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IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

ROZPRAWA DOKTORSKA

lek. Wojciech Malchrzak

Wyszczepialność w zakresie szczepień zalecanych u dzieci urodzonych w latach 2015-2018 ze szczególnym uwzględnieniem szczepienia przeciwko *Streptococcus pneumoniae*

Katedra i Zakład Medycyny Rodzinnej

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Serdecznie dziękuje rodzinie, przyjaciołom
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W szczególności chciałbym podziękować
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za opiekę merytoryczną, wielokierunkowe wsparcie
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1. Wykaz publikacji stanowiących rozprawę doktorską

1. **Malchrzak, W.**; Mastalerz-Migas, A. Epidemiologic Benefits of Pneumococcal Vaccine Introduction into Preventive Vaccination Programs. Advances in Experimental Medicine and Biology. 2021;1324: Medical Research and Innovation:11–19. Doi:10.1007/5584_2020_589.

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2. **Malchrzak, W.**; Babicki, M.; Mastalerz-Migas, A. Vaccination against Streptococcus Pneumoniae in Children Born between 2015 and 2018 in Poland—How Has the Introduction of Free Compulsory Pneumococcal Vaccination Affected Its Uptake? Vaccines 2023, 11, 1654, doi:https://doi.org/10.3390/vaccines11111654.

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3. **Malchrzak, W.**; Babicki, M.; Pokorna-Kałwak, D.; Mastalerz-Migas, A. The Influence of Introducing Free Vaccination against Streptococcus Pneumoniae on the Uptake of Recommended Vaccination in Poland. Vaccines 2023, 11, 1838, doi:https://doi.org/10.3390/vaccines11121838.

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Oświadczenia współautorów określające ich wkład w powstanie poszczególnych prac stanowi załącznik „12.1 Oświadczenia współautorów” niniejszej rozprawy doktorskiej.

2. Wykaz stosowanych skrótów

IChP – Inwazyjna Choroba Pneumokokowa

KOROUN – Krajowy Ośrodek Referencyjny ds. Diagnostyki Bakteryjnych Zakażeń Ośrodkowego Układu Nerwowego

PCV10 (*Pneumococcal Conjugate Vaccine 10-valent*) – 10-walentna skoniugowana szczepionka przeciwko pneumokokom

PCV13 (*Pneumococcal Conjugate Vaccine 13-valent*) – 13-walentna skoniugowana szczepionka przeciwko pneumokokom

PCV20 (*Pneumococcal Conjugate Vaccine 20-valent*) – 20-walentna skoniugowana szczepionka przeciwko pneumokokom

POZ – Podstawowa Opieka Zdrowotna

PPSV23 (*Pneumococcal Polysaccharide Vaccine 23-valent*) – 23-walentna polisacharydowa szczepionka przeciwko pneumokokom

PSO – Program Szczepień Ochronnych

3. Streszczenie w języku polskim

Streptococcus pneumoniae to bakteria wywołująca nie tylko łagodne choroby, ale także ciężkie zakażenia inwazyjne. Najskuteczniejszą swoistą metodą ochrony przed zakażeniem jest szczepienie przeciwko pneumokokom. Pierwsze skuteczne szczepionki składały się z polisacharydów otoczkowych bakterii. Szczepionki polisacharydowe nie wywoływały satysfakcjonującej odpowiedzi immunologicznej u dzieci. Efektywne okazały się dopiero późniejsze szczepionki skoniugowane, w których pneumokokowe polisacharydy są połączone z immunogennym białkiem. Współcześnie stosowane są szczepionki skoniugowane, pokrywające 10, 13, 15 albo 20 serotypów pneumokoków, oraz 23-walentna szczepionka polisacharydowa. W Polsce obowiązkowe, bezpłatne szczepienie przeciwko pneumokokom objęło dzieci urodzone po 2016 roku. Do powszechnych szczepień używany jest skoniugowany preparat 10-walentny, choć można zaszczepić dziecko odpłatnie preparatem 13-walentnym. Wcześniej to szczepienie było obowiązkowe tylko dla wąskiej grupy dzieci z czynnikami ryzyka ciężkiego przebiegu.

Celem pracy była ocena wyszczepialności przeciwko pneumokokom, ukończenia rozpoczętych schematów szczepień, wyboru szczepionki oraz wpływu na decyzję o szczepieniach zalecanych przed i po wprowadzeniu obowiązkowych szczepień przeciwko pneumokokom w Polsce.

Przeanalizowano 1595 kart szczepień z czterech przychodni na terenie miasta oraz dwóch z okolicznych wsi. Zebrano dane o datach wykonywania szczepień przeciwko pneumokokom oraz szczepień zalecanych, wybranym preparacie szczepionkowym, a także ustalono, czy rozpoczęty schemat szczepienia przeciwko pneumokokom został ukończony.

W analizowanej grupie 1595 dzieci, 755 (47,3%) urodziło się w latach 2015 i 2016, czyli przed wprowadzeniem obowiązkowego szczepienia przeciwko pneumokokom, a 840 (52,7%) w latach 2017 i 2018. Kobiety stanowiły 52,2%, a 82,6% analizowanych kart znajdowało się w przychodniach miejskich. Po wprowadzeniu obowiązkowych szczepień przeciwko pneumokokom odsetek dzieci zaszczepionych przeciwko tym bakteriom zwiększył się z poziomu 60,4% do 84,8%. Nie zaobserwowano istotnej różnicy w odsetku nieukończonych schematów szczepień przeciwko pneumokokom (11,8% vs 11,9%). Przed wprowadzeniem obowiązku częściej stosowano preparat 13-walentny (72,3%), a gdy preparat 10-walentny stał się bezpłatny, był on wtedy wybierany przez 80,1% rodziców. Obowiązkowe szczepienia przeciwko pneumokokom były skorelowane z większym odsetkiem dzieci, u których wykonano co najmniej jedno szczepienie zalecane (61,2% vs 66,6%). Przede wszystkim dotyczyło to szczepienia przeciwko meningokokom grupy B (4,8% vs 17,0%), w mniejszym stopniu przeciwko rotawirusom (48,5% vs 54,5%). Analiza dzieci zaszczepionych płatną szczepionką przeciwko pneumokokom w stosunku do pozostałych wykazała, że ta grupa istotnie częściej korzysta ze szczepień zalecanych (54,6% vs 75,9%). Różnice te dotyczyły szczepień skojarzonych 5w1 i 6w1 (73,4 vs 90,0%) oraz szczepień przeciwko rotawirusom (42,4% vs 63,1%), ospie wietrznej (28,1% vs 37,7%) i meningokokom grupy C (7,1% vs 15,5%).

Wprowadzenie obowiązkowych, bezpłatnych szczepień przeciwko pneumokokom zwiększyło wyszczepialność przeciwko tym bakteriom, chętniej wybierano bezpłatny preparat, a jednocześnie nie zmienił się odsetek przerwanych schematów szczepień. Wyniki te potwierdzają, że umieszczenie szczepienia w obowiązkowym kalendarzu pozytywnie wpływa na wyszczepialność. Najprawdopodobniej duże znaczenie ma czynnik ekonomiczny, który w literaturze często jest wskazywany jako główna przeszkoda w wykonywaniu powszechnych szczepień. Zwiększenie popularności szczepień zalecanych po wprowadzeniu obowiązku, a także w grupie dzieci szczepionych odpłatną szczepionką przeciwko pneumokokom, jest kolejnym dowodem wskazującym na koszt szczepienia jako czynnik istotnie wpływający na ich wykonywanie.

4. Streszczenie w języku angielskim

Streptococcus pneumoniae is a bacterium responsible for not only mild diseases but also severe invasive infections. The most effective specific method of protection against infection is vaccination against pneumococci. The first effective vaccines were composed of polysaccharides from the bacterial capsule. Polysaccharide vaccines did not elicit a satisfactory immunological response in children. Later conjugate vaccines, in which pneumococcal polysaccharides are combined with an immunogenic protein, proved to be effective. Currently, conjugate vaccines covering 10, 13, 15, or 20 pneumococcal serotypes, as well as a 23-valent polysaccharide vaccine, are used. In Poland, mandatory, free vaccination against pneumococci was introduced for children born after 2016. For common vaccinations, a 10-valent conjugate preparation is used, although a child can be vaccinated for a fee with a 13-valent preparation. Previously, this vaccination was mandatory only for a narrow group of children with severe disease course risk factors.

The purpose of this study was to assess the coverage of pneumococcal vaccinations, completion of initiated vaccination schedules, choice of vaccine, and the impact on the decision for recommended vaccinations before and after the introduction of mandatory pneumococcal vaccinations in Poland.

A total of 1595 vaccination cards from four clinics in the city and two from surrounding villages were analyzed. Data on the dates of pneumococcal vaccinations and recommended vaccinations, the chosen vaccine preparation, and whether the initiated pneumococcal vaccination schedule was completed were collected.

In the analyzed group of 1595 children, 755 (47.3%) were born in 2015 and 2016, before the introduction of mandatory vaccination against pneumococci, and 840 (52.7%) in 2017 and 2018. Females constituted 52.2%, and 82.6% of the analyzed cards were from urban clinics. After the introduction of mandatory vaccinations against pneumococci, the percentage of children vaccinated against these bacteria increased from 60.4% to 84.8%. No significant difference was observed in the percentage of incomplete pneumococcal vaccination schedules (11.8% vs 11.9%). Before the

obligation, the 13-valent preparation was used more frequently (72.3%), and when the 10-valent preparation became free, it was then chosen by 80.1% of parents. Mandatory vaccinations against pneumococci were correlated with a higher percentage of children who received at least one recommended vaccination (61.2% vs 66.6%). This mainly concerned vaccination against group B meningococci (4.8% vs 17.0%), and to a lesser extent against rotaviruses (48.5% vs 54.5%). Analysis of children vaccinated with a paid pneumococcal vaccine in relation to others showed that this group significantly more often benefits from recommended vaccinations (54.6% vs 75.9%). These differences concerned 5-in-1 and 6-in-1 combined vaccinations (73.4 vs 90.0%) as well as vaccinations against rotavirus (42.4% vs 63.1%), chickenpox (28.1% vs 37.7%) and group C meningococci (7.1% vs 15.5%).

The introduction of mandatory, free vaccinations against pneumococci increased the vaccination coverage against these bacteria, the free preparation was chosen more willingly, and at the same time, the percentage of interrupted vaccination schedules did not change. These results confirm that including vaccination in the mandatory schedule positively influences vaccination coverage. The economic factor, often cited in the literature as the main obstacle to carrying out universal vaccinations, likely plays a significant role. The increased popularity of recommended vaccinations following the introduction of the obligation, and also in the group of children vaccinated with the paid pneumococcal vaccine, is further evidence pointing to the cost of vaccination as a factor significantly influencing their implementation.

5. Wstęp

Streptococcus pneumoniae (dwoinka zapalenia płuc, pneumokok) to gram-dodatnia, fakultatywnie beztlenowa bakteria o kulistym kształcie, należąca do rodzaju paciorkowców. Często występuje w parach, czemu zawdzięcza swoją potoczną nazwę. Pneumokoki to bakterie otoczkowe, na których powierzchni występują specyficzne polisacharydy. Mają one charakter antygenów i stanowią podstawę klasyfikacji pneumokoków według serotypów oraz są jednym z wyznaczników zjadliwości bakterii. Do roku 2020 wyszczególniono około 100 serotypów *S. pneumoniae*. Większość z nich powoduje poważne choroby, ale właśnie kilka najpopularniejszych serotypów odpowiada za większość infekcji pneumokokowych. [1,2]

Spektrum kliniczne zakażeń pneumokokowych obejmuje choroby nieinwazyjne, głównie dróg oddechowych, takie jak zapalenie płuc, zapalenie zatok czy także zapalenie ucha środkowego oraz inwazyjne, przede wszystkim zapalenie płuc z bakteriemią, zapalenie opon mózgowo-rdzeniowych oraz sepsę. Największe ryzyko ciężkiego przebiegu choroby dotyczy dzieci w wieku poniżej 5 lat oraz osób starszych w wieku powyżej 60-65 lat. Pneumokoki często kolonizują drogi oddechowe i mogą być izolowane z nosogardzieli u 5%-90% zdrowych osób. [1] Szczepienia pozostają najskuteczniejszą metodą zapobiegania tym zakażeniom, pozwalają też na ograniczenie narastającej antybiotykooporności bakterii. [3]

Szczepienia przeciwko zakażeniom pneumokokowym mają swój początek w Republice Południowej Afryki, gdzie w 1911 roku Wright et al. opracowali preparat z zabitych bakterii, który następnie testowali na 50 tysiącach pracowników kopalni złota. Początkowo eksperyment przynosił zadowalające rezultaty, ponieważ osoby zaszczepione rzadziej chorowały i umierały z powodu chorób wywołanych przez pneumokoki, jednak po kilku miesiącach trwania eksperymentu różnice pomiędzy grupą kontrolną a badaną zaczęły się zmniejszać. Okazało się, że szczepionka opracowana przez Wrighta nie zmniejszała długofalowo śmiertelności z powodu zakażeń pneumokokowych. [4] W późniejszych badaniach dowiedziono, że zawartość bakterii w tej szczepionce była niewystarczająca do wywołania odpowiedniej odpowiedzi immunologicznej. Pomimo że początkowe próby z użyciem zabitych bakterii nie przyniosły długoterminowego sukcesu, otworzyły one drogę dalszym badaniom.

Następne odkrycia dotyczą polisacharydów otoczkowych. Dochez et al. w roku 1917 odkrył występowanie rozpuszczalnych w wodzie substancji o charakterze białkowym, które wywołują aktywność immunologiczną, ale są oporne na działanie trypsyny. [5] 6 lat później Heidelberger i Avery dowiedli, że związki te są występującymi w otoczkach bakteryjnych polisacharydami. [6]

Pomimo wielokrotnych prób stworzenia efektywnego preparatu zwiększającego odporność przeciwko pneumokokom, udało się to dopiero w latach 70. XX wieku, podczas badań nad 6- i 12-walentną szczepionką polisacharydową w populacji pracowników kopalni złota w Republice Południowej Afryki. Wówczas okazało się, że szczepienie zmniejszało ryzyko zapadnięcia na pneumokokowe zapalenie płuc odpowiednio o 76% i 92%. Wobec dobrej tolerancji szczepionki, w 1977 roku szczepionkę wzbogacono o kolejne dwa serotypy i zarejestrowano ją w USA jako pierwszy preparat ochronny przeciwko pneumokokom. Szczepionka pierwotnie zawierała 14 serotypów *S. pneumoniae*, natomiast już kilka lat później rozszerzono ją o kolejne 9 serotypów, tworząc PPSV23. [7,8]

W obliczu istotnych różnic pomiędzy układem odpornościowym osób dorosłych i dzieci okazało się, że polisacharydy otoczkowe, które są antygenami grasiczozależnymi, u dzieci wywołują zdecydowanie mniej wydajną i trwałą odpowiedź immunologiczną. Dzieci należą do grupy ryzyka ciężkiego przebiegu chorób wywołanych przez *S. pneumoniae*, dlatego naukowcy mieli na celu znaleźć rozwiązanie, które zapewni ochronę również w tej grupie wiekowej. [9,10]

W roku 1930 przeprowadzono badania nad połączeniem otoczkowego polisacharydu z białkiem nośnikowym, które miałoby na celu zwiększenie odpowiedzi immunologicznej. [11] Po wielu latach opracowano najkorzystniejsze połączenie polisacharydów siedmiu serotypów bakteryjnych ze zmodyfikowanym białkiem toksyny błoniczej, które nie wywoływało objawów choroby, ale znacznie zwiększało reakcję układu odpornościowego na dołączone antygeny polisacharydowe. Tym sposobem w roku 2000 udało się stworzyć pierwszą skoniugowaną szczepionkę wywołującą odpowiedni efekt ochronny u dzieci (PCV7). [12] W kolejnych latach ulepszano szczepionkę, dodając kolejne serotypy oraz modyfikując białka nośnikowe. Vesikari et al. zaproponowali preparat 10-walentny połączony z białkiem D bezotoczkowych szczepów *H. Influenzae*. Okazało się, że szczepionka ta jest równie skuteczna i bezpieczna jak jej poprzednia 7-walentna wersja. Finalnie zarejestrowano ją do użytku w 2010 roku. [13] Równolegle naukowcy starali się rozszerzyć liczbę serotypów, zachowując jednocześnie nośnikowe białko zmodyfikowanej toksyny błoniczej. W ten sposób udało się uzyskać preparat obejmujący łącznie 13 serotypów *S. pneumoniae* – PVC13. Szczepionka ta w roku 2010 zastąpiła 7-walentny preparat. Nowa szczepionka była równie skuteczna i bezpieczna, ale obejmowała również te serotypy, które zaczęły przeważać w środowisku po wyparciu szczepów zawartych w 7-walentnej szczepionce. [14,15]

Obecnie trwają badania nad szczepionkami skoniugowanymi, które miałyby zarówno chronić przed większą liczbą serotypów *S. pneumoniae*, jak i wywoływać odpowiedź immunologiczną za pomocą bardziej wydajnych i bezpieczniejszych mechanizmów. W 2021 roku dopuszczono do obrotu szczepionki skoniugowane 15- oraz 20-walentne, których bezpieczeństwo, tolerancja i skuteczność są porównywalne do PCV13 oraz PPSV23 u osób dorosłych. [16–18]

Szczepionka 15-walentna nie jest obecnie dostępna w Polsce, a PCV20 jest zarejestrowana wyłącznie dla dorosłych. Najnowsze badania pokazują, że PCV20 podawana niemowlętom w USA ma podobny profil bezpieczeństwa do poprzednio stosowanej PCV13, wywołuje równie silną odpowiedź immunologiczną i jest odpowiednia do stosowania u dzieci, [19–21] a także wykazano znaczące korzyści finansowe i zdrowotne z jej stosowania. [22]

