Lek. Tomasz Ginda

Czy wewnątrzmaciczna ekspozycja płodu na leki immunosupresyjne stosowane w czasie ciąży przez kobiety po transplantacji narządu ma wpływ na miana przeciwciał odpornościowych przeciwko chorobom zakaźnym u dzieci w obserwacji długoterminowej w porównaniu do populacji ogólnej?

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

Promotor: prof. dr hab. n. med. Bożena Kociszewska-Najman

Klinika Neonatologii i Chorób Rzadkich

Obrona rozprawy doktorskiej przed Radą Dyscypliny Nauk Medycznych

Warszawskiego Uniwersytetu Medycznego

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Słowa kluczowe: *Szczepienia, transplantacja, immunosupresja, choroby wirusowe, choroby bakteryjne, immunogenność, leki immunosupresyjne w ciąży, bezpieczeństwo szczepień, szczepionki wirusowe, szczepionki bakteryjne, dzieci*

Keywords: *Vaccination, transplantation, immunosuppression, viral diseases, bacterial diseases, immunogenicity, immunosuppressive drugs in pregnancy, safety of vaccination, anti-viral vaccination, anti-bacterial vaccination, children*

Rozprawę doktorską dedykuję swoim rodzicom i przyjaciołom, którzy we mnie wierzyli i wspierali w dążeniu do celu. Dziękuję wszystkim, którzy w różny sposób przyczynili się do powstania tej pracy.

W szczególności chciałbym podziękować Pani Promotor Prof. dr hab. n. med. Bożenie Kociszewskiej-Najman i przyjacielowi dr n. med. Karolowi Taradajowi.

2. Wykaz publikacji stanowiących pracę doktorską

I. **Ginda Tomasz**, Taradaj Karol, Kociszewska-Najman Bożena. *The influence of selected factors on the immunogenicity of preventive vaccinations against hepatitis A, B and influenza in solid organ transplant recipients undergoing immunosuppressive therapy - a review.* Expert Rev Vaccines. 2022 Apr;21(4):483-497.
doi:10.1080/14760584.2022.2027241. Epub 2022 Jan 17
Liczba punktów MEiN: 100
Czasopismo wpisane na Listę Filadelfijską, IF = 6,2

II. **Ginda Tomasz**, Taradaj Karol, Stelmaszczyk-Emmel Anna, Tronina Olga, Kociołek Patrycja, Jendro Oliver, Kociszewska-Najman Bożena. *Does Intrauterine Exposure of the Foetus to Immunosuppressive Drugs Used by the Mother-The Organ Recipient-Affect the Development of Post-Vaccination Immunity against Selected Viral Diseases in Children of These Mothers in Postnatal Life?* Vaccines (Basel). 2023 Mar 27;11(4):738.
doi: 10.3390/vaccines11040738.
Liczba punktów MEiN: 140
Czasopismo wpisane na Listę Filadelfijską, IF = 5,2

III. **Ginda Tomasz**, Taradaj Karol, Tronina Olga, Stelmaszczyk-Emmel Anna, Kociszewska-Najman Bożena. *Evaluation of the Development of Post-Vaccination Immunity against Selected Bacterial Diseases in Children of Post-Solid-Organ-Transplant Mothers.* Vaccines (Basel). 2024 May 22;12(6):565.
doi: 10.3390/vaccines12060565.
Liczba punktów MEiN: 140
Czasopismo wpisane na Listę Filadelfijską, IF = 5,2

Impact Factor cyklu prac:	**Liczba punktów MEiN cyklu prac:**
16,6	**380**

Spis treści

3. Wykaz stosowanych skrótów

- **AEFI** – *Adverse Event Following Immunization* (niepożądany odczyn poszczepienny)
- **BCG** – *Bacillus Calmette-Guérin* (szczepionka przeciw gruźlicy)
- **ELISA** – *Enzyme-Linked Immunosorbent Assay* (test immunoenzymatyczny)
- **HAV** – *Hepatitis A Virus* (wirus zapalenia wątroby typu A)
- **HBV** – *Hepatitis B Virus* (wirus zapalenia wątroby typu B)
- **Hib** – *Haemophilus influenzae* typu B
- **IF** – *Impact Factor* (wskaźnik cytowalności czasopisma)
- **IgG** – Immunoglobulina klasy G
- **IgE** – Immunoglobulina klasy E
- **MMF** – Mykofenolan mofetylu (lek immunosupresyjny)
- **MPL** – Monofosforylowany lipid A (adjuwant szczepionkowy)
- **PSO** – Program Szczepień Ochronnych
- **QoL** – *Quality of Life* (jakość życia)
- **SR** – *Seroconversion rate* - Współczynnik serokonwersji
- **WUM** – Warszawski Uniwersytet Medyczny
- **WZW A** – Wirusowe zapalenie wątroby typu A
- **WZW B** – Wirusowe zapalenie wątroby typu B

4. Streszczenie

Dysertacja doktorska porusza ważne klinicznie zagadnienie zdrowia dzieci matek po transplantacji narządu. Pomimo co raz liczniejszych publikacji oceniających różne aspekty wpływu immunosupresji *in utero* na rozwój dzieci matek biorczyń, szczegółowa tematyka będąca podstawą rozprawy do chwili obecnej nie była przedmiotem szerszych analiz. Celem niniejszej rozprawy doktorskiej było określenie, czy wewnątrzmaciczna ekspozycja płodu na leki immunosupresyjne stosowane przez kobiety po transplantacji narządu wpływa na immunogenność szczepień ochronnych u ich dzieci w obserwacji długoterminowej. W ramach pracy dokonano przeglądu dostępnej literatury (publikacja 1) oraz przeprowadzono badania oryginalne (publikacje 2 i 3), oceniające odpowiedź poszczepienną przeciwko wybranym wirusowym i bakteryjnym patogenom wieku dziecięcego w grupie dzieci matek-biorczyń wątroby lub nerki.

