 |
| 1991-1998 | 1,312 (97.62) | 32 (2.38) | 0 | 0 |
| 1999-2015 | 490 (100) | 0 | 0 | 0 |

# Key findings

- With variability by centre and calendar year, prevalence of Thimerosal sensitization significantly decreased over time from 1997 (8.13%) through 2023 (0.95%).
- Average sensitization was 7.19% during 1997-2004 versus 5.69% across the entire study period (1997-2023), yet excluding Trento-Bolzano-Rovigo (contributing only until 2004).
- Excluding Trento-Bolzano-Rovigo, prevalence of positive reactions against Thimerosal decreased from 6.54% during 1997-2009 to 4.25% in 2010-2023, when Trieste updated the respective patch test concentration from 0.1% to 1% pet.
- Thimerosal positivity likely reflected sensitization to the hapten through mandatory childhood vaccinations, reducing in patients born in the 1990ies and after.
- The further drop of sensitizations in patients born after 1998 – with zero positive reactions in those born after 2000 – likely reflected removal of Methiolate from all new vaccine formulations in Europe.

# Occupational risk in healthcare workers

- The role of vaccination in triggering sensitization to Thimerosal is also endorsed by the consistently and significantly higher prevalence of patch test positivity in HCWs – especially during 1997-2004 - , who in addition to childhood immunizations, were also more likely to be immunized against influenza for professional reasons.

- At least until 2008 several influenza vaccines authorized in the European Union in fact still reportedly contained Thimerosal

# Concluding remarks

- Positive patch test reactions peaked in patients born during 1981-1990, when vaccines and medications containing Methiolate were more widespread.
- The higher prevalence of sensitization in HCWs may reflect higher influenza vaccination coverage compared to other occupational categories.
- Difference in sensitization to Thimerosal by center waned after 2009, when Trieste updated the respective patch test concentration from 0.1% to 1% pet.
- Positive patch test reactions to Thimerosal after 2000 are likely clinically irrelevant.

# Muchas Gracias

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