Rozpowszechnienie szczepień przeciwko pneumokokom spowodowało, że zmieniła się dystrybucja ich serogrup w środowisku. Szczepionki zawierają polisacharydy wybranych serotypów pneumokoków, co prowadzi do ograniczenia występowania tych serogrup, ale jednocześnie sprzyja wzrostowi innych, nieobjętych szczepieniem serotypów. Dlatego niezwykle ważnej jest monitorowanie i dostosowywanie szczepionek do zmieniającego się krajobrazu serotypów. [23]

Szczepionka 7-walentna pierwotnie została zarejestrowana w Stanach Zjednoczonych i po krótkim czasie zaobserwowano populacyjny efekt jej działania: zapadalność na IChP zmniejszyła się z 24,3 przypadków na 100 000 osób w latach 1998-1999 do 17,3/100 000 w roku 2001. Zmiana była szczególnie zauważalna w grupie dzieci <2 r.ż. – zapadalność zmniejszyła się z 188/100 000 do 59/100 000, ale również w populacji osób dorosłych widoczna była wyraźna zmiana w epidemiologii IChP. Co szczególnie istotne, szczepienia zmniejszyły o 35% zapadalność na zakażenia wywołane przez pneumokoki oporne na penicylinę. [24] Podobne efekty były widoczne również w Europie: zapadalność dzieci <2 r.ż. na IChP przed wprowadzeniem szczepionki 7-walentnej wynosiła 44,4 przypadki na 100 000 osób ze średnią śmiertelnością 3,5%. Po wprowadzeniu szczepień do programu szczepień danego kraju obserwowano zmniejszenie średniej zapadalności w grupie dzieci <2 r.ż. z 32,5/100 000 do 23,4/100 000. [25]

Przegląd systematyczny prac badających częstość występowania na świecie danego serotypu bakterii wywołującej IChP wykazał, że najczęściej występował serotyp 14, natomiast siedem najczęstszych serotypów (1, 5, 6A, 6B, 14, 19F i 23F) odpowiadało za ponad połowę wszystkich przypadków IChP. [23] W Europie najczęstszymi serotypami były odpowiednio 14, 6B, 19F i 23F – wszystkie wchodziły w skład szczepionki 7-walentnej. Uwzględniając pozostałe serotypy, pokrywała ona 71% bakterii, natomiast PCV10 i PCV13 odpowiednio 7% i 16% więcej. [25] W Polsce w latach 2000-2008 zdecydowana większość serotypów wywołujących IChP była zawarta w szczepionce 7-walentnej. [26] Następnie zostały one zastąpione przez serotypy dotychczas nieobecne w szczepionkach. Dla porównania w 2015 r. serotypy pokrywane przez PCV10 stanowiły 53,6% IChP u dzieci <5 r.ż. w Polsce, a przez PCV13 – 75,0%, natomiast w 2019 r. te odsetki wynosiły odpowiednio 30,2% i 45,3%, a w 2022 r. 8,3% i 64,3%. [27–29] W krajach używających PCV13 zmniejszyła się dystrybucja serotypów

19A, 7F, 1 i 6A, natomiast tam, gdzie używano PCV10, zwiększył się odsetek IChP wywołanych przez serotypy 19A i 3. [30]

Analiza danych KOROUN z Polski z 2022 r. pozwala stwierdzić, że za zgony z powodu IChP były odpowiedzialne przede wszystkim serotypy 3, 4 i 19A. [29] Jeśli w Polsce analogicznie jak w innych krajach Europy stosujących PCV10 dojdzie do zwiększenia dystrybucji serotypów 3 i 19A, to można spodziewać się większego odsetka zgonów z powodu wywołanej nimi IChP, przy jednocześnie mniejszej ogólnej liczbie zgonów z powodu ochrony poszczepiennej przeciwko innym, zawartym w PCV10, serotypom. Wyjaśnienie, dlaczego spośród trzech serotypów zawartych w PCV13, a nieobecnych w PCV10 (3, 6A, 19A) tylko dwa z nich infekują większą liczbę osób, można znaleźć w długoterminowym badaniu wpływu PCV10 na IChP w Finlandii. Badacze wykazali, że dzieci zaszczepione PCV10 wytwarzały nie tylko odporność bezpośrednio na antygeny szczepionkowe, ale także krzyżowo na serotyp 6A. [31]

Pomimo stałego rozwoju szczepionek wyzwaniem pozostają dostępność i akceptacja szczepień w różnych regionach świata. Szczepienia przeciwko pneumokokom są ważną częścią programów szczepień w krajach całego świata. Liczba dawek szczepionki oraz wiek w momencie podania zależą od rodzaju szczepionki, zaleceń krajowych oraz indywidualnych potrzeb pacjenta. Szczepionki skoniugowane (PCV10 lub PCV13) są zalecane głównie dla niemowląt i małych dzieci, ale mogą być również stosowane u dorosłych. Podstawowy schemat szczepienia niemowląt w Polsce (2+1) co do zasady obejmuje dwie dawki szczepienia podstawowego podawane w odstępnie dwumiesięcznym oraz dawkę przypominającą po co najmniej sześciu miesiącach. Schemat trójdawkowy (3+1) obejmuje trzy dawki podawane w odstępie co najmniej miesiąca oraz dawkę przypominającą. Obowiązuje on dzieci z grup ryzyka takie jak dzieci urodzone przedwcześnie. [32] Im starszy pacjent, tym mniej dawek jest potrzebne do uzyskania satysfakcjonującej odporności. U dorosłych zalecana jest jedna dawka PCV13. Po minimum roku ochronę można rozszerzyć poprzez podanie PPSV23. Od niedawna możliwe jest zastosowanie PCV20 uzyskując szeroką ochronę, bez konieczności podawania PPSV23. [33–36]

Szczegółowe schematy szczepień mogą się różnić w zależności od kraju i indywidualnych potrzeb pacjenta. U osób z osłabionym układem odpornościowym plan szczepień może wymagać indywidualnego dostosowania. Na przestrzeni lat próbowano określić, jaki schemat szczepień będzie najkorzystniejszy. Na początku badano schemat 3+1, który przyniósł zadowalające rezultaty i pozwolił na wprowadzenie szczepionek skoniugowanych do powszechnego użytku. Następnie Givon-Lavi et al. badali różnice pomiędzy schematami 3+1, 3+0 i 2+1 uzyskując istotnie słabszą skuteczność u dzieci po zastosowaniu schematu 3+0 w porównaniu do innych opcji. [37] O ile producenci szczepionek skoniugowanych zalecają schemat 3+1 jako podstawowy, a 2+1 jako możliwy do stosowania w ramach programu szczepień ochronnych, według WHO zalecane są schematy 3+0 z co najmniej 4-tygodniowym odstępem między dawkami podstawowymi, lub 2+1 z odstępem minimum 8-tygodniowym pomiędzy dawkami podstawowymi, oraz dawką przypominającą podaną pomiędzy 9 a 18 miesiącem życia dziecka. W przypadku dzieci zakażonych HIV lub wcześniaków zaleca się podać dodatkową dawkę przypominającą (3+1). Zaleca się również, aby szczepienie PCV połączyć ze szczepionką przeciwko błonicy, tężcowi i krztuścowi lub inną, która zawiera komponenty tych bakterii. [38] Okazało się, że schematy 2+1 i 3+0 wywołują zadowalającą odpowiedź immunologiczną, jednak schemat zawierający dawkę przypominającą powoduje istotnie lepszą reakcję przeciwko jednemu z serotypów (6B). [39–41] W latach 2005 – 2018 w Australii stosowano schemat 3+0, jednak okazało się, że pomimo szczepień PCV 13, serotypy zawarte w szczepionce PCV13, ale nie w PCV7, coraz częściej wywoływały IChP u dzieci na tamtym obszarze. Według badaczy szczepionka dawała odpowiednią odporność, ale ochrona zanikała z czasem, zwłaszcza w ciągu 7 lat od zaaplikowania ostatniej dawki szczepionki, co wskazało na istotność dawki przypominającej. Dzięki tym odkryciom władze Australii w roku 2017 wprowadziły zmianę schematu szczepień z 3+0 na 2+1. [42,43]

Wybór preparatu przeciwko pneumokokom w różnych krajach jest podyktowany czynnikami takimi jak profil epidemiologiczny, polityka zdrowotna i dostępność szczepionek. Szczepionki skoniugowane (zwłaszcza PCV13 i PCV10) są najczęściej stosowane na świecie, oferując skuteczną ochronę przeciwko pneumokokom u dzieci i dorosłych. Do interesujących wniosków prowadzi sytuacja w Belgii, gdzie w 2007 roku wprowadzono szczepionkę 7-walentną do programu szczepień ochronnych. Wówczas liczba przypadków IChP sukcesywnie spadała, a 4 lata później zmieniono ją na PCV13, po czym odnotowywano dalsze zmniejszanie się liczby inwazyjnych zakażeń pneumokokowych. W latach 2015-2016 ze względów ekonomicznych postanowiono zmienić preparat na tańszą PCV10, gdyż obie szczepionki uznano za równie skuteczne. Jednak już po dwóch latach od tej zmiany zanotowano zwiększenie liczby przypadków IChP, przy czym odpowiadał za to głównie serotyp 19A, którego częstość występowania zwiększyła się dziesięciokrotnie. [44]

W Polsce od 2017 roku szczepienie przeciwko pneumokokom zostało zawarte w Programie Szczepień Ochronnych jako obowiązkowe i bezpłatne dla dzieci urodzonych po 31.12.2016 r. Do powszechnych szczepień używana jest PCV10 w schemacie 2+1, a w wybranych przypadkach 3+1. PCV13 jest stosowana bezpłatnie wyłącznie u dzieci urodzonych przed ukończeniem 27 tygodnia ciąży. [32,45] Na własne życzenie opiekun dziecka może odpłatnie zaszczepić je z użyciem PCV13.

Chęć podjęcia szczepień i ukończenie rozpoczętego schematu to kluczowe aspekty dla zapewnienia pełnej ochrony przed chorobami zakaźnymi. Wiele czynników może wpływać na to, czy szczepienia są realizowane zgodnie z zaleceniami. Wśród nich można wyróżnić:

- koszt szczepienia: część rodzin decyduje się na zaniechanie szczepień zalecanych, szczególnie jeśli są one odpłatne lub wymagają wielokrotnych wizyt w placówce medycznej. Wykazano, że możliwość bezpłatnego szczepienia przekłada się na większą liczbę zaszczepionych, a koszt szczepionki jest jedną z częstszych przyczyn uzasadniającą brak wykonania szczepienia. [46–48]
- obowiązkowość szczepienia: zależnie od polityki kraju nierealizowanie obowiązku może uniemożliwić przyjęcie dziecka do przedszkola czy

szkoły, pozbawić rodziców benefitów finansowych lub podatkowych bądź narazić ich na sankcje finansowe czy nawet pozbawienie wolności. [49]

- liczba koniecznych do przyjęcia dawek: im większa liczba dawek szczepionki, tym większa szansa na przerwanie szczepień. Na przykład wykazano, że w przypadku szczepienia przeciwko rotawirusom dzieci rzadziej osiągały kompletny schemat trójdawkowy w porównaniu z dwudawkowym. [50–52] Podobnych obserwacji dokonano w przypadku szczepionki przeciwko *N. meningitidis* grupy B, gdzie większa elastyczność w zastosowaniu szczepionki MenB-4C sprawiła, że była częściej podawana w pełnym schemacie w porównaniu ze szczepionką MenB-Fhbp. [53,54] Dodatkowo większa liczba dawek szczepienia zalecanego wiąże się z większym obciążeniem finansowym dla rodziców.
- złe doświadczenia po podaniu poprzednich dawek: dotyczy to zarówno działań niepożądanych takich jak gorączka, ból w miejscu wkłucia, ale też strach dziecka przed szczepieniem i związany z nim stres wywołany u rodziców. [55]
- intencjonalne unikanie kolejnych dawek z powodu błędnego przekonania, że już podane dawki są w pełni wystarczające. [56]
- aspekty organizacyjne i dostępność: część badań wskazuje, że wpływ na przerwanie szczepień może mieć odległość od przychodni, co może powodować trudności z transportem do miejsca szczepienia.
- brak odpowiedniego nadzoru nad kalendarzem szczepień: nierzadko rodzic zapomina o konieczności umówienia dziecka na podanie kolejnej dawki szczepionki. W takim wypadku pracownicy ochrony zdrowia powinni powiadomić pacjenta o potrzebie uzupełnienia szczepienia. To zadanie ułatwia współczesna technologia, gdzie dzięki zautomatyzowaniu tego procesu można efektywnie przypomnieć o dawce szczepienia bez konieczności angażowania personelu medycznego. [58]

- zaangażowanie personelu medycznego w promocję szczepień, przypominanie o kolejnych wizytach i przekazywanie rzetelnej wiedzy rodzicom. [59]
- miejsce zamieszkania: ogólnokrajowe statystyki nie podają informacji o miejscu zamieszkania dzieci nieszczepionych. [60] W badaniu postaw wobec szczepienia przeciwko COVID-19 przeprowadzonemu w Polsce, to mieszkańcy wsi częściej obawiali się tego szczepienia i nie wykazywali chęci przyjęcia szczepionki. [61] Jednocześnie inne badania nie pokazują jednoznacznie, czy fakt umiejscowienia przychodni w mieście lub poza nim wpływał na szczepienie. [62]

Obowiązek szczepień rozwiązuje część powyższych problemów – znika bariera ekonomiczna, zwiększa się świadomość o szczepieniach, poprawia się nadzór nad wykonywaniem szczepień. Inaczej ma się sprawa w kontekście wykonywania szczepień zalecanych. Decyzja o wykonaniu dobrowolnych, odpłatnych szczepień jest skomplikowanym procesem, na który również wpływa szereg czynników.

Jednym z nich są koszty szczepień. W badaniu Liao SL et al. większość rodziców przyznała, że zaszczepiliby swoje dziecko, gdyby szczepionki były dostępne nieodpłatnie, lub płatne tylko częściowo. [63] Po wprowadzeniu bezpłatnych szczepień przeciwko grypie dla kobiet w ciąży i dzieci <12 roku życia w Korei nastąpił znaczny wzrost wskaźników wyszczepialności w obu grupach. [64] Z drugiej strony szczepienie przeciwko grypie, które jest relatywnie tanie, wzbudza mniejsze zaufanie społeczne z uwagi na konieczność corocznego powtarzania szczepienia. [65] Pozytywny wpływ na chęć szczepienia ma koadministracja szczepionek, choć część rodziców stanowczo sprzeciwia się łączeniu szczepionek podczas jednej wizyty. [65,66] Polskie badanie sprawdzające determinanty wpływające na szczepienia zalecane wykazało, że korzystnie na chęć wykonania szczepień wpływa: wiek rodzica >25 r.ż., rekomendacja pracownika ochrony zdrowia, wyższy status społeczno-ekonomiczny. [67] Niezmiennie ważnym czynnikiem pozostaje także wiedza i świadomość na temat szczepień. [68]

6. Założenia i cele pracy

Wprowadzenie obowiązkowych, bezpłatnych szczepień przeciwko pneumokokom powinno wpłynąć na wzrost wyszczepialności przeciwko pneumokokom. Można założyć, że dostęp do bezpłatnych szczepień zwiększa odsetek zaszczepionych dzieci, a także wpływa korzystnie na częstość ukończenia rozpoczętych schematów szczepień. Zmiana ta może także mieć korzystny wpływ na realizację szczepień zalecanych.

Cele pracy:

- porównanie wyszczepialności przeciwko pneumokokom przed i po wprowadzeniu obowiązku szczepień
- ocena wpływu bezpłatnego szczepienia na ukończenie rozpoczętych schematów szczepienia przeciwko pneumokokom
- analiza preferencji w zakresie wyboru szczepionki
- analiza wpływu wprowadzenia bezpłatnego szczepienia przeciwko pneumokokom na realizację szczepień zalecanych (odpłatnych dla pacjenta)

7. Materiał i metoda pracy

Do realizacji założonych celów kluczowe było pozyskanie wiarygodnych danych dotyczących szczepień. Za najlepszy wybór uznano analizę kart szczepień dzieci urodzonych w latach 2015-2018, to jest dwa lata przed i dwa lata po wprowadzeniu obowiązkowego szczepienia przeciwko pneumokokom. Karty te zawierają dokładne informacje o szczepieniach wykonanych u danego dziecka, na ich podstawie możliwe jest sprawdzenie kompletności rozpoczętego schematu szczepień.

Karty szczepień są przechowywane w przychodniach POZ, przed uzyskaniem dostępu do kart szczepień konieczne było uzyskanie zgody kierownika przychodni. Zgoda ta pozwalała na pozyskanie danych z kart szczepień do bazy danych pod warunkiem zapewnienia anonimowości pacjentów. Uzyskano zgody z sześciu przychodni, czterech z Wrocławia i z dwóch z okolicznych wsi. Na podstawie liczby deklaracji złożonych do lekarza POZ oszacowano, że te sześć przychodni zapewni zebranie przynajmniej 1500 unikalnych rekordów. Jednocześnie pozyskanie danych z sześciu placówek pozwoli na dobre zróżnicowanie populacji pod kątem demograficznym.

Badanie zostało przeprowadzone zgodnie z Deklaracją Helsińską, a także uzyskało pozytywną opinię Komisji Bioetycznej przy Dolnośląskiej Izbie Lekarskiej, numer opinii: 1/PNDR/2023.