W badaniach oceniono stężenia przeciwciał poszczepiennych klasy IgG przeciwko wirusom WZW A, WZW B, odrze, polio oraz przeciwko bakteriom: *Mycobacterium tuberculosis, Haemophilus influenzae typu B, Streptococcus pneumoniae, Clostridium tetani, Bordetella pertussis i Corynebacterium diphtheriae*. Grupa badawcza obejmowała dzieci matek po przeszczepieniu narządu, a wyniki zostały porównane z grupą kontrolną dobraną pod względem wieku i płci z ogólnej populacji pediatrycznej. Do oceny stężeń przeciwciał użyto metody ELISA.

Przeprowadzona analiza statystyczna wykazała brak istotnych różnic w immunogenności większości szczepień pomiędzy badanymi grupami. Nie stwierdzono wpływu rodzaju przeszczepionego narządu (nerka *vs.* wątroba) na odpowiedź poszczepienną dzieci. Wyjątkiem było wyższe miano przeciwciał przeciwko BCG u dzieci matek po przeszczepieniu nerki, jednak przyczyna tej zależności pozostaje niejasna i wymaga dalszych badań. Nie obserwowano zwiększonej częstości wystąpienia niepożądanych odczynów poszczepiennych w badanej grupie, co potwierdza bezpieczeństwo stosowanych szczepień.

Uzyskane wyniki sugerują, że aktualnie obowiązujący program szczepień ochronnych jest odpowiedni również dla dzieci kobiet po transplantacji narządu, bez potrzeby jego modyfikacji. W szczególności należy podkreślić, że szczepienia w tej grupie są nie tylko skuteczne, ale również bezpieczne – odsetek niepożądanych odczynów poszczepiennych nie różnił się od obserwowanego w ogólnej populacji pediatrycznej. Brak istotnych odchyleń w odpowiedzi immunologicznej dzieci eksponowanych prenatalnie na immunosupresję stanowi ważny argument na rzecz kontynuowania szczepień zgodnie z obowiązującym dla populacji

ogólnej schematem. Wyniki mogą mieć istotne znaczenie praktyczne, zarówno dla klinicystów, jak i dla decydentów zdrowia publicznego, ponieważ wzmacniają zaufanie do profilaktyki szczepiennej w populacji niemowląt i dzieci szczególnego ryzyka.

5. Abstract

This doctoral dissertation addresses a clinically significant issue concerning the health of children born to mothers who have undergone organ transplantation. Despite an increasing number of publications examining various aspects of in utero exposure to immunosuppressive agents and its impact on the development of children born to transplant recipients, the specific subject of this dissertation has not yet been the focus of in-depth analysis. The aim of this study was to determine whether fetal exposure to immunosuppressive medications administered to women after organ transplantation affects the long-term immunogenicity of routine childhood vaccinations in their offspring.

The research involved a review of the existing literature (Publication 1) as well as original studies (Publications 2 and 3), which assessed post-vaccination immune responses to selected viral and bacterial pathogens common in childhood. These analyses were conducted in a cohort of children born to liver or kidney transplant recipients.

The studies evaluated IgG antibody concentrations following immunization against the following pathogens: hepatitis A virus (HAV), hepatitis B virus (HBV), measles virus, poliovirus, and the bacteria Mycobacterium tuberculosis, Haemophilus influenzae type b, Streptococcus pneumoniae, Clostridium tetani, Bordetella pertussis, and Corynebacterium diphtheriae. The study group included children of organ transplant recipients, and results were compared with an age- and sex-matched control group drawn from the general pediatric population. The enzyme-linked immunosorbent assay (ELISA) method was used for antibody measurement.

Statistical analysis revealed no significant differences in vaccine immunogenicity for most of the antigens tested between the study and control groups. The type of transplanted organ (kidney vs. liver) did not influence the children's immune response to vaccination. An exception was a higher antibody titer against BCG in children of kidney recipients; however, the underlying cause of this finding remains unclear and warrants further investigation. No increased incidence of adverse vaccine reactions was observed in the study group, supporting the safety of vaccinations administered to this population.

The findings suggest that the current national immunization schedule is appropriate for children born to organ transplant recipients and does not require modification. Importantly, the results underscore that vaccinations in this group are not only effective but also safe—the incidence of adverse post-vaccination reactions did not differ from that in the general

pediatric population. The absence of significant deviations in immune responses among children prenatally exposed to immunosuppression provides strong support for adhering to the standard vaccination regimen. The results may have important practical implications for both clinicians and public health decision-makers, as they strengthen confidence in vaccine prophylaxis in populations of infants and children at particular risk.