Stworzona baza danych zawierała dane dotyczące pacjenta: płeć i datę urodzenia (niezbędne do prowadzenia analiz) oraz inicjały pacjenta, które pozwalały na weryfikację bazy celem odnalezienia duplikatów. Po zakończeniu przenoszenia danych do bazy usunięto z niej inicjały i tym samym dokonano pełnej anonimizacji. W bazie umieszczono informacje dotyczące szczepień przeciwko pneumokokom oraz szczepień zalecanych. Zawarto w niej nazwę zastosowanego preparatu oraz daty podania każdej dawki danej szczepionki. Do badania włączono wszystkie karty szczepień dzieci urodzonych w latach 2015-2018 zadeklarowanych do przychodni i łącznie zebrano 1595 unikalnych rekordów.

Dokładne daty podania każdej dawki wraz z datą urodzenia dziecka pozwoliły na sprawdzenie, w jakim wieku ją podano. W analizie uwzględniono szczepienia, które zostały wykonane w ciągu pierwszych dwóch lat życia pacjenta. Takie założenie było konieczne, gdyż w przeciwnym wypadku dzieci z najwcześniejszych badanych roczników miałyby więcej czasu na ich wykonanie. Celem pracy była ocena kompletności szczepień przeciwko pneumokokom oraz realizacji szczepień zalecanych. W przypadku szczepienia przeciwko rotawirusom również oceniono kompletność schematu szczepień, ponieważ, w odróżnieniu od innych szczepień, istnieje maksymalny czas na podanie ostatniej dawki (32 tydzień życia) i po jego przekroczeniu dalsze szczepienie nie jest zalecane. Z tego powodu za wykonanie szczepienia zaleconego uznawano kompletne szczepienie przeciwko rotawirusom, a w przypadku pozostałych szczepień zalecanych – przyjęcie przynajmniej jednej dawki szczepionki.

Przed wprowadzeniem obowiązku szczepień przeciwko pneumokokom zarówno PCV10, jak i PCV13 były, z nielicznymi wyjątkami, płatne. Po wprowadzeniu obowiązku PCV10 była bezpłatna, ale nadal istniała możliwość odpłatnego wykonania szczepienia za pomocą PCV13. Z tego powodu do grupy pacjentów zaszczepionych płatną szczepionką przeciwko pneumokokom włączono wszystkie dzieci, które otrzymały PCV13 oraz dzieci urodzone w latach 2015-2016, które otrzymały PCV10.

Do porównania zmiennych jakościowych wykorzystano test Chi kwadrat. Przy analizie wykonywania szczepień zalecanych wykonano analizę regresji logistycznej jednoczynnikowej, gdzie zmienną zależną było rozpoczęcie szczepienia zalecanego, a zmienną niezależną był okres przed i po wprowadzeniu obowiązku szczepień przeciwko pneumokokom w Polsce. W następnym kroku wykonano analizę regresji logistycznej wieloczynnikowej z dodatkowym uwzględnieniem wpływu wieku oraz miejsca zamieszkania dziecka. Istotność statystyczną przyjęto na poziomie <0,05. Obliczenia przeprowadzono przy użyciu programu Statistica 13 firmy TIBCO Software Inc.

8. Wyniki

8.1. Epidemiologic Benefits of Pneumococcal Vaccine Introduction into Preventive Vaccination Programs

Pierwsza publikacja wchodząca w skład cyklu stanowiącego niniejszą rozprawę, to praca przeglądowa podsumowująca obecny stan wiedzy o szczepieniach przeciwko pneumokokom.

Publikacja opisuje czym są pneumokoki i jakie choroby wywołują. Następnie przedstawia historię szczepień przeciwko pneumokokom: od pierwszych prób zapobiegania zapaleniom płuc na początku ubiegłego wieku, aż do współczesnych szczepionek skoniugowanych. W szczególności uwzględnia preparaty dostępne w Polsce i używane do szczepienia dzieci. Praca pokazuje też wpływ szczepień przeciwko pneumokokom na zmniejszenie zapadalności i śmiertelności na choroby wywoływane przez serotypy zawarte w szczepionce. Szczegółowo omówione zostały możliwe do przeprowadzenia schematy szczepień, w tym ich wpływ na efektywność szczepień, a także wpływ szczepień przeciwko pneumokokom na występowanie antybiotykooporności wśród tych bakterii. Na koniec przedstawia perspektywy rozwoju i przyszłość szczepień przeciwko pneumokokom.

8.2 Vaccination against Streptococcus Pneumoniae in Children Born between 2015 and 2018 in Poland—How Has the Introduction of Free Compulsory Pneumococcal Vaccination Affected Its Uptake?

Celem pracy była ocena wpływu wprowadzenia obowiązkowych szczepień przeciwko pneumokokom na odsetek zaszczepionych dzieci, ukończonych schematów szczepień oraz preferencję wyboru preparatów szczepionkowych.

Z kart szczepień do bazy danych przeniesiono 1595 kompletnych rekordów, 755 (47,3%) stanowiły dzieci urodzone w latach 2015 i 2016, a 840 (52,7%) – urodzone w latach 2017 i 2018. Dzieci płci żeńskiej stanowiły 52,2%, a pacjenci z przychodni na terenie miasta 82,6%.

Po wprowadzeniu obowiązku szczepień przeciwko pneumokokom odsetek dzieci w pełni zaszczepionych przeciwko pneumokokom zwiększył się z 60,4% do 84,8% ($p < 0,001$), natomiast odsetek dzieci, które nie otrzymały ani jednej dawki zmniejszył się z 27,8% do 3,3% ($p < 0,001$). Nie zaobserwowano zmiany w nieukończonych schematach szczepień (11,8% vs 11,9%).

Zmienił się najczęściej wybierany preparat szczepionki. Przed wprowadzeniem obowiązku PCV10 była wybierana przez 27,7% rodziców, a gdy stała się bezpłatna to już przez 80,1%. PCV13 zaś zmniejszyła swój udział z 72,3% do 19,9% ($p < 0,001$).

Płeć nie wpływała na kompletność schematu szczepień ($p = 0,989$), natomiast w przypadku preparatu szczepionki różnica nie była istotna statystycznie ($p = 0,093$), choć nieco częściej przerywano szczepienie PCV13 w stosunku do PCV10 (15,8% vs 12,6%). Co ciekawe dzieci z przychodni wiejskich częściej były w pełni zaszczepione przeciwko pneumokokom (84,8% vs 70,8%), a także rzadziej przerywano szczepienia (6,5% vs 13,0%, $p < 0,001$).

Na granicy istotności statystycznej znalazła się różnica w przerywaniu szczepień przed i po wprowadzeniu obowiązku w przypadku PCV10 – 16,6% przerwanych szczepień przed obowiązkiem oraz 11,7% po wprowadzeniu obowiązku ($p = 0,105$). W przypadku PCV13 nie zaobserwowano istotnej statystycznie różnicy – 16,2% vs 14,8% ($p = 0,675$).

8.3 The Influence of Introducing Free Vaccination against Streptococcus Pneumoniae on the Uptake of Recommended Vaccination in Poland

Celem tej pracy było sprawdzenie wpływu wprowadzenia obowiązkowych szczepień przeciwko pneumokokom na wykonywanie szczepień zalecanych. Dodatkowym celem było określenie różnic w szczepieniach zalecanych u dzieci, które były zaszczepione płatną szczepionką przeciwko pneumokokom oraz dzieci, które otrzymały szczepionkę bezpłatną albo w ogóle nie były szczepione przeciwko pneumokokom.

Do analizy włączono tę samą grupę pacjentów, która została omówiona w poprzednim podrozdziale. Szczepienie zalecane było uznane za wykonane, jeśli dziecko otrzymało przynajmniej jedną dawkę szczepionki. Wyjątkiem było szczepienie przeciwko rotawirusom – w tym przypadku zaliczany był tylko kompletny schemat szczepień. Szczepienie przeciwko meningokokom grupy A, C, W135 i Y liczono łącznie ze szczepieniem przeciwko meningokokom grupy C.

Po wprowadzeniu obowiązkowych szczepień przeciwko pneumokokom istotnie częściej przeprowadzano szczepienia przeciwko rotawirusom (48,5% vs 54,5%, p = 0,018) oraz przeciwko meningokokom grupy B (4,8% vs 17,0%, p < 0,001). Zwiększył się też odsetek dzieci, u których wykonano jakiekolwiek szczepienie zalecane (61,2% vs 66,6%, p = 0,026). Analiza wieloczynnikowej regresji logistycznej uwzględniającej wiek oraz miejsce zamieszkania pacjenta wykazała czterokrotnie większą szansę na szczepienie przeciwko meningokokom grupy B przy porównaniu lat 2015-2016 i 2017-2018.

Przy porównaniu dzieci zaszczepionych płatną szczepionką przeciwko pneumokokom z grupą pozostałych dzieci wykazano, że istotnie częściej wykonywano jakiekolwiek szczepienie zalecane (54,6% vs 75,9%, p < 0,001). Różnice wykazano także w stosunku do szczepień skojarzonych 5w1 i 6w1 (73,4% vs 90,0%, p < 0,001), przeciwko rotawirusom (42,4% vs 63,1%, p < 0,001), ospie wietrznej (28,1% vs 37,7%, p < 0,001) oraz meningokokom grupy C (7,1% VS 15,5%, p < 0,001). Co ciekawe nie zaobserwowano różnicy w szczepieniach przeciwko meningokokom grupy B (10,9% vs 11,6%, p = 0,685).

9. Wnioski

1. Wprowadzenie obowiązku szczepień zwiększyło wyszczepialność przeciwko pneumokokom.
2. Wprowadzenie obowiązku szczepień nie zredukowało odsetka przerywanych schematów szczepienia przeciwko pneumokokom.
3. Gdy zarówno PCV10, jak i PCV13 były płatne, to rodzice częściej decydowali się na PCV13. Po wprowadzeniu obowiązku szczepień rodzice częściej wybierali bezpłatną PCV10.
4. Po wprowadzeniu obowiązku szczepień przeciwko pneumokokom rodzice dzieci chętniej decydowali się na szczepienia zalecane przeciwko innym chorobom, w szczególności przeciwko meningokokom grupy B.
5. Rodzice decydujący się na płatne szczepienia przeciwko pneumokokom istotnie statystycznie częściej wybierali inne szczepienia zalecane, w szczególności szczepionki wysokoskojarzone 5w1 i 6w1, przeciwko rotawirusom (wówczas jeszcze płatne), ospie wietrznej oraz meningokokom grupy C.

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11. Cykl publikacji stanowiących rozprawę doktorską

1. Malchrzak, W.; Mastalerz-Migas, A.
   Epidemiologic Benefits of Pneumococcal Vaccine Introduction into Preventive Vaccination Programs.
2. Malchrzak, W.; Babicki, M.; Mastalerz-Migas, A.
   Vaccination against Streptococcus Pneumoniae in Children Born between 2015 and 2018 in Poland—How Has the Introduction of Free Compulsory Pneumococcal Vaccination Affected Its Uptake?
3. Malchrzak, W.; Babicki, M.; Pokorna-Kałwak, D.; Mastalerz-Migas, A.
   The Influence of Introducing Free Vaccination against Streptococcus Pneumoniae on the Uptake of Recommended Vaccination in Poland.

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Epidemiologic Benefits of Pneumococcal Vaccine Introduction into Preventive Vaccination Programs

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Abstract

Vaccination against pneumococci is one of the most effective methods of preventing pneumococcal diseases. Currently, 10- and 13-valent conjugate vaccines (PCV10 and PCV13) and 23-valent polysaccharide vaccine (PPSV23) are used. Only the conjugate vaccines are used in children. The PCV can be used both in children and adults, but children can receive only PCV. A side effect of vaccination was that bacterial serotypes not included in a vaccine started increasingly emerging in pneumococcal infections, replacing the serotypes eliminated by the vaccine. The basic vaccination schedule consists of three or four doses, according to the country's recommendation. In Poland, it consists of two primary doses followed by a supplementary dose of the PCV-10, with some modifications in case of specific risk factors. The use of preventive vaccinations has helped reduce antibiotic resistance, as serotypes characterized by a rapid acquisition of drug resistance are included in the vaccine serologic spectrum, making their environment prevalence decrease. The research is currently underway on conjugate vaccines that contain a greater number of bacterial serotypes and on more universal vaccines that would eliminate the emergence of new serotypes.

Keywords

Pneumococcal vaccine · *Streptococcus pneumoniae* · Invasive pneumococcal disease · Vaccination program

1 Introduction

Pneumococcal diseases, especially invasive forms of infections, are a common cause of illness and death in patients of all ages. Children under the age of 5 and the elderly 60–65+ are at the greatest risk of developing a severe disease course. To prevent infection, vaccines are used to induce specific immunity against bacteria. The first was a polysaccharide vaccine that contained purified antigens from the bacterial envelope. Currently, the polysaccharide antigens are available in the 23-valent vaccine, PPSV23, that works through mechanisms other than T lymphocytes and, thus, is unable to induce adequate immunity in young children. To induce an effective immune response in children, a combination of bacterial polysaccharide with a carrier protein has been developed, a pneumococcal conjugate vaccine (PCV). This vaccine was initially available in a 7-valent form (Prevenar), in which the CRM197 protein was a carrier, followed by 10-valent (Synflorix) and 13-valent (Prevenar 13) forms in

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which the protein D and CRM197 were used as carriers, respectively. There is also a 10-valent vaccine (Pneumosil) that uses the CRM197 protein, available on the Indian market.

Two pneumococcal vaccines are in use in Poland: Synflorix (PCV10) and Prevenar 13 (PCV13). The first is indicated for the use in children from 6 weeks to 5 years of age, while the other is for children from 6 weeks of age and adults. Currently, 146 countries use the preventive pneumococcal vaccines as part of vaccination programs, with 138 programs being national. As of March 2020, 15 other countries plan to introduce such vaccination. Most developed countries have a schedule of two primary immunizations and a booster dose. The estimation has been that more than 61 million infants have been vaccinated against pneumococci, which is about half infants worldwide (IVAC 2020).

2 Invasive Pneumococcal Disease: Definition and Epidemiology

Streptococcus pneumoniae (*S. pneumoniae*) is a common pathogen in people of all ages. In some instances, it does not cause clinical symptoms, although is present in the upper respiratory tract. In other cases, it is responsible for infections that can be divided categorized as non-invasive (e.g., otitis media, paranasal sinusitis, or pneumonia without bacteremia) and invasive (e.g., meningitis, sepsis, or pneumonia with bacteremia). In the latter case, the contagion and its genetic material are isolated from the physiologically sterile site (EC 2002).

The occurrence of invasive pneumococcal disease (IPD) must be obligatorily reported to provincial sanitary and epidemiologic stations in Poland. In 2018, there were 1,354 IPDs reported in the country, with the incidence of 3.52/100,000, of which only one patient was not hospitalized. Additionally, there is a voluntary case reporting system to the National Reference Center for Bacterial Meningitis (NRCBM), which includes the determination of bacterial serotypes. In this system, laboratory confirmation of IPD was obtained in 1,037 cases, which translates into an average detection rate of 2.70/100,000 in 2018; these figures were 1,088 and 2.83/100,000, respectively in 2019. More than half of the diagnosed cases resulted in death, which translates into a mortality rate of 39.8% (NRCBM 2020; NIPH-NIH 2019; NRCBM 2019). Overall, the incidence of IPD-related meningitis or encephalitis in children of up to 5 years of age and adults 60+ was above the average of all registered cases. The NRCBM recommends the use of a term detectability rather than morbidity because the incidence of IPD is likely underestimated due to the early initiation of antibiotic therapy and scarce blood culturing. For comparison, 24,663 cases of IPD were reported in the European Economic Area in 2018, which gives a detection rate of 6.39/100,000. Data on the mortality rate have been reported by only 18 EU countries, with an average of 15.3%. Like in Poland, children below 5 and adults above 65 years of age were most often affected (ECDC 2020).

3 Historical Vignette on Pneumococcal Vaccination

The first large-scale research into a vaccine to prevent pneumococcal disease began in 1911. It was then that pneumococcal disease decimated miners working in South African gold mines. Wright et al. (1914) used killed bacteria to perform vaccinations and their research group consisted of over 50,000 mine workers. In the short term, there seemed to have been an impression that although vaccinated subjects fell ill, they died less frequently. This difference became indistinguishable about 4 months after vaccination, and detailed analysis showed the vaccine failed to reduce the risk of death in the course of pneumococcal disease. In a later research, Lister (1916), who described eight different serotypes of *S. pneumoniae*, has suggested that the dose of killed bacteria originally administered by Wright was too low. Soon afterward, Dochez and Avery (1917) found that bacteria produce a water-soluble proteinaceous substance that is resistant to the action of trypsin and induce immunological activity. The next milestone was set 6 years later by Heidelberger and Avery (1923) who showed that this substance was a polysaccharide on the pneumococci capsule. Later on, attempts were made to create an effective vaccine, but the first significant effects were achieved no sooner than in the 1970s. Smit et al. (1977) investigated the effectiveness of 6-valent and 12-valent polysaccharide vaccines among gold miners in South Africa. The results were remarkably good as the vaccines were well tolerated and reduced the risk of pneumococcal pneumonia by 76% and 92%, respectively. Those findings contributed to the approval of the first pneumococcal vaccine in the USA in 1977, consisting of 14 serotypes, which was increased to 23 serotypes in 1983.

The empirical experience has been that children are much more vulnerable to pneumococcal infections than are adults. The reason is that the immune system of children weakly responds to bacterial polysaccharides administered in the vaccine (Davies 1937). The cause of this phenomenon was brought to light by Stein (1992) who showed that the polysaccharides of bacterial envelope belong to thymus-independent antigens; the immune response develops at a later age as also does the immune memory that upholds the effect of vaccination. A resolution to this issue became a combining of a carrier protein to the bacterial polysaccharide. Although successful research on the issue had already been performed in animal models in the 1930s (Avery and Goebel 1931), it took decades more to replicate that in a safe way for humans, developing the most advantageous polysaccharide-protein combination. The effectiveness of the conjugate vaccine has been verified toward the end of the twentieth century in the youngest children (Ahman et al. 1998), followed by a registration of the first pneumococcal conjugate vaccine (PCV) in 2000. It contained polysaccharides of seven bacterial serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) combined with a diphtheria toxin protein variant (CRM197). This protein did not cause disease symptoms but significantly increased the response of the immune system to polysaccharide antigens linked to it. The PCV vaccine has been repeatedly improved since, by adding more serotypes and modifying the carrier proteins and finally by changing the carrier protein for a single serotype only. Multicenter studies have shown that a 10-valent vaccine based on a combination of most polysaccharides with a protein D of non-enveloped *Haemophilus influenzae* strains is as effective and safe as a 7-valent vaccine used before but covers a wider spectrum of pneumococci (Bermal et al. 2009; Vesikari et al. 2009). A 10-valent vaccine containing conjugated polysaccharides of the serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F got final approval in 2010.

Concurrently, research was underway to further expand the number of serotypes available in a 7-valent vaccine while maintaining a modified diphtheria toxin as a carrier protein. Conjugated polysaccharides of serotypes 1, 3, 5, 6A, 7F, and 19A were added to the previously known 7-valent vaccine, resulting in a vaccine covering 13 serotypes of *S. pneumoniae*. The new vaccine appeared equally effective and safe as its predecessor and has protected against the serotypes whose occurrence increased in the environment due to the use of a 7-valent vaccine in previous years (Bryant et al. 2010; Kieninger et al. 2010; Dinleyici and Yargic 2009). Ultimately, the 13-valent vaccine was approved in 2010, replacing the 7-valent vaccine. New conjugate vaccines that protect against more serotypes using novel mechanisms to induce immune response are currently under development. The future epidemiologic situation will likely depend on the effects of new vaccines as the serotypes present in the current vaccines are going to be reduced or eliminated from the environment.

4 Influence of Vaccination on Epidemiology of Pneumococcal Diseases

In 2000, it was estimated that 826,000 children younger than 5 years died from pneumococcal diseases, which accounted for 11% of all deaths (O'Brien et al. 2009). Eight years later, after the introduction of vaccination against pneumococci, the number of deaths decreases to 541,000 or 6% of all deaths in this age group. Most fatalities occurred in Asia and Africa, although they also occurred in Europe and North America (WHO 2008). The death rate has kept on decreasing in further years. In 2015, there were 317,300 children in this age group who died from pneumococcal diseases. Wahl et al. (2018) estimated that the conjugate vaccine prevented the death of approximately 250,000 children between 2010 and 2015. Mass use of pneumococcal vaccination is believed to be a primary cause of death reduction.

A 7-valent vaccine was originally approved in the USA and its introduction resulted in decreased IPD incidence from 24.3/100,000 in 1998/99 to 17.3/100,000 in 2001. The decrease was most notable in children less than 2 years of age where it was from 188/100,000 to 59/100,000. Importantly, vaccination reduced the incidence of penicillin-resistant pneumococcal infections by 35% (Whitney et al. 2003). Similar effects were noticed in Europe where the IPD incidence in children was 44.4/100,000 with an average mortality of 3.5% before PCV7 introduction and decreased to 32.5–23.4/100,000, depending on a country, after PCV7 introduction (Isaacman et al. 2009). A systematic review of studies examining the worldwide prevalence of pneumococcal serotypes causing IPD has shown that seven serotypes (1, 5, 6A, 6B, 14, 19F, and 23F) account for more than half of all IPD cases, with the serotype 14 being the most common among them (Johnson et al. 2010). Serotypes included in PCV7 cover 71% of bacteria, while PCV10 and PCV13 cover 7% and 16% more, respectively (Isaacman et al. 2009).

5 Optimal Vaccination Schedule

As recommended by the WHO, pneumococcal vaccination using conjugate vaccines can be performed either on the 3 + 0 schedule, starting at 2 months of age, with a minimum interval between doses of 4 weeks, or on a 2 + 1 schedule with an 8-week interval between the primary doses followed a booster dose between 9 and 18 months of age. The timing for a booster dose is, however, rather poorly defined. An additional booster dose should be given to HIV-infected or premature babies (WHO 2019a). Pneumococcal vaccination should be combined with diphtheria, tetanus, and pertussis vaccines or any other vaccine containing components thereof (WHO 2019b). Studies show that the 2 + 1 schedule increases the antibody content more than the 3 + 0 schedule, but both provide a satisfactory increase over the protective level. The only exception is the serotype 6B for which the 2 + 1 schedule provides a significantly better immune response (IVAC 2017; Conklin et al. 2011).

Initially, studies on the conjugate vaccine guided by manufacturers pointed to the effectiveness of a 3 + 1 schedule that was registered for the general use. Later, a 2 + 1 schedule has been accepted as a possible alternative, particularly when the vaccine is given as part of a vaccination program. Givon-Lavi et al. (2010) compared the 3 + 1, 3 + 0, and 2 + 1 schedules and showed that the reduced 2 + 1 schedule resulted in lower levels of postprimary IgG content in children when compared to the 3 + 1 and 3 + 0 schedules for serotypes 6B, 18C, 19F, and 23F. Although both 3 + 1 and 2 + 1 had pronounced booster responses in the second year, the latter responded less. The 3 + 0 schedule resulted in the lowest levels of IgG responses in the second year. In another study, a comparison of two-primary with three-primary doses shows that both schedules induce a strong immune response, with the three-dose schedule yielding higher protective antibody titers, especially for serotypes 6B and 23F (Scott et al. 2011).

A concentration of protective antibodies is a good and easy method of determining the vaccine immunogenicity, but it is impossible to directly translate that to the clinical protection of a patient. Dagan et al. (2012) investigated how a given vaccination schedule affects the carriage of *S. pneumoniae* in the upper respiratory tract. A three-prime dose schedule was found to better prevent against carrying the serotypes against which the vaccine protects compared to a two-prime dose schedule, but the difference disappeared with a booster dose, and giving two booster doses further reduced this risk of infection.

A booster dose immunization schedule is used in most developed countries, except Australia where the 3 + 0 schedule was in place used between 2005 and 2018. At that time, the effectiveness of PCV7 and its replacement, PCV13, in 2011 in preventing IPD was investigated. While there was a small, stable number of IPDs caused by vaccine serotypes in case of PCV7, their number caused by serotypes included in PCV13 gradually increased. Serotype 19A was the leading cause of IPD in Australian children despite being contained in PCV13. Studies indicate that the vaccine is effective but the protection it offers wears off over time, especially within 2 years after the last dose. Thus, it is essential to give a booster dose. Since it is given to an older child, it elicits a stronger immune response and protects during the time of a greater hazard of invasive infection. In effect, the Australian government has changed the vaccination schedule from 3 + 0 to 2 + 1 as of September 2017 (Australian Government 2020; Jayasinghe et al. 2018).

6 Preventive Vaccinations in Poland

In Poland, vaccination against pneumococci became available free of charge only to children at risk as of 2008. The situation has changed in 2017 when mass vaccination against pneumococci for children born after 31 December 2016 was introduced into the Preventive Vaccination Program. In most cases, the 2 + 1 schedule is used, i.e., two doses of primary vaccination 8 weeks apart and one dose at least 6 months after the last primary dose. The 3 + 1 schedule is reserved for children at risk due to epidemiologic or clinical reasons and children born before the 37th week of pregnancy or with a birth weight < 2,500 g. The PCV10 is primarily used, except for children from risk groups or those born before the 27th week of pregnancy when the PCV13 is preferable. A child qualifying for a free PCV10 may be immunized with PCV13 at the guardian's expense.

Before introducing pneumococcal immunization for all children at the country level, some municipalities implemented local preventive programs to reduce IPD and other pneumococcal diseases. An example of the greatest success is the city of Kielce, inhabited by about 200,000 people. In 2006, free PCV7 immunization was introduced there for all children under 2 years of age in a 2 + 1 schedule. After 5 years, PCV7 was changed to PCV13. The program proved successful, vaccination coverage was almost 100%, and the number of deaths due to pneumococcal pneumonia in children <2 years of age decreased by 82.9%, and it also decreased in adults >65 years of age by 43.5%. Apart from confirming that pneumococcal vaccination reduces the incidence of IPDs in children, this program has shown that the issue of herd immunity is not insignificant, as the immunization of children also protects the elderly from the disease (Patrzałek et al. 2016). It is possible that indirect immunity to the elderly, achieved by mass immunization of children, is more effective than direct immunization of children. A postulated explanation of this phenomenon is a weaker immune response in the elderly (Patrzałek et al. 2012; Simonsen et al. 2011). The percentage of 2-year-old children vaccinated against pneumococci in Poland was 94.1% in 2018 (NIPH-NIH 2019). A primary goal of mass vaccination is to reduce the incidence of IPDs. However, vaccination also protects against other pneumococcal diseases, which raises prospects of a reduction in pneumococcal pneumonia or acute otitis media (Gajewska et al. 2020; Górska-Kot et al. 2019). A detailed evaluation of the epidemiologic effects on the general population of mass pneumococcal vaccination in children requires a much longer time than the 4 years elapsing now from its launch in Poland.

7 Vaccinations and Distribution of Serotypes

In Belgium, PCV7 was introduced into the immunization program in 2007. The number of IPD cases was since then steadily decreasing. The PCV7 was switched to the PCV13 in 2011, with a further reduction in IPDs. In 2015/16, the PCV13 was switched to a 10-valent version, as both vaccines were considered equally effective. However, just 2 years after this switch, the number of IPDs began to increase, due mainly to serotype 19A whose appearance increased tenfold (Desmet et al. 2018). The increasing use of pneumococcal vaccines has changed the distribution of pneumococcal serotypes. Initially, between 2000 and 2008, most serotypes causing IPD were contained in PCV7. Due to active and specific immunity-induced against vaccine serotypes, they were later replaced by serotypes originally absent in vaccines. For comparison, in 2015, PCV10 covered serotypes accounting for 53.6% of IPD in children <5 years of age in Poland and PCV13–75.0%, while in 2019 these percentages dropped to 30.2% and 45.3%, respectively (NRCBM 2020).

After the introduction of PCV7 into the general vaccination program in Europe, a reduction in IPDs caused by the vaccine serotypes was noticed, with an increase in the appearance of other serotypes such as 1, 3, 7F, and 19A. Where the PCV13 was used, the incidence of IPD caused by serotypes 1, 6A, 7F, and 19A decreased, and where PCV10 was used, the incidence caused by serotypes 3 and 19A increased (Htar et al. 2015; Weil-Olivier et al. 2012). The 2019 epidemiologic Polish data show that the IPD-related deaths are mainly caused by serotypes 3, 4, and 19A (NRCBM 2020). Since, akin to other European countries, Poland uses the PCV10, a higher IPD mortality rate could be expected due to an increase in serotypes 3 and 19A, with lower mortality due to other serotypes contained in PCV10. A biologically plausible explanation of why only two out of three PCV13 serotypes absent in PCV10 (3, 6A, and 19A) infect a significant number of people can be found in a long-term study of PCV10 effects on IPD in Finland. That study shows that PCV10-vaccinated children not only produce immunity directly to the vaccine antigens but also cross-reactive immunity to serotype 6A that is absent in this vaccine (Rinta-Kokko et al. 2018).

8 Antibiotic Resistance

The introduction of mass vaccination against pneumococci has made it possible to reduce the number of strains resistant to antibiotics, but the problem of antibiotic resistance is still present. Mass vaccination with PCV7 increased the incidence of IPD caused by serotype 19A that aside from being a common cause of IPD also is characterized by frequent antibiotic resistance (Isturiz et al. 2017; Dagan and Klugman 2008). Serotypes most frequently resistant to a spectrum of antibiotics in Poland in 2019 were 6B, 6C, 6D, 14, 19A, and 19F. The use of PCV13 could ultimately prevent 83%, 100%, and 77% of infections caused by strains resistant to penicillin, third-generation cephalosporins, and erythromycin, respectively, and as many as 89% of infections caused by multi-drug-resistant strains (NRCBM 2020). This underlines the importance of vaccination in reducing the problem of antibiotic resistance, particularly when the number of resistant bacteria is constantly increasing.

9 Future of Pneumococcal Vaccination

Conjugate vaccines are currently in a research phase, covering more serotypes of bacteria. A 15-valent vaccine containing two serotypes (22F and 33F) more than a 13-valent vaccine shows satisfactory immunogenicity and safety (Stacey et al. 2019). A 20-valent variant containing additional serotypes 8, 10A, 11A, 12F, and 15B has successfully passed initial clinical trials (Thompson et al. 2019). The number of pneumococcal serotypes is quite large, so it has been decided to search for alternate ways of vaccine development other than adding on serotypes. Whole-cell vaccines prepared from selected strains of *S. pneumoniae* with reduced virulence seem a promising breakthrough in vaccination against pneumococci. Such vaccines would result in the production of antibodies directed at different pneumococcal antigens regardless of their serotypes and obviate the need to purify individual polysaccharides, sparring vaccine costs. Initial clinical trials are quite promising, and a whole-cell vaccine may shortly join the range of pneumococcal vaccines (Morais et al. 2019).

The most appropriate direction in the development of pneumococcal vaccination seems a search of a vaccine that protects against the bacterium, regardless of its serotype. This idea is supported by the constantly changeable distribution of serotypes toward other than those present in the spectrum of hitherto available vaccines. Given a large number of pneumococcal serotypes, it would be very difficult to develop a polysaccharide or conjugate vaccine protecting each serotype. Finding a universal pneumococcal target for the vaccine seems the only reasonable way out of this predicament.

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Article

Vaccination against *Streptococcus pneumoniae* in Children Born between 2015 and 2018 in Poland—How Has the Introduction of Free Compulsory Pneumococcal Vaccination Affected Its Uptake?

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Abstract: Starting from 2017, pneumococcal vaccination was added to the Polish vaccination calendar as mandatory for all children born after 2016. The 10-valent conjugate vaccine was selected as mandatory and therefore free of charge. This paper aims to examine the impact of introducing mandatory vaccination on vaccine uptake. For this purpose, an analysis was conducted for 1595 vaccination record sheets from outpatient clinics in Wrocław and surrounding villages for children born 2015–2018. After the introduction of compulsory vaccination, the percentage of children fully vaccinated against *pneumococcus* increased (60.4% vs. 84.8%, $p < 0.001$). A significant decrease in the number of children who did not receive any dose of the vaccine was observed (27.8% to 3.3%, $p < 0.001$). The introduction of compulsory vaccination did not affect the completion of the pneumococcal schedule (11.8% vs. 11.9%). Compulsory PCV10 vaccination resulted in the less frequent choice of the 13-valent vaccine (72.3% vs. 19.9%, $p < 0.001$). More children in rural outpatient clinics were vaccinated against *pneumococcus* compared to urban outpatient clinics (84.8% vs. 70.8%, $p < 0.001$). The introduction of free pneumococcal vaccination increased the proportion of children vaccinated, although it did not affect the rate of discontinuation of the initiated schedule. In Poland, the increased popularity of the 10-valent vaccine at the expense of the 13-valent one translated into a change in the proportion of pneumococcal serotypes causing invasive pneumococcal disease.

Keywords: invasive pneumococcal disease; pneumococcal vaccine; *Streptococcus pneumoniae*; vaccination program

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1. Introduction

Streptococcus pneumoniae is a bacterium that mainly causes non-invasive respiratory infections such as middle ear infections and pneumonia. In some cases, it can cause infection of physiologically sterile parts of the body. When this happens, the most common clinical manifestations are pneumonia with bacteremia, meningitis, or sepsis—collectively known as invasive pneumococcal disease (IPD) [1]. In 2021, 8962 cases of IPD were reported in Europe, of which 955 were in Poland [2]. In an era of ever-increasing bacterial resistance to antibiotics, their effectiveness is increasingly limited. It is, therefore, crucial to take preventive measures against IPD, and immunization still remains the most effective method of preventing the disease [1].

Currently, conjugate vaccines (PCVs) immunizing against ten (PCV10—Synflorix, GlaxoSmithKline Biologicals, Belgium) or thirteen (PCV13—Prevenar 13, Pfizer Europe MA EEIG, Belgium) *S. pneumoniae* serotypes are used for the general vaccination of children in Poland [3]. Seven-valent vaccines have been used in the past, and fifteen- and twenty-valent vaccines have also emerged in recent years, but they are not available in Poland for the pediatric population. The 20-valent vaccine has so far been registered only for adult patients. Polysaccharide (PPSV) vaccines are not suitable for the youngest children due to their inability to adequately stimulate the child's immature immune system [4].

The Polish vaccination calendar for 2023 distinguishes between mandatory vaccinations, which are free of charge, and recommended vaccinations—for which the child's parents must pay [3]. Until the end of 2016, pneumococcal vaccination was not mandatory in Poland. Free vaccination was available only to children from specific risk groups, including those with HIV infection, bone marrow or organ transplants, cochlear implants, or children with certain chronic diseases, as well as premature babies and children with a birth weight of less than 2500 g [5]. If parents wanted to vaccinate a child ineligible for mandatory vaccination, they had to bear the cost of the vaccination. In Poland, universal mandatory free vaccination against *S. pneumoniae* was introduced in 2017 and is continued to this day. Currently, the PCV10 vaccine is used for the general public in a 2+1 schedule (two doses of primary vaccination and one booster dose), or in some cases 3+1 (three doses of primary vaccination and one booster dose). The 3+1 schedule applies to babies born prematurely and those at risk of severe pneumococcal disease [3].