6. Wstęp

Transplantologia jest jedną z najdynamiczniej rozwijających gałęzi medycyny. Postęp tej dziedziny jaki miał miejsce w ostatnich latach doprowadził do znacznego wydłużenia się wieku przeżywania pacjentów poddanych tej procedurze z powodu schyłkowej niewydolności wątroby lub nerek. Opieka potransplantacyjna skupiona jest w głównej mierze na utrzymaniu funkcji graftu oraz ograniczeniu powikłań związanych z koniecznością stosowania leczenia immunosupresyjnego. Cel ten realizowany jest m.in. poprzez dobór optymalnego schematu terapii immunosupresyjnej. Specjaliści transplantologii coraz częściej zwracają uwagę na konieczność prowadzenia holistycznej opieki nad pacjentami po przeszczepieniu narządu. Oprócz ciągłej dbałości o odpowiednią funkcję narządu przeszczepionego istotnym elementem leczenia jest zapewnienie odpowiedniej jakości życia biorców (*Quality of Life - QoL*). Ogół tych działań sprawia, że opieka potransplantacyjna stała się obecnie dziedziną interdyscyplinarną, w której rozwój zaangażowani są specjaliści z różnych dziedzin medycyny. Ważnym aspektem wpływającym na jakość życia jest m.in. zdolność do rozrodczości i realizacja planu posiadania potomstwa, która w przeszłości była ograniczona u biorczyń narządu z uwagi na niedostateczną wiedzę dotyczącą wpływu immunosupresji na rozwój pre- i postnatalny. Obecnie wiadomo, że stosowanie immunosupresji w ciąży jest związane z wyższym odsetkiem powikłań położniczych, w tym wcześniactwa czy małej masy urodzeniowej. Ciąże pacjentek po przeszczepieniu narządu prowadzone są w ośrodkach referencyjnych posiadających odpowiednie doświadczenie w tym zakresie. Fakt ekspozycji płodu na leki immuosupresyjne stosowane przez matkę celem utrzymania funkcji graftu wymusza konieczność objęcia tej grupy dzieci wnikliwym nadzorem. Jak wynika z dotychczas przeprowadzonych badań, nie obserwuje się istotnych odstępstw w rozwoju dzieci matek biorczyń w porównaniu z ogólną populacją pediatryczną. Narażenie na działanie leków immunosupresyjnych w trakcie życia płodowego ma wpływ na odmienne kształtowanie się układu immunologicznego. Autorzy nielicznych dostępnych w literaturze badań obserwowali zmniejszony odsetek limfocytów T i B oraz immoglobulin IgE u dzieci matek biorczyń w pierwszych miesiącach życia w porównaniu do populacji ogólnej dzieci nienarażonych na ekspozycję na leki immunosupresyjne *in-utero*. W dalszej 12-miesięcznej obserwacji różnic tych już nie stwierdzano. Przytoczone wnioski sugerują, że leki immunosupresyjne powodują supresję układu odpornościowego dzieci w pierwszym roku życia. Badania były prowadzone na niewielkich populacjach. Z tego powodu istnieje potrzeba długoterminowej obserwacji funkcji układu odpornościowego w tej szczególnej grupie pacjentów.

Jedną z wykładni prawidłowo funkcjonującego układu immunologicznego jest zdolność organizmu do przeciwdziałania rozwojowi infekcji. Cel ten wspomagany jest m.in. poprzez wytworzenie sztucznej czynnej odpowiedzi przeciwko patogenom bakteryjnym i wirusowym w następstwie stosowania szczepień ochronnych. Wspomniana wcześniej dysregulacja układu odpornościowego w pierwszym okresie życia postnatalnego oraz brak dostępnej wiedzy dotyczącej długofalowych następstw ekspozycji prenatalnej na leki immunosupresyjnej pozostawia otwarte pytanie na temat kształtowania się funkcji układu immunologicznego w późniejszych latach życia. Istotna rola jaką dla zdrowia dziecka odgrywa adekwatna odpowiedź poszczepienna skłoniła autora dysertacji do podjęcia inicjatywy badawczej mającej na celu ocenę immunogenności szczepień ochronnych przeciwko wybranym, istotnym klinicznie chorobom zakaźnym wieku dziecięcego w szczególnej grupie pacjentów jaką stanowią dzieci matek po transplantacji narządów.