Documentation of the course of immunization is maintained by the primary healthcare facility in which the child is enrolled. Each patient has his individual vaccination record sheet, which contains information related to each vaccine administered. After the vaccination, an entry is made in the clinic's records as well as in the child's health record that belongs to the parents [6]. It is very difficult to assess the level of pneumococcal vaccination in Poland in the period before mandatory vaccination was introduced due to the lack of registration by state institutions. Such data was analyzed nationwide only from 2017. According to a 2022 report by the National Institute of Public Health of the National Institute of Hygiene, about 96% of children in the 2017–2018 age group have been vaccinated against *pneumococcus* [7]. According to WHO data, in 2018, the percentage of fully vaccinated children in Poland was 60%. This compares with 78% and 47% in Europe and the world, respectively [8].

This study aims to assess the effect of introducing free mandatory vaccination against *S. pneumoniae* on its uptake, as well as on decisions on the choice of formulations, and to analyze the completeness of the vaccination schedules carried out. Since the introduction of free pneumococcal vaccination in Poland, to the best of the authors' knowledge, no similar study has been conducted before. Also, there is no nationwide data available that would provide answers to the above questions.

2. Materials and Methods

Data for this study was collected by analyzing the vaccination record sheets kept for children born in 2015–2018 and residing in Wrocław (a city of more than 500,000 residents) and two nearby villages. The analysis included all available vaccination record sheets for children. Inclusion criteria were that the participants had to be patients of the clinic at the time of data collection and be born between 2015 and 2018. Relevant approvals were obtained from the managers of medical facilities before the record sheets were analyzed.

The database created contained information about the date of each PCV dose and the formulation used. Information on gender and date of birth was also collected, which was necessary to determine which vaccination schedule was performed. The data contained in the database do not allow the identification of the patient. Based on the date of administration of each PCV dose, the patient's age at the time of the dose, the interval between doses, and the total number of doses administered were determined. These data made it possible to assign patients to the following groups:

a. not vaccinated;
b. not fully vaccinated;
c. vaccinated completely.

Patients who did not receive any dose of PCV were included in the "not vaccinated" group. The group of patients with a complete vaccination schedule consisted of children who, at the time of the vaccination study, had received the full vaccination schedule in accordance with current recommendations. These criteria differed between the periods analyzed, and their detailed description is shown in Tables 1 and 2 [3,5,9,10]. Any child who received at least one dose of PCV but did not meet the conditions to be considered completely vaccinated was categorized as "not fully vaccinated."

Table 1. The "vaccinated completely" group criteria for children born in 2015 and 2016.

<table>
<tr><th>Patient's Age</th><th>PCV10 [1]</th><th>PCV13 [2]</th></tr>
<tr><td>From 6 weeks to 6 months of age</td><td>3+1
1. Three primary doses with an interval of at least 1 month between doses.
2. A booster dose at least after the last primary dose and from the age of 9 months.</td><td>3+1
1. Three primary doses with an interval of at least 1 month between doses.
2. A booster dose is recommended between 11 and 15 months of age.</td></tr>
<tr><td>7 months–11 months</td><td>2+1
1. Two primary doses with an interval of at least 1 month between doses.
2. A booster dose in the second year of life, at least 2 months after the last primary dose.</td><td>2+1
1. Two primary doses with an interval of at least 1 month between doses.
2. A booster dose is recommended in the second year of life</td></tr>
<tr><td>12 months–23 months</td><td rowspan="2">2+0
1. Two doses with an interval of at least 2 months between doses.</td><td>2+0
1. Two doses with an interval of at least 2 months between doses</td></tr>
<tr><td>24 months–5 years</td><td rowspan="2">1+0
1. One single dose</td></tr>
<tr><td>5 years and above</td><td>Not registered for use.</td></tr>
</table>

[1] PCV10—10-valent conjugate pneumococcal vaccine; [2] PCV13—13-valent conjugate pneumococcal vaccine.

Table 2. The "vaccinated completely" group criteria for children born in 2017 and 2018.

<table>
<tr><th>Patient's Age</th><th>PCV10 [1]</th><th>PCV13 [2]</th></tr>
<tr><td>From 6 weeks to 6 months of age</td><td>3+1
1. Three primary doses with an interval of at least 1 month between doses.
2. A booster dose at least 6 months after the last primary dose and from the age of 9 months.
OR
2+1
1. Two primary doses with an interval of at least 2 months between doses.
2. A booster dose at least 6 months after the last primary dose and form the age of 9 months.</td><td>3+1
1. Three primary doses with an interval of at least 1 month between doses.
2. A booster dose is recommended between 11 and 15 months of age.
OR
2+1
1. Two primary doses with an interval of at least 2 months between doses.
2. A booster dose is recommended between 11 and 15 months of age.</td></tr>
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1. One single dose</td></tr>
<tr><td>5 years and above</td><td>Not registered for use.</td></tr>
</table>

[1] PCV10—10-valent conjugate pneumococcal vaccine; [2] PCV13—13-valent conjugate pneumococcal vaccine.

Description of Statistics

Based on the number of doses and the interval between them, it was possible to determine whether the vaccination schedule had been carried out correctly or whether it had been interrupted. This allowed each patient to be assigned to one of three groups. The Chi-squared test was used to compare qualitative variables. Statistical significance was assumed at the level of <0.05. Calculations were performed using Statistica 13 software by TIBCO Software Inc. (Palo Alto, CA, USA).

3. Results

3.1. Characteristics of the Sample Group

Included in the analysis were 1595 unique analyzed vaccination record sheets. Children born in 2015–2016 accounted for 47.3%, and those born in 2017–2018 accounted for 52.7%. Slightly more than half (52.2%) were women. Patients from municipal clinics accounted for 82.6% of the total. Detailed sociodemographic data is shown in Table 3. The distribution of the records is presented in Figure 1.

Table 3. Characteristics of the sample group.

Patient		Total Population *N* (%)	2015 and 2016 Age Group N (%)	2017 and 2018 Age Group *N* (%)	*p*
Gender	Male	763 (47.8)	387 (46.5)	445 (53.5)	0.525
	Female	832 (52.2)	368 (48.2)	395 (51.8)	
Place	Urban area	1318 (82.6)	630 (47.8)	688 (52.2)	0.417
	Rural area	277 (17.4)	125 (45.1)	152 (54.9)	

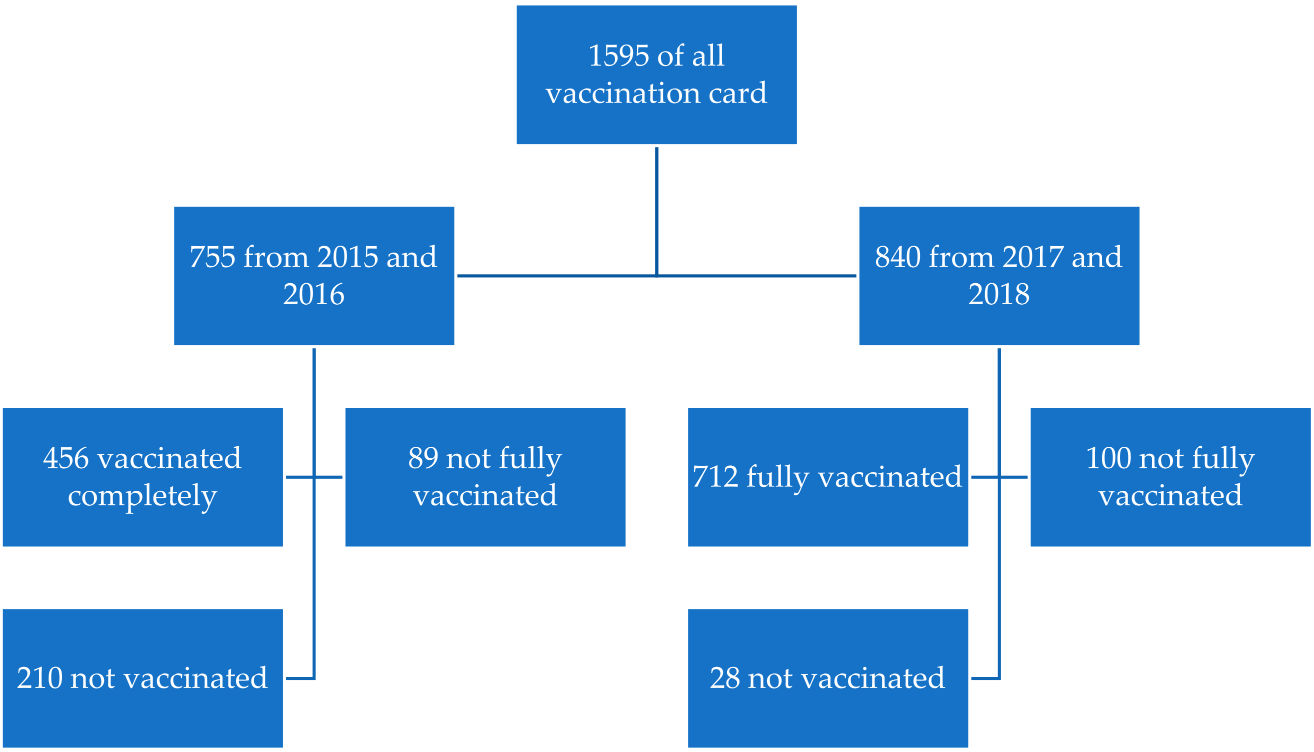

Figure 1. Distribution of analyzed records.

3.2. Comparison of Vaccination in the Period before and after the Introduction of Mandatory Vaccination

In the analyzed group, an increase in the percentage of children with a completed vaccination schedule was observed after the implementation of mandatory vaccination (60.4% vs. 84.8%, $p < 0.001$). What is more, the percentage of children who did not receive even one dose of PCV vaccination dropped significantly, from 27.8% to 3.3%, $p < 0.001$. The percentage of children who did not complete the vaccination schedule remained similar (11.8% vs. 11.9%).

In the analysis of preference for the formulation used, it was observed that, among children born in 2015–2016 who received at least one dose of the vaccine, the majority were vaccinated with PCV13 (72.3%), while, in 2017–2018, this percentage decreased to 19.9% in favor of PCV10, whose share was then 80.1% ($p < 0.001$). Table 4 presents information on the patients' vaccination status, including an incomplete vaccination schedule.

Table 4. Vaccination status and vaccine used.

Patient		Total Population *N* (%)	2015 and 2016 Age Group *N* (%)	2017 and 2018 Age Group *N* (%)	*p*	Cramér's V
Vaccinated against *pneumococcus*	Yes	1168 (73.2)	456 (60.4)	712 (84.8)	<0.001	0.275
	No	427 (26.8)	299 (39.6)	128 (15.2)		
Vaccination schedule	Completed	1168 (73.2)	456 (60.4)	712 (84.8)	<0.001	0.346
	Not completed	189 (11.8)	89 (11.8)	100 (11.9)		
	No vaccination	238 (15.0)	210 (27.8)	28 (3.3)		
Product (*N* = 1357)	PCV10 [1]	801 (59.0)	151 (27.7)	650 (80.1)	<0.001	0.521
	PCV13 [2]	556 (41.0)	394 (72.3)	162 (19.9)		

[1] PCV10—10-valent conjugate pneumococcal vaccine; [2] PCV13—13-valent conjugate pneumococcal vaccine.

In the analysis of individual sociodemographic variables on vaccination status, no significant differences were observed regarding the gender of the child ($p = 0.989$). However, a difference was observed depending on the place of residence. Patients living in rural areas were significantly more likely to be vaccinated against *pneumococcus*, with rates of 84.8% vs. 70.8% in rural and urban outpatient clinics, respectively ($p < 0.001$). There were no significant differences in the completion of the vaccination schedule depending on the vaccine used ($p = 0.093$). Table 5 shows the status of pneumococcal vaccination with uncompleted schedules according to sociodemographic data. Table 6 shows these figures broken down for 2015–2016 and 2017–2018.

Table 5. Pneumococcal vaccination by gender, place, and vaccine type.

Variable		Pneumococcal Vaccination *N* (%)			Completed Schedule *N* (%)			
		Yes	No	*p*	Vaccinated Completely	Not Fully Vaccinated	Not Vaccinated	*p*
Gender	Male	608 (73.1)	224 (26.9)	0.886	608 (73.1)	99 (11.9)	125 (15.0)	0.989
	Female	560 (73.4)	203 (26.6)		560 (73.4)	90 (11.8)	113 (14.8)	
Place	Urban area	933 (70.8)	385 (29.2)	<0.001	933 (70.8)	171 (13.0)	214 (16.2)	<0.001
	Rural area	235 (84.8)	42 (15.2)		235 (84.8)	18 (6.5)	24 (8.7)	
Vaccine	PCV10 [1]	—	—	—	700 (87.4)	101 (12.6)	—	0.093
	PCV13 [2]	—	—		468 (84.2)	88 (15.8)	—	

[1] PCV10—10-valent conjugate pneumococcal vaccine; [2] PCV13—13-valent conjugate pneumococcal vaccine.

Table 6. Pneumococcal vaccination in 2015–2016 and 2017–2018 by gender, locality, and vaccine.

Variable			Pneumococcal Vaccination N (%)			Completed Schedule N (%)			
			Yes	No	p	Vaccinated Completely	Not Fully Vaccinated	Not Vaccinated	p
Gender	2015–2016	Male	228 (58.9)	159 (41.1)	0.393	228 (58.9)	49 (12.7)	110 (28.4)	0.635
		Female	228 (62.0)	140 (38.0)		228 (62.0)	40 (10.9)	100 (27.2)	
	2017–2018	Male	380 (85.4)	65 (14.6)	0.532	380 (85.4)	50 (11.2)	15 (3.4)	0.817
		Female	332 (84.1)	63 (15.9)		332 (84.1)	50 (12.7)	13 (3.3)	
Place	2015–2016	Urban area	364 (57.8)	266 (42.2)	<0.001	364 (57.8)	77 (12.2)	189 (30.0)	0.003
		Rural area	92 (73.6)	33 (26.4)		92 (73.6)	12 (9.6)	21 (16.8)	
	2017–2018	Urban area	569 (82.7)	119 (17.3)	<0.001	569 (82.7)	94 (13.7)	25 (3.6)	0.002
		Rural area	143 (94.1)	9 (5.9)		143 (94.1)	6 (3.9)	3 (2.0)	
Vaccine	2015–2016	PCV10 [1]	—	—	—	126 (83.4)	25 (16.6)	—	0.930
		PCV13 [2]	—	—		330 (83.8)	64 (16.2)	—	
	2017–2018	PCV10 [1]	—	—	—	574 (88.3)	76 (11.7)	—	0.279
		PCV13 [2]	—	—		138 (85.2)	24 (14.8)	—	

[1] PCV10—10-valent conjugate pneumococcal vaccine; [2] PCV13—13-valent conjugate pneumococcal vaccine.

An analysis was carried out in terms of the percentage of interrupted vaccinations with a particular formulation before and after the introduction of the obligation. It showed no significant differences, but, in the case of PCV10, a trend on the verge of statistical significance can be seen—after mandatory vaccination was introduced, the percentage of interrupted vaccination decreased from 16.6% to 11.7%. Details are shown in Table 7.

Table 7. Percentage of completed and uncompleted vaccination schedules in 2015–2016 vs. 2017–2018 depending on the vaccine used.

Vaccine	2015 and 2016 Age Group N (%)		2017 and 2018 Age Group N (%)		p
	Schedule Completed	Schedule Not Completed	Schedule Completed	Schedule Not Completed	
PCV10 [1]	126 (83.4)	25 (16.6)	574 (88.3)	76 (11.7)	0 = 0.105
PCV13 [2]	330 (83.8)	64 (16.2)	138 (85.2)	24 (14.8)	0 = 0.675

[1] PCV10—10-valent conjugate pneumococcal vaccine; [2] PCV13—13-valent conjugate pneumococcal vaccine.

4. Discussion

The present study is based on an analysis of birth charts of children from Wrocław (Poland) and surrounding villages. For the purpose of the study, 1595 birth charts from three medical facilities of children born between 2015–2016 (755) and 2017–2018 (840) were analyzed. The number of births in the region in the period 2015–2016 was 53,432, and for 2017–2018, 55,853 newborns. This indicates that 1.5 per cent of babies born in the periods indicated were analyzed [11–14]. The results of the present study indicate that vaccine uptake increased in the analyzed period in the examined population after the introduction of mandatory pneumococcal vaccination. There was also a change in preference for the most commonly used formulation to PCV13 in favor of PCV10. However, there was no change in the frequency of discontinuation of a commenced vaccination schedule. Differences were also shown between vaccination rates in urban and rural outpatient clinics.

In Poland, in 2023, in the first year of life, vaccinations against tuberculosis, diphtheria, tetanus, pertussis (3-in-1), *Haemophilus influenzae* type B, poliomyelitis, hepatitis B, and pneumococcal (from 2017) and rotavirus infections (from 2021) are mandatory (free of charge). Before the introduction of mandatory pneumococcal vaccination, state institutions did not record data on vaccination rates, so it is not possible to compare the percentage of unvaccinated children from the survey (27.8%) to nationwide data. After the introduction of compulsory vaccination, registration began, and the percentage of unvaccinated children in the country, in 2017–2018, was 3.8% [7], which is consistent with the results of this survey (3.3%). This shows a significant increase in pneumococcal vaccine uptake among Polish children. An analogous trend has been observed, for example, in Bulgaria. PCV10 was introduced to the vaccination calendar in that country in 2010, and the percentage of vaccinated children increased from 69% in 2010 to 94% in 2011 [8,15].

Acceptance of vaccinations is a complex phenomenon, and receiving any vaccination depends on many factors. Studies have shown evidence of the effectiveness of several patient-centered interventions. These include making vaccinations more accessible, reducing their cost, reminders to vaccinate, and requiring vaccinations for enrollment in schools or other institutions [16]. The introduction of mandatory pneumococcal vaccination has had several effects. First, the financial barrier was removed, as the vaccination has since become free for all children born since 2017 [17]. It has been proven many times in the literature that free vaccination translates into a higher number of vaccinated individuals, and the cost of the vaccine is one of the more common reasons used to justify not vaccinating [18–20]. Second, the introduction of mandatory vaccination has also undoubtedly increased its popularity. Information campaigns in the media have made some parents aware of this vaccination. Parents were more likely to discuss vaccination with their doctor or seek information on their own, and this could ultimately translate into a positive decision to vaccinate their children. Studies confirm that increasing awareness of a particular vaccination, as well as popularizing knowledge about it, significantly increases the number of vaccinated patients [21]. On the other hand, it is also important to keep in mind the negative consequences of introducing mandatory vaccination. Willingness to receive compulsory vaccination is closely linked to trust in the authorities who introduce such an obligation. This is related to the history of introducing vaccination and the attitude of the community towards limiting their freedom of choice in favor of their own health and that of the population [22]. Moreover, as a result of reactance, forcing a parent to vaccinate a child may result in a desire to do the opposite. When giving a child a mandatory vaccination, they will decline another vaccination that they would normally have their child receive. This is what has been observed in Germany, where vaccine uptake for other diseases declined after measles vaccination became mandatory in 2020. A survey confirmed that compulsory measles vaccination in some social groups has triggered resistance to pneumococcal vaccination and the 6-in-1 combination vaccine [23]. Similar observations were made in another study by Léna G. Dietrich et al. among Swiss healthcare workers, where they were mostly opposed to mandatory vaccination both in the general population against measles and among healthcare workers against influenza. Some employees declared that they would resign if the obligation was introduced at their workplace [24]. Nevertheless, mandatory vaccination, in general, increases the percentage of vaccinations administered and thus improves public health [21]. Some parents, however, decide not to vaccinate their children despite the introduced obligation. A study by Cooper et al. divided parents who refuse vaccination into two groups: “Neoliberal logic” and “Social exclusion.” The first includes well-educated people from higher-income countries who value their individuality and independence to the point of distrusting the “system,” and thus resist vaccinating their children. The second group includes poorer people who are more excluded from society on many levels and see universal vaccination as a social construct from which they want to isolate themselves [25]. Nevertheless, trust in vaccination has been shown to be positively correlated with trust in science in general, and negatively correlated with belief in horoscopes [26]. This confirms the fact that better awareness of science, and thus vaccination, positively influences the acceptance of vaccination. To reach those parents who, for various reasons, are not convinced about vaccination, it seems effective to raise awareness and dispel doubts about immunization [27]. In Poland, most people approve of mandatory vaccinations, and some also support imposing sanctions on parents who evade vaccinating their children [28,29]. If mandatory vaccination were not widely accepted, the increase in the percentage of vaccinated children in the survey conducted would not have been so noticeable. An important element affecting the implementation of mandatory vaccinations is the government’s policy, which varies from country to country. A parent’s failure to comply with the obligation can prevent their child from being admitted to kindergarten or school, deprive parents of financial or tax benefits, or expose them to financial sanctions or even imprisonment [30]. However, in addition to legal provisions, the inevitability of the penalties provided for depriving a child of vaccination is also important—according to the classification proposed by Attwell et al., Poland is close to a system of "informal nonenforcement," in which theoretically there is an obligation but compliance with it in practice is rarely enforced [31]. The complicated course of legal action and the possibility of dragging out the procedure means that a possible fine is imposed late and only in about 10% of cases of vaccination evasion [32]. This, in turn, makes the obligation likely to be ignored by parents, particularly if they accept a priori that they will pay the fine as the price for standing by their views.

Failure to complete a schedule that has been started is also a significant problem. In this study, it was observed that 11.8% of children started but did not complete the pneumococcal vaccination schedule. This percentage did not differ significantly between before and after the introduction of free vaccinations, at 11.8% and 11.9%, respectively. After analyzing patients who received at least one dose of pneumococcal vaccination, it was observed that the percentage of discontinued schedules for PCV10 decreased from 16.6% to 11.7%. The difference is on the verge of statistical significance but it makes it possible to observe a trend and further observations are required to make more conclusions. Completion of the vaccination schedule is important because of the protective potential. The number of PCV doses needed to achieve satisfactory immunity varies depending on the child's age at which vaccination was started. Since IPD is most threatening to the youngest children, vaccination should be started as early as possible. Failure to administer all required primary doses decreases and/or shortens immunity against IPD, as does skipping a booster dose [33,34]. Completion of the vaccination schedule is affected by a great many factors including the number of doses required. Previous studies have shown that the greater the number of doses of vaccine, the greater the chance of discontinuing vaccination. A study by Krishnarajah et al. and a similar study by Luna-Casas et al. found that, when vaccinated against rotavirus, children were less likely to receive all doses of a three-dose vaccine compared to a two-dose vaccine [35,36]. Similar observations were made for *N. meningitidis* type B vaccines, where greater flexibility in the use of the MenB-4C vaccine made it more likely to be administered in the full schedule compared to the MenB-Fhbp vaccine [37]. A similar relationship can be seen in this study, where PCV10, administered in a 2+1 schedule was interrupted slightly less often than PCV13 that had to be administered in principle in a 3+1 schedule, since the 2+1 schedule is a conditional alternative in its case. It should also be borne in mind that a reason for parents' refusal to have their child receive subsequent doses of vaccination is a negative experience after previous doses. This includes adverse reactions such as fever, pain at the injection site, and also the child's fear of needles [38]. Another reason for not completing the vaccination schedule also continues to be the intentional avoidance of subsequent doses resulting from the belief that the doses already received are sufficient, which is a misconception [39]. In addition, organizational problems may also play a role—some studies indicate that the distance from the outpatient clinic translating into transportation difficulties may also have an impact on discontinuing vaccinations [40]. On the other hand, it should be mentioned that sometimes the interruption of the schedule is unintentional and results from the patient forgetting the need for another dose of vaccine. In such cases, healthcare workers should notify the patient of the need to complete the vaccination. This task is facilitated by modern technology, in which the automation of this process makes it possible to effectively remind about a vaccination dose without burdening the medical staff [41]. Differences have also been observed between rural and urban areas. In rural outpatient clinics, 84.8% of children were vaccinated against *pneumococcus*, while in urban ones, the figure was 70.8%. Moreover, in urban areas, 13% of children started but did not complete the vaccination schedule, while in rural areas this number was 6.5%. Nationwide statistics do not provide information on the place of residence of unvaccinated children [7]. In contrast, in a survey of attitudes toward COVID-19 vaccination conducted in Poland, it was rural residents who were more likely to have concerns about the vaccine and show no willingness to receive it [42]. At the same time, other studies do not clearly show whether the location of the clinic in or outside an urban area affects vaccination [43]. What is emphasized, however, is the fact that the involvement of medical personnel in promoting vaccination, reminding people of their next appointments, and passing on reliable knowledge to parents has a great impact [16]. It is possible that, in rural clinics with fewer patients, doctors may spend more time with patients and thus encourage vaccination more effectively.

Before the introduction of mandatory vaccination, parents were more likely to opt for PCV13 compared to PCV10, at a rate of 72.3% vs. 27.7%, respectively. Since parents were paying the cost of the vaccine anyway, they would be opting for the one with a broader spectrum. After the introduction of compulsory vaccination, this proportion reversed and most children were now vaccinated with PCV10—80.1% vs. 19.9%. Pneumococcal vaccination has been made compulsory in many European countries and, in most cases, vaccination is provided with PCV13 in a 2+1 schedule [44]. The introduction of vaccination has changed the distribution of serotypes that cause IPD [44–46]. In countries where PCV10 was used, the incidence of IPD caused by serotypes 3, 6A, and 19A contained in PCV13 but not in PCV10 increased. The increase is particularly noticeable for serotypes 3 and 19A [44,47]. In Poland, the number of IPD cases caused by serotypes contained in PCV10 has decreased every year since 2017, and, as in other countries, they are being replaced by non-vaccine serotypes and serotypes 3, 6A, and 19A, found in PCV13 but not in PCV10. Especially in the group of children under 5 years of age, the percentage of IPDs caused by serotype 19A has been increasing in recent years. That percentage was 11.54%, 34.43%, and 32.95% in 2020, 2021, and 2022, respectively [48,49]. In the analyzed population, the vast majority of children have been vaccinated with PCV10 since 2017, which is consistent with the observed trend of increase in the percentage of serotypes not included in PCV10. Data from European countries show that the introduction of mandatory pneumococcal vaccination has reduced the incidence of IPD. This effect was demonstrated for both PCV10 and PCV13 [50,51]. The difference is seen in the case of serotypes 6C and 19A, where PCV10 offers no significant protection. This could explain why, in countries using mainly PCV10 instead of PCV13, the percentage of IPD caused by this serotype increases. Also, data from outside Europe seem to confirm the superiority of PCV13 in protecting against the serotypes responsible for most IPD cases. In Canada, PCV13 showed about twice as much protection against serotypes in each of the analyzed regions of the country [52]. Protection against serotype 19A may be a factor responsible for reducing the number of antibiotic-resistant pneumococcal strains [53]. On the other hand, in systematic reviews, such conclusions are drawn with greater caution due to the wide variation in data in individual regions [54]. PCV10 induces cross-immunity against serotype 19A but, unlike PCV13, it does not reduce the carriage of this bacterium, thus providing less effective protection against this serotype [55].

Data from Poland may also indicate a positive impact of mandatory vaccinations on the incidence of IPD among children. In the data presented by the National Institute of Hygiene in 2014–2016, the incidence of pneumococcal meningitis and pneumococcal encephalitis among children aged 0–4 years was 1.07, 1.05, and 1.28 per 100,000, respectively. [56–58] From 2017 to 2021, a decreasing trend in incidence was observed, which was 0.85, 1.26, 0.94, 0.26, and 0.75, respectively [59–63]. Nevertheless, the last two years of the report, i.e., 2020 and 2021, should be treated with caution due to the current COVID-19 pandemic and restrictions in force that could definitely affect the above values [64]. Unfortunately, the analyzed data do not include information on the most common serotypes causing IPD.

The authors are aware of the limitations of the present study, namely the selection of a sample group that is not representative of the Polish population, and therefore further observations on a larger group of patients are necessary. Also, the reason for discontinuing vaccination is not known.

In conclusion, the introduction of mandatory pneumococcal vaccination has contributed to a significant increase in the percentage of vaccinated children. It also contributed to a change in the trend of the formulation used with a predominance toward PCV10. Better vaccination coverage will most likely translate into reduced mortality among infants and children up to 5 years of age. This is one of the assumptions of goal 3.3 of the Sustainable Development Goals created by the United Nations. Making vaccines free of charge is also part of the implementation of goal 3.8, which concerns ensuring financially accessible modern medical methods [65].

5. Conclusions

The introduction of free mandatory pneumococcal vaccination has increased the percentage of vaccinated children but has not affected the percentage of uncompleted vaccination schedules. Introducing free-of-charge compulsory pneumococcal vaccination with the PCV10 vaccine has resulted in changes in the contribution of specific pneumococcal serotypes to the etiology of invasive pneumococcal disease in Poland.

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The Influence of Introducing Free Vaccination against *Streptococcus pneumoniae* on the Uptake of Recommended Vaccination in Poland

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Abstract: Since 2017, pneumococcal vaccination has evolved from a recommended chargeable vaccination to a mandatory, and therefore free, vaccination for all children. While a 10-valent vaccine is commonly used, parents have the option to use a 13-valent vaccine for a fee. This study aimed to investigate whether and how the introduction of free pneumococcal vaccination affected the uptake of recommended vaccination and to assess the association of chargeable pneumococcal vaccination with recommended vaccination. Data from 1595 vaccination record cards kept by six primary care clinics in urban and rural areas of Poland were collected and analyzed for children born between 2015 and 2018. Belonging to the clinic and the year of birth were the only inclusion criteria. Following the introduction of free universal pneumococcal vaccination, more children were vaccinated with the recommended vaccination (61.2% vs. 66.6%, $p = 0.026$). The most significant change was in vaccination against rotavirus (48.5% vs. 54.4%, $p = 0.018$) and against meningococcal B bacteria (4.8% vs. 17.0%, $p < 0.001$). Children who received chargeable pneumococcal vaccination were also significantly more likely to be vaccinated with recommended vaccines (54.6% vs. 75.9%, $p < 0.001$). In particular, this was the case for multivalent vaccinations—against rotavirus, chickenpox, and meningococcal C bacteria. Reducing the impact of the economic factor, for example, by introducing free vaccinations, should have a positive impact on the uptake of other recommended vaccinations.

Keywords: pneumococcal vaccine; vaccination program; voluntary vaccination

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1. Introduction

In Poland, the Preventive Vaccination Program (PVP) consists of mandatory and recommended vaccinations. Some compulsory vaccinations apply to all children, while others are dedicated exclusively to specific risk groups. All compulsory vaccinations are financed by the state budget. The recommended vaccination, on the other hand, is at the discretion of the parent, who bears the full cost [1,2].

Over the years, the PVP has expanded to include further compulsory vaccinations. One of these is the vaccination against *Streptococcus pneumoniae*, which, until the end of 2016, was only mandatory for a small group of patients with specific risk factors [3]. In 2017, this vaccination became mandatory for all children born after 1 January 2017. The same was true for the rotavirus (RV) vaccination, which was a recommended vaccination until 2021, and it has been on the mandatory vaccination list since 2021. According to the 2023 PVP in Poland, mandatory vaccinations include vaccination against tuberculosis (BCG), hepatitis B virus (HBV), rotavirus (RV), diphtheria, tetanus, pertussis (DTwP, whole-cell pertussis component or DTaP, cell-free pertussis component), H. Influenzae type B (HiB), pneumococcus (PCV), poliomyelitis (IPV), and measles, mumps, and rubella (MMR). On the other hand, the recommended vaccinations possible in the first two years of life include vaccination against *Neisseria meningitidis* group B (MenB), *N. meningitidis* group C (MenC), or groups A, C, W135, and Y (MenACWY), chickenpox (VZV), tick-borne encephalitis (TBE), and hepatitis A (HAV) [4].

It is also possible to opt for paid multivalent vaccinations instead of the standard DTwP, IPV, HiB, and HBV vaccinations. Two conjugate vaccines are available: a five-valent ('5in1'), DTaP + IPV + HiB, and a six-valent ("6-in-1"), DTaP + IPV + HiB + HBV [4]. The 5-in-1 formulations are publicly reimbursed for children with contraindications to the whole-cell pertussis vaccine and for all children born before 37 weeks gestation or with a birth weight of less than 2500 g. The 6-in-1 vaccination is not state-funded [4]. Smallpox vaccination is compulsory for immunocompromised children and those around them, as well as for children in social and therapeutic institutions and those attending nursery school [4]. Pneumococcal vaccination in the youngest children can be performed with two conjugated vaccines: 10-valent (PCV10) or 13-valent (PCV13). PCV10 is used for universal mandatory vaccination. Parents can opt for PCV13, but in that case, they have to cover its cost. The only exception is infants born before 27 weeks gestation, as PCV10 is not registered for use in this patient group. Selecting PCV13 extends protection to three additional serotypes. Due to the similarity of pneumococcal antigens, immunity is also produced against some serotypes not included in the vaccine. This also happens with other vaccinations. For example, the smallpox vaccine can prevent monkeypox [5].

Nowadays, immunization is widely available. Nevertheless, their acceptance level, which has gradually decreased in recent years, is an enormous challenge. The increasing anti-vaccination movements are setting an increasing number of people against vaccination [6–8]. Acceptance of vaccination depends on many different factors, such as knowledge about vaccination or trust in the health system [9,10]. Economic issues are also relevant, as the price of vaccination can be a real barrier to its uptake [11]. Many studies have shown that pneumococcal vaccination is effective in preventing the disease, and thus money spent on vaccination saves money spent on treatment. Cost-effectiveness has been demonstrated not only for the elderly but also specifically for children [12,13]. Factors related to the vaccination itself are also important, such as the effectiveness of the vaccine and the risk of side effects. Observations carried out in connection with vaccination against COVID-19 in developing countries allow us to conclude that greater compliance and a lower risk of side effects have a positive impact on the reception of the vaccine in society [14]. Introducing a vaccination into the mandatory vaccination calendar and thus making it free of charge increases vaccination coverage and also reduces the incidence of a particular infection. The factor that is eliminated in such a case is the financial barrier [15,16]. However, it is not clear how the introduction of one vaccination into the calendar affects the performance of other vaccinations, particularly those that are not listed as free of charge. Many studies show that compulsory vaccination has an overall positive effect on vaccination uptake [17]. However, some studies suggest that compulsory vaccination may lead to reduced trust in the health system and paradoxically worsen acceptance not only of compulsory but also of other vaccinations [18,19].

Therefore, this study aims to assess whether the introduction of universal, compulsory, free pneumococcal vaccination in Poland in 2017 affected the implementation of recommended vaccination in this group of children. In addition, it assesses whether parents choosing paid pneumococcal vaccination are opting for a recommended vaccination. To the best of the authors' knowledge, no similar study has been carried out since the introduction of compulsory vaccination. Nor is analogous data available from other countries.

2. Materials and Methods

2.1. Study Design

To be able to process the material, we had to prepare a database containing information on pneumococcal vaccinations and recommended vaccinations. These data can be found on vaccination cards that are kept in the primary health care facilities to which the patient belongs. To further diversify the study population, we searched for both urban and rural facilities.

2.2. Obtaining Data

After obtaining consent from the managers of six primary health care facilities, the vaccination record cards of children born between 2015 and 2018 residing in Wrocław (a Polish city of more than 500,000 inhabitants, four facilities) and in two surrounding villages (one facility in each) were placed in the database and then analyzed. All the available vaccination record cards were analyzed; the only inclusion criteria were being born in the year 2015–2018 and being a patient of the clinic at the time of data collection.