7. Uzasadnienie połączenia publikacji w cykl

Rozprawa doktorska składa się ze zbioru trzech powiązanych tematycznie publikacji. W skład cyklu wchodzą: jedna praca poglądowa i dwie prace oryginalne. Założono, że pierwsza z prac będących przedmiotem rozprawy doktorskiej ma stanowić analizę aktualnego stanu wiedzy dotyczącego badanego zagadnienia, umożliwiając szersze zrozumienie tematu i merytoryczne przygotowanie doktoranta do podjęcia inicjatywy badawczej. Nowatorski charakter projektu sprawia, że w momencie przygotowywania projektu badawczego w bazach publikacji medycznych nie były dostępne wyniki badań oceniających immunogenność szczepień w grupie dzieci matek po transplantacji narządów litych. Tym samym podjęto decyzję o rozszerzeniu analizy literatury o prace oceniające możliwy wpływ leków immunosupresyjnych na immunogenność szczepień ochronnych oraz próby identyfikacji modyfikowalnych czynników, mogących poprawić immunogenność szczepień w grupie pacjentów stosujących przewlekłą immunosupresję z powodu transplantacji narządu litego. Uzyskane wnioski pozwoliły na przemyślane i ustrukturyzowane przygotowanie projektu badań własnych, którego efektem są dwie prace oryginalne dopełniające niniejszy cykl. W pracach oceniano immunogenność szczepień ochronnych przeciwko wybranym, istotnym klinicznie patogenom bakteryjnym i wirusowym wywołującym choroby zakaźne wieku dziecięcego. W każdej z prac grupa badawcza została porównana do grupy kontrolnej z ogólnej populacji pediatrycznej. Ze względu na odmienną etiopatogenezę chorób zakaźnych (czynniki bakteryjne i wirusowe) wyniki przedstawiono w dwóch odrębnych publikacjach, których konkluzje przedstawiono w podrozdziałach 7.2 oraz 7.3. Artykuły wchodzące w skład cyklu publikacji zostały opublikowane w czasopismach, znajdujących się na Liście Filadelfijskiej z wysokim wskaźnikiem oddziaływania IF. Doktorant pozostaje pierwszym autorem w każdej z trzech publikacji. Zbiór opublikowanych artykułów stanowi spójną całość spełniającą ideę szczegółowej analizy zagadnienia odpowiedzi poszczepiennej u dzieci matek po transplantacji narządów litych.

7.1 Publikacja 1. pt. *The influence of selected factors on the immunogenicity of preventive vaccinations against hepatitis A, B and influenza in solid organ transplant recipients undergoing immunosuppressive therapy - a review.*

Publikacja nr 1. to obszerny przegląd dotychczas opublikowanych badań analizujących wpływ wybranych czynników na immunogenność szczepień ochronnych u pacjentów po transplantacji narządu litego stosujących przewlekłe leczenie immunosupresyjne. Analizą objęto prace oryginalne i meta-analizy dostępne w bazach PubMed i Embase opublikowane w latach 1999 – 2021. Do przeglądu włączono publikacje oceniające immunogenność szczepień przeciwko grypie, HAV, HBV u pacjentów po przeszczepieniu wątroby, nerki i płuc, stosujących różne schematy immunosupresji. Bazując na dostępnej literaturze oceniano wpływ takich czynników jak:

- Schematy zawierające większą liczbę dawek szczepionki
- Szczepionki zawierające adjuwanty
- Alternatywne drogi podania
- Większe dawki jednostkowe szczepionki

Jak wynika z przeprowadzonej analizy piśmiennictwa, wpływ przewlekłej terapii immunosupresyjnej na efektywność szczepień ochronnych w tej grupie pacjentów nie został dogłębnie zbadany. Cytowane prace obejmują względnie nieliczne grupy pacjentów, a różnorodna metodyka badawcza zastosowana w poszczególnych pracach nie pozwala na przeprowadzenie meta-analizy. Z tego powodu jako formę analizy piśmiennictwa, mającą na celu zapoznanie się z zagadnieniem będącym przedmiotem dysertacji posłużono się przeglądem literatury.

Pomimo rozbieżności metodologicznych poszczególnych autorów, wyniki analizowanych prac jednoznacznie wskazują na gorszą odpowiedź poszczepienną u pacjentów stosujących immunosupresję po transplantacji narządów w porównaniu z populacją ogólną. Modyfikacja schematów szczepień może zwiększyć współczynnik serokonwersji (*Seroconversion rate – SR)* u pacjentów po transplantacji. Działaniem obarczonym najmniejszym ryzykiem w połączeniu z korzystnym efektem wzrostu SR wydaje się być zastosowanie dodatkowych dawek lub zwiększenie dawek jednostkowych szczepionek przeciwko grypie, WZW A i WZW B.

Kolejnym z analizowanych czynników mogącym zwiększać immunogenność szczepień u chorych po transplantacji jest stosowanie preparatów szczepionek zawierających adjuwanty. Postuluje się, że ich działanie opierające się na indukcji miejscowego odczynu zapalnego po podaniu szczepionki, może powodować intensyfikacje migracji leukocytów, wzmacniając odpowiedź humoralną. Wykazano pozytywny wpływ stosowania adjuwantu MF-59 (w przypadku szczepień przeciwko wirusowi grypy) i MPL *(monophosphoryl lipid A)* w przypadku szczepień przeciwko WZW B na współczynnik serokonwersji.

Niektórzy badacze analizowali wpływ śródskórnej drogi podania szczepionki jako alternatywy dla iniekcji domięśniowej na immunogenność szczepień. Badania te prowadzono dla szczepień przeciwko grypie i HBV. W obu przypadkach nie wykazano jednoznacznej przewagi śródskórnej drogi podania preparatu w porównaniu do standardowego postępowania.