The database contained patient data in the form of date of birth and sex without the possibility of identifying the patient. The database also included dates of pneumococcal vaccinations with the formulation used, as well as information on multivalent (5-in-1 and 6-in-1) vaccinations against rotavirus infection, chickenpox, meningococcal disease, tick-borne encephalitis, and hepatitis A.

2.3. Study Group Settings

The records were then subdivided based on the child's year of birth. The first group included children born in 2015 and 2016, and the second in 2017 and 2018. The cut-off point was when free pneumococcal vaccination was introduced.

A breakdown was also made, taking into account the cost of pneumococcal vaccination. One group consisted of children who had received a chargeable pneumococcal vaccination and the other of those who had received either a free vaccine or none at all. Payments for pneumococcal vaccination are shown in Table 1, and the breakdown of records into groups is shown in in Figure 1.

Table 1. Payments for pneumococcal vaccination.

Vaccine	Until 2016	From 2017
PCV10 [1]	Recommended; chargeable	Mandatory; free of charge
PCV13 [2]	Recommended; chargeable	Recommended; chargeable

[1] PCV10—10-valent conjugate pneumococcal vaccine. [2] PCV13—13-valent conjugate pneumococcal vaccine

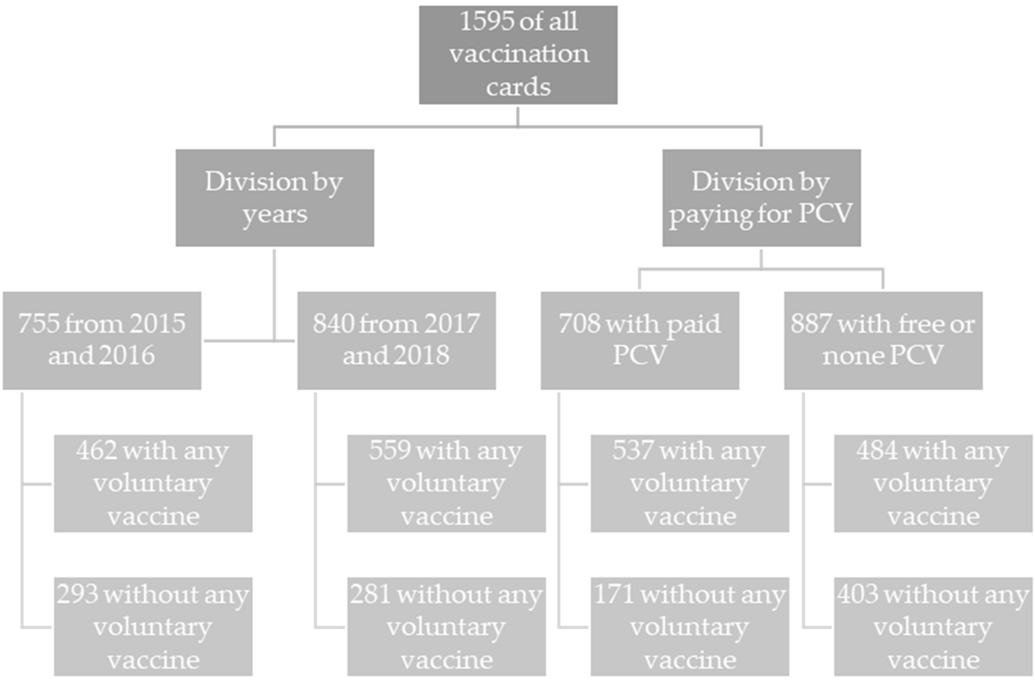

Figure 1. Flowchart of the breakdown of records into groups.

2.4. Used Assumptions

Due to the different intervals between doses of recommended vaccination (if required), the administration of at least one dose of vaccination qualified the patient for the group of children who initiated recommended vaccination. The exception to this was the rotavirus vaccination, as there is a time limit to the completion of the vaccination schedule (32 weeks of age at the latest). In this way, it is possible to assess the willingness of parents to have a particular recommended vaccination.

Patients vaccinated against MenACWY were analyzed together in a group with patients vaccinated against MenC due to the epidemiological predominance of this meningococcal group.

The study was conducted in accordance with the Declaration of Helsinki and received a positive opinion from the Bioethics Committee of the Lower Silesian Medical Chamber. Opinion number 1/PNDR/2023.

2.5. Statistical Methods

The Chi-squared test was used to compare qualitative variables. In addition, a univariate logistic regression analysis was performed, where the dependent variable was the start of the recommended vaccination and the independent variable was the period before and after the introduction of compulsory pneumococcal vaccination in Poland. In the next step, a multivariate logistic regression analysis was performed while additionally taking into account the influence of the child's age and place of residence. Statistical significance was assumed at the level of <0.05 Calculations were performed using Statistica 13 software from TIBCO Software Inc. (Palo Alto, CA, USA).

3. Results

3.1. Characteristics of the Study Group

The database yielded 1595 unique entries from vaccination record cards. Of these, 47.3 percent were children born in 2015–2016 and 52.7 percent were born in 2017–2018. Women constituted 52.2%. Clinics in urban areas accounted for 82.6% of the data. Full socio-demographic data are presented in Table 2.

Table 2. Characteristics of the study group.

Patient		Total Population *N* (%)	2015 and 2016 Age Group *N* (%)	2017 and 2018 Age Group *N* (%)	*p*
Sex	Male	763 (47.8)	387 (46.5)	445 (53.5)	0.525
	Female	832 (52.2)	368 (48.2)	395 (51.8)	
Place	Urban area	1318 (82.6)	630 (47.8)	688 (52.2)	0.417
	Rural area	277 (17.4)	125 (45.1)	152 (54.9)	

3.2. Differences in Recommended Vaccination before and after Introducing Compulsory Pneumococcal Vaccination

Analysis of the results showed that after the introduction of free pneumococcal vaccination, immunization against rotavirus (48.5% vs. 54.4%, $p = 0.018$) and against meningococcal B bacteria (4.8% vs. 17.0%, $p < 0.001$) increased significantly. There was also a difference on the verge of statistical significance for tick-borne encephalitis vaccination (0.8% vs. 1.8%, $p = 0.083$). Furthermore, there was an increase in the proportion of children who received any recommended vaccination (61.2% vs. 66.6%, $p = 0.026$). Detailed data comparing the uptake of recommended vaccinations before and after the introduction of compulsory pneumococcal vaccination are shown in Table 3.

Table 3. Implementation of recommended vaccination before and after the introduction of compulsory pneumococcal vaccination.

Recommended Vaccination		Total Population *N* (%)	2015 and 2016 Age Group *N* (%)	2017 and 2018 Age Group *N* (%)	*p*
5-in-1 or 6-in-1 conjugate vaccines	Yes	1288 (80.8)	608 (80.5)	680 (81.0)	0.831
	No	307 (19.2)	147 (19.5)	160 (19.0)	
Against rotavirus	Yes	823 (51.6)	366 (48.5)	457 (54.4)	0.018
	No	772 (48.4)	389 (51.5)	383 (45.6)	
Against chickenpox	Yes	516 (32.4)	231 (30.6)	285 (33.9)	0.156
	No	1079 (67.6)	524 (69.4)	555 (66.1)	
Against *N. meningitidis* B	Yes	179 (11.2)	36 (4.8)	143 (17.0)	<0.001
	No	1416 (88.8)	719 (95.2)	697 (83.0)	
Against *N. meningitidis* C	Yes	173 (10.8)	82 (10.9)	91 (10.8)	0.986
	No	1422 (89.2)	673 (89.1)	749 (89.2)	
Against tick-borne encephalitis	Yes	21 (1.3)	6 (0.8)	15 (1.8)	0.083
	No	1574 (98.7)	749 (99.2)	825 (98.2)	
Against hepatitis A	Yes	15 (0.9)	8 (1.1)	7 (0.8)	0.640
	No	1580 (99.1)	747 (98.9)	833 (99.2)	
Any recommended vaccinations	Yes	1021 (64.0)	462 (61.2)	559 (66.6)	0.026
	No	574 (36.0)	293 (38.8)	281 (33.5)	

Univariate logistic regression analysis showed that after the introduction of compulsory pneumococcal vaccination, parents were significantly more likely to vaccinate their children against rotavirus and meningococcal B bacteria. Importantly, it also showed that the introduction of compulsory pneumococcal vaccination contributed to an increase in the uptake of recommended vaccination. These observations were also confirmed in a multivariate analysis that took into account the age and sex of the child. The exact results are shown in Table 4 and Figures 2 and 3.

Table 4. Univariate and multivariate logistic regression analysis.

Recommended Vaccinations	Univariate Analysis 2015–2016 vs. 2017–2018		Multivariate Analysis * 2015–2016 vs. 2017–2018	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Conjugate (5-in-1 or 6-in-1) vaccines	1.028 (0.801–1.318)	0.831	1.022 (0.796–1.311)	0.867
Against rotavirus	1.268 (1.041–1.544)	0.018	1.271 (1.044–1.549)	0.017
Against chickenpox	1.165 (0.944–1.438)	0.156	1.166 (0.944–1.439)	0.154
Against *N. meningitidis* B	4.098 (2.802–5.992)	<0.001	4.099 (2.803–5.995)	<0.001
Against *N. meningitidis* C	0.997 (0.727–1.368)	0.986	1.000 (0.728–1.372)	0.998
Against tick-borne encephalitis	2.270 (0.876–5.880)	0.091	2.278 (0.879–5.905)	0.090
Against hepatitis A	0.784 (0.283–2.174)	0.640	0.773 (0.278–2.148)	0.621
Any recommended vaccinations	1.262 (1.028–1.548)	0.026	1.265 (1.030–1.552)	0.025

* age, place of residence.

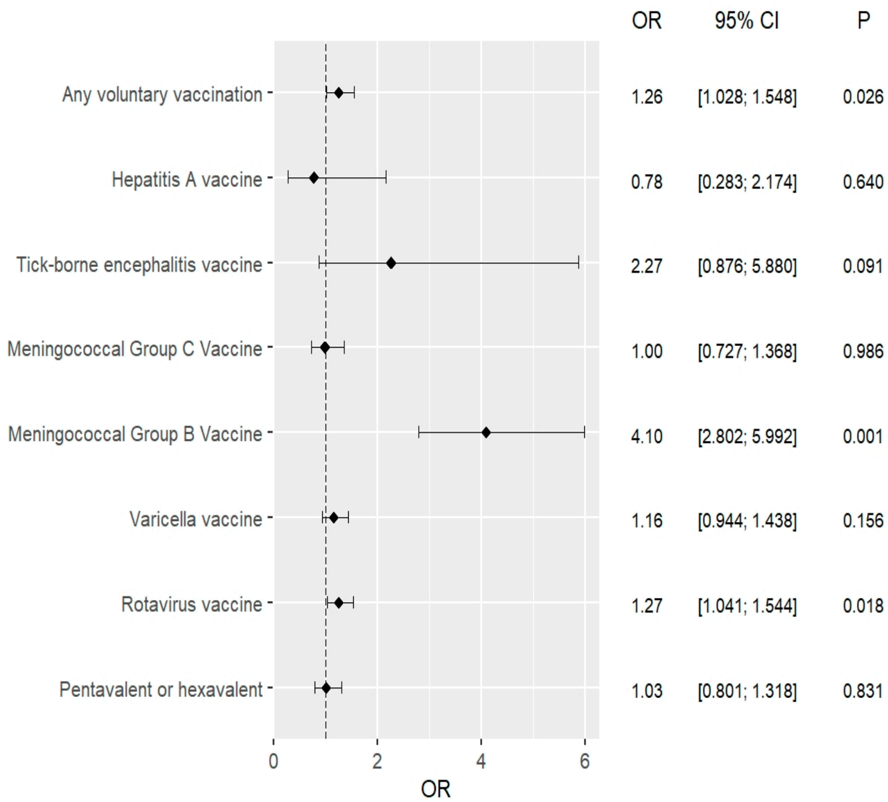

Figure 2. Univariate logistic regression assessing the impact of the introduction of compulsory pneumococcal vaccination in Poland on the performance of individual recommended vaccinations.

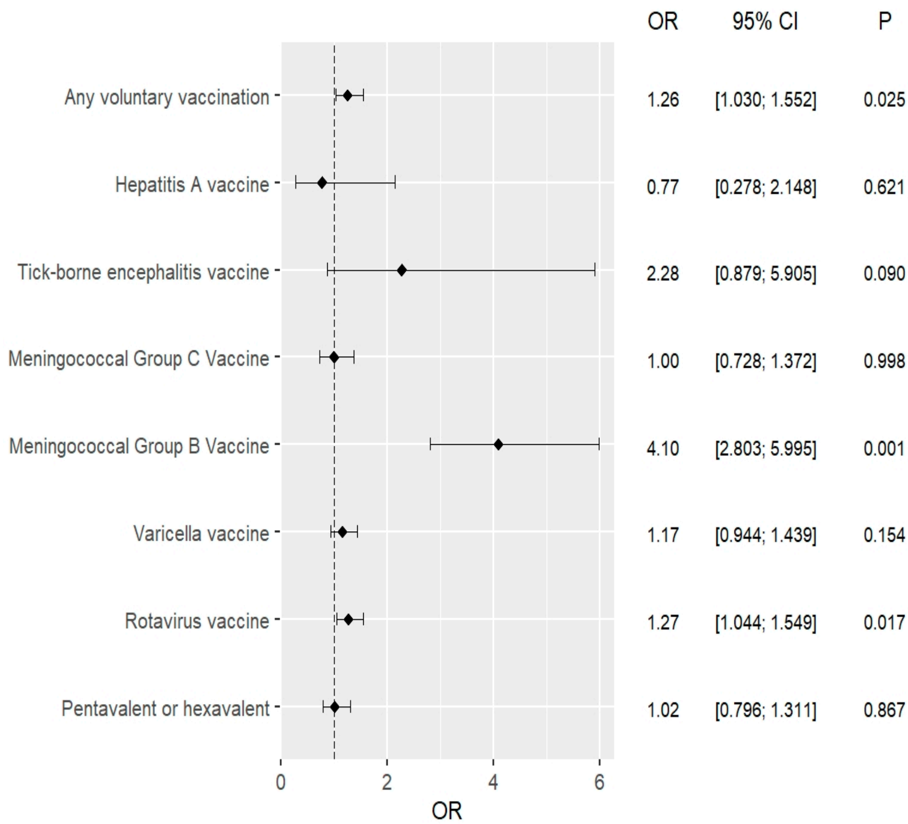

Figure 3. Multivariate logistic regression assessing the impact of the introduction of compulsory pneumococcal vaccination in Poland on the performance of individual recommended vaccinations, taking into account the age and place of residence of the child.

3.3. Differences in Recommended Vaccination Depenging on Vaccination with Chargeable PCV

Interestingly, comparing patients whose parents paid for the pneumococcal vaccination with those who had it free or were not vaccinated at all, it was shown that parents who paid the cost of the pneumococcal vaccination were also more likely to choose either the 5-in-1 or 6-in-1 conjugate vaccines against rotavirus infection, chickenpox, and meningococcal C bacteria ($p < 0.001$). These children were significantly more likely to receive any of the recommended vaccines (54.6% vs. 75.9%). The exact data has been collected in Table 5.

Table 5. Children with recommended vaccination vaccinated with chargeable PCV vs. vaccinated with free PCV or not vaccinated against pneumococcus.

Recommended Vaccination		Total Population *N* (%)	Free PCV or no PCV *N* (%)	Chargeable PVC *N* (%)	*p*
5-in-1 or 6-in-1 conjugate vaccines	Yes	1288 (80.8)	651 (73.4)	637 (90.0)	<0.001
	No	307 (19.2)	236 (26.6)	71 (10.0)	
Against rotavirus	Yes	823 (51.6)	376 (42.4)	447 (63.1)	<0.001
	No	772 (48.4)	511 (57.6)	261 (36.9)	
Against chickenpox	Yes	516 (32.4)	249 (28.1)	267 (37.7)	<0.001
	No	1079 (67.6)	638 (71.9)	441 (62.3)	
Against *N. meningitidis* B	Yes	179 (11.2)	97 (10.9)	82 (11.6)	0.685
	No	1416 (88.8)	790 (89.1)	626 (88.4)	
Against *N. meningitidis* C	Yes	173 (10.8)	63 (7.1)	110 (15.5)	<0.001
	No	1422 (89.2)	824 (92.9)	598 (84.5)	
Against tick-borne encephalitis	Yes	21 (1.3)	11 (1.2)	10 (1.4)	0.764
	No	1574 (98.7)	876 (98.8)	698 (98.6)	
Against hepatitis A	Yes	15 (0.9)	5 (0.6)	10 (1.4)	0.081
	No	1580 (99.1)	882 (99.4)	698 (98.6)	
Any recommended vaccinations	Yes	1021 (64.0)	484 (54.6)	537 (75.9)	<0.001
	No	574 (36.0)	403 (45.4)	171 (24.2)	

4. Discussion

The above study covered approx. 1.5 percent of all children born during the specified time period in the region—755 and 840 records in 2015–2016, and 2017–2018, respectively, out of 54,432 and 55,853 children [20–23]. It was shown that the introduction of compulsory pneumococcal vaccination may have influenced the frequency of recommended vaccination in the subgroup analyzed. First and foremost were vaccinations against meningococcal B bacteria and rotavirus. Notwithstanding the above change, it was observed that parents who opted for paid pneumococcal vaccination were more likely to have the recommended vaccination for their children. In this case, the difference was in conjugate vaccination against rotavirus, chickenpox, and meningococcal C bacteria.

Information on recommended vaccinations is provided to parents at clinic visits. Primarily during preventive appointments, such as patronage visits, health checks, and mandatory vaccination visits. The decision to have the recommended vaccination is entirely voluntary. There are notable benefits of vaccination. In the study group, 64% of the children had at least one recommended vaccination. This means that just over a third of parents stop at mandatory vaccinations only. This raises the question of why they do not want to protect their child against other diseases and what factors influence these decisions.