Mnogość schematów immunosupresji stosowanych w opiece potransplantacyjnej utrudnia porównanie wyników badań poszczególnych autorów, jak również określenie wpływu poszczególnych leków immunosupresyjnych na immunogenność szczepień ochronnych. Jednakże wyniki pojedynczych badań wskazują mykofenolan mofetylu *(Mycophenolate mofetil - MMF)* jako lek obniżający SR w przypadku szczepień przeciwko grypie i WZW A. Jednocześnie nie określono wpływu pozostałych, powszechnie stosowanych w opiece potransplantacyjnej leków na utrzymanie się odpowiedzi poszczepiennej, co wymaga dalszych badań.

Przeprowadzona analiza piśmiennictwa pozwoliła na szersze zapoznanie się z zagadnieniem wpływu terapii immunosupresyjnej na immunogenność szczepień ochronnych. Poznanie aktualnego stanu wiedzy i wyników dotychczas przeprowadzonych badań umożliwiło rzetelne zaplanowanie i przygotowanie projektu badawczego, którego wyniki zostały opublikowane w publikacjach nr 2 i 3.

7.2 Publikacja 2. pt. ***Does Intrauterine Exposure of the Foetus to Immunosuppressive Drugs Used by the Mother-The Organ Recipient-Affect the Development of Post-Vaccination Immunity against Selected Viral Diseases in Children of These Mothers in Postnatal Life?***

Publikacja nr 2 przedstawia wyniki własnych badań przeprowadzonych na populacji dzieci matek po transplantacji narządu litego. Oceniano stężenia przeciwciał poszczepiennych przeciwko chorobom wywołanych przez patogeny wirusowe: WZW A, WZW B, wirus odry, wirus polio. Grupa badawcza składała się z 9 dzieci matek po transplantacji wątroby i 9 dzieci matek po transplantacji nerki w wieku 6-16 lat. Pacjenci rekrutowani byli spośród dzieci kobiet będących pod opieką poradni działającej przy Klinice Transplantologii, Immunologii, Nefrologii i Chorób Wewnętrznych WUM. Grupę kontrolną stanowiło 21 dzieci dobranych względem wieku i płci, rekrutowanych z ogólnej populacji pediatrycznej. Oceniano stężenia przeciwciał poszczepiennych w klasie IgG: anti-HBsAg IgG, anti-measles IgG, anti-poliomyelitis 1-3 IgG. Miana przeciwciał oceniano metodą Elisa.

Nie zaobserwowano różnic w immunogenności szczepień przeciwko wirusowemu zapaleniu wątroby typu B, polio i odrze między dziećmi matek po przeszczepieniu wątroby lub nerki a dziećmi z populacji ogólnej. Na podstawie badania nie stwierdzono różnic w immunogenności szczepień u dziecka w zależności od rodzaju przeszczepionego narządu u matki. Z przeprowadzonej analizy wynika, że szczepienie dzieci matek biorczyń jest bezpieczne, a odsetek niepożądanych zdarzeń poszczepiennych nie różni się od populacji ogólnej. Uzyskane wyniki nie wskazały na potrzebę modyfikacji programu szczepień przeciwko HBV, odrze i polio w tej grupie pacjentów. Ze względu na mnogość stosowanych schematów immunosupresji oraz małą liczebność grup uwarunkowaną szczególną i trudno dostępną populacją jaką są dzieci matek po transplantacji narządu – w pracy nie porównano wpływu poszczególnych schematów immunosupresji na miana przeciwciał odpornościowych.

Kontynuacją badań była analiza mian przeciwciał przeciwko patogenom bakteryjnym na tożsamej grupie pacjentów, będąca przedmiotem publikacji nr 3.

7.3 Publikacja 3. pt. *Evaluation of the Development of Post-Vaccination Immunity against Selected Bacterial Diseases in Children of Post-Solid-Organ-Transplant Mothers.*

Publikacja nr 3 jest kontynuacją badań własnych doktoranta, której celem jest uzupełnienie wiedzy na temat odpowiedzi poszczepiennej dzieci matek – biorczyń narządu przeciwko wybranym, istotnym klinicznie patogenom bakteryjnym: M. tuberculosis, H. influenzae, S. pneumoniae, C. tetani, B. pertussis, C. diphtheriae. W tożsamej dla publikacji 2. grupie pacjentów oceniano miana przeciwciał Anti-tuberculosis BCG IgG, Anti-Hemophilus influenzae B IgG, Anti-S. pneumococcal Vaccine IgG, Anti-Tetanus Toxoid IgG, Anti-B. pertussis antigens IgG, Anti-Diphtheria Toxin/Toxoid IgG.

Nie stwierdzono różnic w immunogenności szczepień przeciwko błonicy, tężcowi, krztuścowi, gruźlicy, pneumokokom u dzieci matek po przeszczepieniu narządu litego w porównaniu z ogólną populacją pediatryczną. Zwiększoną immunogenność szczepionki BCG (Bacillus Calmette-Guérin) wykazano u dzieci matek po przeszczepieniu nerki w porównaniu z dziećmi z populacji ogólnej. Przyczyna tego związku jest jednak niejasna i wymaga dalszych badań na większej populacji pacjentów. W grupie badawczej nie obserwowano zwiększonego odsetka występowania niepożądanych odczynów poszczepiennych w porównaniu do grupy kontrolnej. Tym samym wykazano, że profil bezpieczeństwa analizowanych szczepionek bakteryjnych u dzieci matek po przeszczepieniu narządu litego jest porównywalny z populacją ogólną. Na podstawie przeprowadzonej analizy nie ma dowodów na zasadność modyfikacji schematów szczepień bakteryjnych u dzieci matek po przeszczepach narządów stałych. Sugeruje się utrzymanie istniejących schematów szczepień i szczepienie dzieci matek biorców narządów zgodnie z kalendarzem szczepień obowiązującym dla dzieci w populacji ogólnej.

8. Osiągnięcia naukowe kandydata na tle dotychczasowego stanu wiedzy

Mimo znacznego rozwoju transplantologii jaki poczynił się w ostatnich dziesięcioleciach, zagadnienie ciąży pacjentek po transplantacji narządu i zdrowia ich dzieci nadal jest przedmiotem zainteresowania badaczy. Na początku ery transplantologii ciąże u biorczyń narządu nie były rekomendowane. Pierwsze udane porody po transplantacji nerki były opisywane w latach 60. i 70. XX w. Od tego czasu wiedza dotycząca wpływu różnych schematów terapii immunosupresyjnej stosowanych w transplantologii na przebieg ciąży, porodu oraz okresu połogowego znacząco się poszerzyła. Ciąża u biorczyń narządu należy do ciąż podwyższonego ryzyka i powinna być prowadzona w ośrodkach posiadających odpowiednie doświadczenie. Do najpoważniejszych powikłań matczyno-płodowych immunosupresji stosowanej w trakcie ciąży należą stan przedrzucawkowy, rzucawka, poród przedwczesny i mała masa urodzeniowa noworodka. Wiedza na temat ciąży i rozwoju dzieci matek po transplantacji jest przedmiotem licznych analiz badawczych. Istnieją dedykowane rejestry zbierające dane dotyczące tego zagadnienia, jak: *Transplant Registry International* (USA, Philadelphia) czy *Australia and New Zealand Dialysis and Transplant Registry* (Australia, Adelaide), które obejmują analizą łącznie blisko 4000 dzieci matek po transplantacji. W odniesieniu do rozwoju postnatalnego, dane zebrane w przytoczonych rejestrach, a także w bazach publikacji medycznych w przeważającej mierze skupiają się na okresie poporodowym i wczesnych latach rozwoju dziecka. Mimo wielu lat prowadzonych badań, autorzy publikacji stale podkreślają potrzebę poszerzenia wiedzy w zakresie oceny zdrowia i rozwoju dzieci w późniejszych latach życia. Niniejsza praca doktorska wpisuje się w ten nurt, uzupełniając dotychczasowy stan wiedzy o zagadnienie immunogenności i bezpieczeństwa szczepień ochronnych dzieci matek biorczyń narządów w obserwacji długoterminowej, które nie było do tej pory przedmiotem innych analiz. Praca obejmuje analizą większość szczepień wykonywanych w ramach Programu Szczepień Ochronnych. Wyniki pracy mają szczególne znaczenie w dobie kryzysu wakcynologii, związanego z oddziaływaniem ruchów antyszczepionkowych, powodujących problemy zdrowia publicznego. Brak stwierdzenia różnic w immunogenności i profilu bezpieczeństwa szczepień pomiędzy dziećmi matek po transplantacji narządu a ogólną populacją pediatryczną potwierdza potrzebę i możliwość szczepienia tej szczególnej grupy dzieci zgodnie z PSO. Fakt opublikowania wszystkich trzech prac wchodzących w skład cyklu w wiodących czasopismach z zakresu wakcynologii (łączny IF cyklu 16,6) wskazuje na istotny wkład dorobku naukowego doktoranta w rozwój tej dziedziny medycyny.

9. Założenia i cel pracy

Założeniem dysertacji jest określenie wpływu stosowania leków immunosupresyjnych przez kobiety po transplantacji wątroby lub nerki w trakcie ciąży na funkcję układu immunologicznego ich dzieci poprzez ocenę mian przeciwciał poszczepiennych przeciwko wybranym, ważnym klinicznie patogenom wieku dziecięcego. Potencjalny negatywny wpływ immunosupresji *in utero* na odpowiedź immunologiczną skłonił doktoranta do poszerzenia zakresu pracy o zagadnienia związane z profilem bezpieczeństwa szczepień. Przyjęta metodologia zakłada ocenę odpowiedzi poszczepiennej w obserwacji długoterminowej, co było jak dotąd przedmiotem analiz innych badaczy. Ponadto podjęto próbę identyfikacji czynników modyfikowalnych mogących zwiększyć immunogenność stosowanych szczepionek w omawianej grupie pacjentów, a tym samym przyczynić się do ograniczenia występowania chorób zakaźnych wieku dziecięcego u dzieci matek po transplantacji narządu.

Założenia dysertacji zweryfikowano poprzez odpowiedź na następujące pytania badawcze:

- Czy wewnątrzmaciczna ekspozycja płodu na leki immunosupresyjne stosowane przez kobiety ciężarne po przeszczepieniu narządu celem podtrzymania funkcji graftu ma wpływ na zdolność wytworzenia i utrzymania przeciwciał poszczepiennych w późniejszych etapach rozwoju dziecka?