A Canadian systematic review found that vaccination uptake largely depends on confidence in vaccination and, more broadly, in the healthcare system. Mere knowledge about vaccinations is not a sufficient factor. Socio-economic factors are also linked to the willingness to vaccinate. Nevertheless, research indicates that a sufficiently high level of trust in healthcare professionals is able to offset the impact of these factors [24]. Similar conclusions were reached after a Swiss study in which parents' doubts about vaccination were linked to a lack of trust in healthcare professionals [25]. Determining what is involved in reluctance to vaccinate is very difficult. A systematic review of studies from 2007 to 2012 noted many factors that may be associated with vaccine aversion but did not prove any of them to be universally associated [9]. Moreover, socioeconomic status: both low incomes and high incomes can account for reluctance to vaccinate. Similarly, a high level of education sometimes reinforces the decision to vaccinate and sometimes is a hindrance [26]. A 2015 study in Wrocław, the same city where the presented study was conducted, assessed immunization rates against pneumococcal infections, influenza, and pertussis. The pertussis vaccination was compulsory, and the other two were chargeable. Against pneumococcus, 36.8% of children were vaccinated, and against influenza—8%. Importantly, the authors pointed to the price of pneumococcal vaccination as a factor responsible for low vaccination rates. However, this still did not explain the even lower popularity of the relatively cheap flu vaccine [11]. In the presented study, following the introduction of free pneumococcal vaccination in children, recommended vaccinations were more frequently opted for. The situation was different with regard to vaccination against rotavirus, especially against meningococcal B bacteria. This study showed that the uptake of vaccination against these bacteria increased from 4.8% to 17%, representing a spectacular change. Studies comparing the determinants of pneumococcal and meningococcal vaccination indicate that they are largely similar [27]. Meningococcal B vaccine was placed on the market in 2012 [28] and became realistically available in Poland in 2014 [29]. It should be pointed out that there have been information campaigns on vaccinations in Poland, including against meningococci [30]. The campaign disseminated information about invasive meningococcal disease, its epidemiology, and, above all, vaccination [31]. Research confirms that disseminating information about vaccination improves vaccination uptake [32,33]. The primary objective is to address vaccination against a specific risk (in this case, the disease it protects against) and to dispel doubts that arise among patients [34]. Such campaigns have also been conducted with regard to other vaccinations. Approximately 5 years after the widespread meningococcal group B vaccination campaign, rotavirus vaccination campaigns were launched [35], but the effect was not as spectacular as for meningococci.

Fear of disease is undoubtedly a factor motivating vaccination—if a parent feels that the disease is not too dangerous, they will most probably be reluctant to vaccinate their child [36], or at least they will be willing to spend less on a potential chargeable vaccination [37]. Meanwhile, the 4CMenB vaccine, which is used in Poland, has very high efficacy, with a 79% to 100% reduction in the risk of invasive meningococcal disease compared to unvaccinated patients [38]. In Poland, theoretically, the vaccine should cover 86.6% of circulating group B meningococci. [39]. The effectiveness of the vaccine is also confirmed by the steadily decreasing incidence of invasive meningococcal disease. In 2021, it was 0.28/100,000, in 2017, 0.59, and in 2012, 0.63 [40–42]. For many years in Poland, the majority of cases of invasive meningococcal disease have been caused by type B bacteria [43]. Meningococcal vaccination is recommended for adults and children, with an emphasis on starting vaccination as early as possible, as meningococci are more dangerous the younger a child is [44]. The present study showed that the use of paid pneumococcal vaccination was associated with more frequent vaccination against meningococcal C infection and, more broadly, A, C, W135, and Y infection, as these types were part of the polyvalent vaccine used fairly frequently. In this case, too, vaccination shows effectiveness in preventing meningococcal disease [45].

Naturally, the limiting factor for vaccination is its cost. Sometimes the financial obstacle is insurmountable, and, despite the parents' willingness, the child will not be vaccinated. Several studies have shown that the possibility of free vaccination increases the willingness to vaccinate [46]. Making pneumococcal vaccination free has removed the financial barrier. It is likely that some parents spent the money they would have spent on pneumococcal vaccination on other vaccinations. This study indirectly points to the importance of the financial factor. Parents who purchased the chargeable pneumococcal vaccine were also much more likely to opt for other recommended vaccinations (75.9% vs. 54.6%) compared to those parents who did not opt for the paid pneumococcal vaccine. A Polish study from 2013 found that a high cost of vaccines was associated with a five times lower chance of a child being vaccinated with them [47]. Moreover, if parents opt for chargeable vaccines, they will go for the multivalent variants of the mandatory vaccines first [48].

Among infants born in 2017–2018, more than half were vaccinated against rotavirus. This vaccine has a high efficacy level [49,50]. A factor that works in favor of this vaccination is the oral form of the vaccine. Parents do not have to overcome their child's unwillingness to have an injection. Due to the efficacy and safety, as well as the cost-effectiveness of the vaccination, it was introduced into the Polish mandatory vaccination calendar in 2021 [51]. Of the other recommended vaccinations analyzed, no differences were observed among tick-borne encephalitis or hepatitis A vaccinations. These vaccinations are relatively unpopular, in addition to being possible after the age of one and being non-reimbursable. Only the chickenpox vaccination was received by about a third of children. Chickenpox vaccination, according to other studies, is accepted and even desired by parents, but cost remains the main obstacle to vaccination [52–55].

Despite the strength of the study, the authors are aware of its limitations. Undoubtedly, it should be mentioned that the study group is not representative of children in the Polish population born during this period. Nevertheless, it covers 1.5% of all births in the analyzed region. The study also did not assess parents' opinions on vaccinations or their reasons for not opting for a particular vaccination. Juxtaposing such information with the data obtained from the vaccination record cards would allow the probable causes of the observed changes to be determined with more confidence. The authors believe that there is a need for further research on this topic, particularly on a larger sample of children, taking into account the representativeness of the group for the population of Polish children.

5. Conclusions

The introduction of compulsory pneumococcal vaccination has contributed to an increase in the frequency of opting for recommended vaccinations in the study group. A significant increase in the percentage of children vaccinated against meningococcal type B infections has been observed. This is probably related to the reduction of the economic barrier, which shows that one of the important aspects of the decision to vaccinate may be the economic factor. However, this hypothesis should be verified in further studies aimed at assessing the impact of economic factors on the willingness to vaccinate.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Bioethics Committee of Lower Silesian Medical Chamber. Opinion number 1/PNDR/2023.

Informed Consent Statement: Not applicable.

Data Availability Statement: The heads of the primary care facilities where the data were collected agreed only to the collective presentation of the analysis results without the possibility of publishing the full database.

Conflicts of Interest: The authors declare no conflict of interest.

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12. Załączniki

12.1 Oświadczenia współautorów

Wrocław, 18.12.2023 r.

Lek. Wojciech Malchrzak
Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu
Katedra i Zakład Medycyny Rodzinnej

Oświadczenie

Oświadczam, że w pracy **Malchrzak, W.**; Mastalerz-Migas, A. Epidemiologic Benefits of Pneumococcal Vaccine Introduction into Preventive Vaccination Programs. Advances in Experimental Medicine and Biology. 2021;1324: Medical Research and Innovation:11–19. doi:10.1007/5584_2020_589 mój udział polegał na opracowaniu zakresu badania, przeglądzie literatury, przygotowaniu i korekcie tekstu manuskryptu, a także ostatecznej akceptacji publikacji.

Wojciech Malchrzak
LEKARZ
3558689

Oświadczam, że w pracy **Malchrzak, W.**; Babicki, M.; Mastalerz-Migas, A. Vaccination against Streptococcus Pneumoniae in Children Born between 2015 and 2018 in Poland—How Has the Introduction of Free Compulsory Pneumococcal Vaccination Affected Its Uptake? Vaccines 2023, 11, 1654, doi:https://doi.org/10.3390/vaccines11111654 mój udział polegał na konceptualizacji, opracowaniu metodologii, zebraniu danych, analizie i interpretacji danych, przygotowaniu i korekcie tekstu manuskryptu, a także ostatecznej akceptacji publikacji.

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Oświadczenie

Oświadczam, że w pracy Malchrzak, W.; **Mastalerz-Migas, A.** Epidemiologic Benefits of Pneumococcal Vaccine Introduction into Preventive Vaccination Programs. Advances in Experimental Medicine and Biology. 2021;1324: Medical Research and Innovation:11–19. doi:10.1007/5584_2020_589 mój udział polegał na współpracy przy opracowaniu zakresu badania, korekcie tekstu manuskryptu, a także ostatecznej akceptacji publikacji.

Oświadczam, że w pracy Malchrzak, W.; Babicki, M.; **Mastalerz-Migas, A.** Vaccination against Streptococcus Pneumoniae in Children Born between 2015 and 2018 in Poland—How Has the Introduction of Free Compulsory Pneumococcal Vaccination Affected Its Uptake? Vaccines 2023, 11, 1654, doi:https://doi.org/10.3390/vaccines11111654 mój udział polegał na konceptualizacji, współpracy przy opracowaniu metodologii, korekcie tekstu manuskryptu, pozyskaniu funduszy, a także ostatecznej akceptacji publikacji.

Oświadczam, że w pracy Malchrzak, W.; Babicki, M.; Pokorna-Kałwak, D.; **Mastalerz-Migas, A.** The Influence of Introducing Free Vaccination against Streptococcus Pneumoniae on the Uptake of Recommended Vaccination in Poland. Vaccines 2023, 11, 1838, doi:https://doi.org/10.3390/vaccines11121838 mój udział polegał na konceptualizacji, współpracy przy opracowaniu metodologii, korekcie tekstu manuskryptu, pozyskaniu funduszy, a także ostatecznej akceptacji publikacji.

Uniwersytet Medyczny we Wrocławiu
KATEDRA I ZAKŁAD MEDYCYNY RODZINNEJ
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dr hab. n. med. Agnieszka Mastalerz-Migas

Wrocław, 18.12.2023 r.

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Katedra i Zakład Medycyny Rodzinnej

Oświadczenie

Oświadczam, że w pracy Malchrzak, W.; **Babicki, M.**; Mastalerz-Migas, A. Vaccination against Streptococcus Pneumoniae in Children Born between 2015 and 2018 in Poland—How Has the Introduction of Free Compulsory Pneumococcal Vaccination Affected Its Uptake? Vaccines 2023, 11, 1654, doi:https://doi.org/10.3390/vaccines11111654 mój udział polegał na analizie i interpretacji danych, przygotowaniu obliczeń statystycznych, korekcie tekstu manuskryptu, a także ostatecznej akceptacji publikacji.

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3439559

Oświadczam, że w pracy Malchrzak, W.; **Babicki, M.**; Pokorna-Kałwak, D.; Mastalerz-Migas, A. The Influence of Introducing Free Vaccination against Streptococcus Pneumoniae on the Uptake of Recommended Vaccination in Poland. Vaccines 2023, 11, 1838, doi:https://doi.org/10.3390/vaccines11121838 mój udział polegał na analizie i interpretacji danych, przygotowaniu obliczeń statystycznych, korekcie tekstu manuskryptu, a także ostatecznej akceptacji publikacji.

Mateusz Babicki
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Katedra i Zakład Medycyny Rodzinnej

Oświadczenie

Oświadczam, że w pracy Malchrzak, W.; Babicki, M.; **Pokorna-Kałwak, D.**; Mastalerz-Migas, A. The Influence of Introducing Free Vaccination against Streptococcus Pneumoniae on the Uptake of Recommended Vaccination in Poland. Vaccines 2023, 11, 1838, doi:https://doi.org/10.3390/vaccines11121838 mój udział polegał współpracy przy interpretacji danych, korekcie manuskryptu, a także ostatecznej akceptacji publikacji.

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Uniwersytet Medyczny we Wrocławiu
KATEDRA I ZAKŁAD MEDYCYNY RODZINNEJ
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12.2 Nota biograficzna autora

Wojciech Malchrzak urodził się 6 czerwca 1994 roku w Rawiczu. Ukończył z wyróżnieniem w 2019 r. kierunek lekarski na Uniwersytecie Medycznym im. Piastów Śląskich we Wrocławiu, a od października 2019 r. jest uczestnikiem Szkoły Doktorskiej na tymże Uniwersytecie. Pracuje także na stanowisku asystenta w Katedrze i Zakładzie Medycyny Rodzinnej.

W listopadzie 2020 r. rozpoczął szkolenie specjalizacyjne w trybie rezydentury z medycyny rodzinnej w Centrum Medycznym AD-MED przy ul. Zakładowej 18F we Wrocławiu. Jest członkiem Polskiego Towarzystwa Medycyny Rodzinnej – pełni funkcję przewodniczącego sekcji Młodych Lekarzy Rodzinnych. Członek Polskiego Towarzystwa Wakcynologii oraz Polskiego Towarzystwa Leczenia Otyłości. Angażuje się w działalność edukacyjną i szkoleniową lekarzy rodzinnych. Jego główne zainteresowania to infekcje i metody ich profilaktyki oraz leczenie i zapobieganie chorobom cywilizacyjnym. Jest autorem lub współautorem 14 publikacji naukowych (w tym 8 posiadających Impact Factor) oraz 3 doniesień zjazdowych.

12.3 Wykaz dotychczasowych osiągnięć autora

12.3.1. Publikacje w czasopismach naukowych

12.3.1.1 Publikacje w czasopiśmie z IF

Lp.	Opis bibliograficzny	IF	Punkty
1	**Malchrzak Wojciech**, Mastalerz-Migas Agnieszka: Epidemiologic benefits of pneumococcal vaccine introduction into preventive vaccination programs, Advances in Experimental Medicine and Biology, 2021, vol. 1324: Medical Research and Innovation, s. 11-19, [Publikacja w serii wydawnictwa Springer], DOI:10.1007/5584_2020_589	3,65	20
2	**Malchrzak Wojciech**, Mastalerz-Migas Agnieszka, Sroka Zbigniew, Spiegel Maciej: One year of the COVID-19 pandemic. What do we know and what is yet to come? - the summarising review, International Journal of Public Health, 2021, vol. 66, art.1603975 [10 s.], DOI:10.3389/ijph.2021.1603975	5,1	100
3	Babicki Mateusz, **Malchrzak Wojciech**, Hans-Wytrychowska Anna, Mastalerz-Migas Agnieszka: Impact of vaccination on the sense of security, the anxiety of COVID-19 and quality of life among Polish. A nationwide online survey in Poland, Vaccines, 2021, vol. 9, nr 12, art.1444 [14 s.], DOI:10.3390/vaccines9121444	4,961	140
4	Babicki Mateusz, **Malchrzak Wojciech**, Mastalerz-Migas Agnieszka: Assessment of attitudes, main concerns and sources of knowledge regarding COVID-19 vaccination in Poland in the unvaccinated individuals - a nationwide survey, Vaccines, 2022, vol. 10, nr 3, art.381 [17 s.], DOI:10.3390/vaccines10030381	7,8	140
5	**Malchrzak Wojciech**, Babicki Mateusz, Pokorna-Kałwak Dagmara, Doniec Zbigniew, Mastalerz-Migas Agnieszka: COVID-19 vaccination and Ukrainian refugees in Poland during Russian-Ukrainian war - narrative review, Vaccines, 2022, vol. 10, nr 6, art.955 [7 s.], DOI:10.3390/vaccines10060955	7,8	140
6	**Malchrzak Wojciech**, Babicki Mateusz, Mastalerz-Migas Agnieszka: Vaccination against Streptococcus pneumoniae in children born between 2015 and 2018 in Poland - how has the introduction of free compulsory pneumococcal vaccination affected its uptake?, Vaccines, 2023, vol. 11, nr 11, art.1654 [13 s.], DOI:10.3390/vaccines11111654	7,8*	140

7	**Malchrzak Wojciech**, Babicki Mateusz, Pokorna-Kałwak Dagmara, Mastalerz-Migas Agnieszka: The influence of introducing free vaccination against Streptococcus pneumoniae on the uptake of recommended vaccination in Poland, Vaccines, 2023, vol. 11, nr 12, art.1838 [12 s.], DOI:10.3390/vaccines11121838	7,8*	140
8	Jan Lubomski, **Wojciech Malchrzak**, Mateusz Babicki, Karolina Kłoda, Szymon Suwała, and Agnieszka Mastalerz-Migas. Teleconsultation as a Modern Form of Health Care Service in the Case of Poland: Assessment of Its Potential Use from the Perspective of Health Care Providers and Patients. Telemedicine and e-Health. doi.org/10.1089/tmj.2023.0204 Online Ahead of Print:July 5, 2023	4,7	70
	Podsumowanie	49,611	890

**IF 2022*

12.3.1.2 Publikacje w czasopiśmie bez IF

Lp.	Opis bibliograficzny	Punkty
1	Zdrojewicz Zygmunt, Głośna Martyna, **Malchrzak Wojciech**: Jedz dynię, będziesz zdrowszy, Academy of Aesthetic and Anti-Aging Medicine, 2018, nr 1, s. 73-78	2
2	**Malchrzak Wojciech**, Rymer Weronika, Inglot Małgorzata: Imported malaria caused by Plasmodium falciparum - case report = Zawleczona malaria wywołana przez Plasmodium falciparum - opis przypadku, Przegląd Epidemiologiczny, 2018, vol. 72, nr 3, s. 363-370, DOI:10.32394/pe.72.3.12	12
3	Głośna Martyna, **Malchrzak Wojciech**, Zdrojewicz Zygmunt: Rola żywienia w płodności mężczyzn, Academy of Aesthetic and Anti-Aging Medicine, 2019, nr 2, s. 68-71, [Publikacja w czasopiśmie spoza listy MNiSW]	5
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	Podsumowanie	34

12.3.2. Abstrakty

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