- Czy istnieje różnica w immunogenności szczepień ochronnych przeciwko poszczególnym chorobom zakaźnym pomiędzy grupami dzieci matek biorczyń wątroby lub nerki oraz ogólną populacją pediatryczną?

- Czy występują różnice w częstości i nasileniu niepożądanych odczynów poszczepiennych między pomiędzy dziećmi matek biorczyń narządu a populacją ogólną?

- Czy istnieje potrzeba modyfikacji stosowanych schematów szczepień ochronnych w grupie dzieci matek po transplantacji narządu?

- Czy istnieją czynniki mogące zwiększać immunogenność szczepień u dorosłych pacjentów stosujących przewlekłą immunosupresję u chorych po transplantacji narządu litego?

Expert Review of Vaccines

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The influence of selected factors on the immunogenicity of preventive vaccinations against hepatitis A, B and influenza in solid organ transplant recipients undergoing immunosuppressive therapy – a review

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REVIEW

The influence of selected factors on the immunogenicity of preventive vaccinations against hepatitis A, B and influenza in solid organ transplant recipients undergoing immunosuppressive therapy – a review

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ABSTRACT

Introduction: Immunization is the most effective form of the primary prevention of infectious diseases. Knowledge on the efficacy and immunogenicity of vaccinations in the group of organ transplant patients taking chronic immunosuppressive treatment remains incomplete.

Areas covered: The aim of this paper was to analyze factors influencing the post-vaccination response in patients undergoing chronic immunosuppressive therapy based on a literature review. Only publications that evaluated the immunogenicity of influenza, HAV and HBV vaccinations in patients on immunosuppressive therapy were reviewed.

Expert opinion: The following methods are used to potentially increase the immunogenicity of vaccinations against HAV and HBV amongst post-transplantation patients: increasing the number of doses, increasing dose volumes, the method of administering as well as the addition of adjuvant. Immunogenicity is also impacted by the immunosuppression mechanism. Overall, vaccination has been concluded to be safe for post-transplantation patients and adverse events following immunization (AEFI) have typically been rated as mild or moderate. The instances of transplant rejections as observable in the long term have not been related to administered vaccinations. The data shows certain correlations of some factors with increased immunogenicity, however it is necessary to repeat the studies on a more representative group of patients.

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Vaccination; transplantation; immunosuppression; viral diseases; influenza; hepatitis A; hepatitis B; immunogenicity

1. Introduction

Patients undergoing chronic immunosuppressive therapy are at an increased risk of infection. Therefore, the implementation of effective infection prophylaxis in this group of patients is of particular importance [1,2]. The influence of immunization on reducing infections in individuals from the general population is well documented. This influence may be different in patients undergoing chronic immunosuppressive therapy due to the drug-dependent, time-of-use and dose-dependent effects on the immune system. Chronic immunosuppressive treatment is used in many areas of medicine, including transplantation, rheumatology and dermatology. Many scientific societies recommend immunization in patients taking chronic immunosuppressive drugs because of the advantage of the benefits of vaccination over possible adverse effects. With respect to vaccinating post-transplantation patients, it is recommended to vaccinate prior to transplantation, if possible, and monitor the level of antibodies to provide an adequate level of protection to organ recipients [3]. Despite the undeniable benefits of immunization, this group of patients remains under-vaccinated [4]. Researchers aim to clarify the role of factors that may influence the development of post-vaccination immunity in this particular group of patients to ensure the maximum possible vaccine efficacy.

2. Purpose of the study

The aim of this study was to collect and analyze the factors influencing the post-vaccination response in a group of patients treated with chronic immunosuppressive drugs based on a literature review. The aim was also to summarize current guidelines on vaccination methods in this patient group.

3. Methodology

PubMed and Embase databases were searched twice on 14/06/2021 and 8/11/2021. The search strategy was not limited by the publication language or geographic scope it applied to. The review included original articles, review papers and meta-analyses published between 1999 and 2021. The search was conducted by two independent researchers. To ensure the consistency of the review conducted, the study focused on papers that analyzed the effect of various factors on the immunogenicity of vaccinations in groups of patients on chronic immunosuppressive therapy in LTRs *(liver transplant recipients)* or KTRs *(kidney transplant recipients)*. The analysis included papers evaluating the immunogenicity of influenza, HAV *(hepatitis A)* and HBV *(hepatitis B)* vaccines. The search included: 'immunogenicity,' the 'influenza vaccine,' the 'HAV

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vaccine,' the 'HBV vaccine,' 'liver transplant recipients,' 'kidney transplant recipients' and 'immunosuppression' as keywords in a variety of combinations. With regard to influenza, 36 publications were found, all study summaries were read and 10 were of particular relevance for the study, 3 articles were rejected as published prior to the time frame under analysis. From 10 fully studied papers, 7 were subjected to a comprehensive analysis (Table 1). As far as HAV is concerned, 4 articles were found, all were studied in full, 1 paper was rejected as it was dated prior to the analyzed timeframe (Table 2).

6 articles assessing the immunogenicity and safety of vaccinations against HBV in post-transplantations patients were found (evaluating the percentage of seroconversion and seroprotection). All of six studies were included in the analysis to elaborate the discussion on the influence of various factors on the immunogenicity of HBV vaccination (Table 3).

4. Review

4.1. Influenza

The influenza vaccination is one of the most common immunizations among the vaccines recommended in highly developed countries. Two types of formulations are currently used. These are: the trivalent and quadrivalent vaccine, developed annually according to WHO (*World Health Organization*) recommendations, adequately to the strains epidemiologically relevant in a given epidemic period. The available formulations can be divided into those containing live and attenuated as well as killed, inactivated strains of influenza viruses type A and B. Vaccination is particularly recommended in high-risk groups, which include people with chronic respiratory and cardiovascular diseases, but the benefits of the vaccination benefit all individuals aged 6 months and older [5]. A special group of patients, to whom the vaccination is recommended, are patients after organ transplantations due to the possible severe course of the disease. The fact that immunosuppressive therapy is used in this group of patients to maintain graft functions may limit the efficacy of a vaccination. At the same time the reduced activity of the immune system poses a risk of a severe course of the disease [6,7], hence vaccination in this group is an important form of prophylaxis. The seroconversion rate (SR), which describes the percentage of seronegative (at the baseline) vaccinated persons showing the presence of protective antibodies of IgG class against antigens contained in a given preparation, is the most important for the objective assessment of the immunogenicity of immunization.

Strategies are being sought that, if implemented, could increase seroconversion rates after influenza vaccination in immunocompromised patients. The first strategy is dose pluralization. Cordero et al. [8], in the study of a group of 499 patients after solid organ transplantation, compared SR using a one-dose or two-dose schedule of the TIV (*Trivalent influenza vaccine*) vaccine administered intramuscularly. The booster dose in the two-dose group was administered 5 weeks apart. Based on the analysis, there was a statistically significantly higher seroprotection with the two-dose regimen compared to the single-dose regimen for the following influenza virus serotypes: 54% vs 43% for A (H1N1) pdm, 57% vs. 46% for A (H3N2) and 84% vs. 72% for B ($p < 0.05$) in a short-term (10 weeks) observation. After 12 months of the follow-wp, differences were not statistically significant. Seroconversion was statistically significant only with regard to the A(H1N1) strain in a short-term observation, 47% vs. 33% ($p < 0.05$). After 12 months of observation, differences in SR were no more statistically significant. During the follow-up only 1% ($n = 5$) of patients was diagnosed with influenza. According to a literature review by Bosaeed et al. [9], not all studies on the use of a second additional dose indicated an improvement in SR [10].

On the other hand, Manuel et al. [11] evaluated the efficacy of an additional dose of TIV administered intradermally (intramuscular + booster intradermal) on a group of 60 patients after lung transplantations. In the study group, intramuscular administration was associated with a statistically significant increase in the seroprotection rate compared to the baseline for serotypes A-H1N1, A-H3N2 and B. A second dose of the vaccine administered intradermally was not associated with an increase of the seroprotection rate ($p > 0.05$). The differences in the seroconversion rate were not statistically significant (Table 1). Researchers concluded that the booster intradermal dose of the influenza vaccine does not improve immunogenicity in lung transplant patients. None of the patients developed influenza.

In the next study Manuel et al. [12] compared the immunogenicity of intradermal low dose administration and the intramuscular administration of a standard dose of the flu vaccine. The overall seroconversion rate was low, but it was similar between groups. There was no statistically significant difference in the seroconversion rate between groups. Seroprotection rates were higher in the intramuscular group for the A-H3N2 (98% vs 83%; $p = 0.02$) and B-strain (58% vs 29%; $p = 0.01$). 2 patients (4,8%) in the intradermal group and none in the intramuscular group developed influenza. Baluch et al. [13] compared the immunogenicity of a high dose intradermal vaccine administration and a standard dose vaccination administered intramuscularly. In the overall cohort, seroconversion and seroprotection rates to both vaccines were low and there were no significant differences in the vaccine response. Three patients developed influenza. Another strategy that was explored to improve the immunogenicity of the influenza vaccination in organ transplant recipients is the use of adjuvanted vaccines. There are publications comparing the immunogenicity of vaccines containing the additional hydrophobic component MF59 versus non-adjuvanted vaccines [14–16]. The potential mechanism of action of adjuvants is based on the induction of local inflammation at the site of the vaccine administration, which, through leukocyte migration, may contribute to the escalation of the humoral response, and thus improve SR. Kumar et al. [17] conducted such a study on a group of 128 renal transplant patients comparing the efficacy of MF59 and the non-adjuvanted vaccine. The authors showed that seroconversion for at least 1 of the 3 viral antigens was higher with the adjuvanted vaccine compared to the non-adjuvanted vaccine (70.0% vs. 55.2%), but the differences were not statistically significant ($p = 0.21$). In relation to the various viral strains of

Table 1. A summary of the results of studies evaluating the immunogenicity of influenza vaccines in organ transplant recipients.

Author	Vaccine Formulation	Group	Administration	Results	Conclusion	Safety and adverse effects
Cordero et al. 2017	Single dose (n = 211) vs double dose (n = 213) 5 weeks apart TIV (Mutarip, Sanofi-Pasteur MSD) 0,5 ml	499 SOTR after liver, kidney, heart and lung transplant >1 month after transplant Country: Spain	Each dose contained: 0,5 ml Intramuscular (15 µg antigen from each strain)	** **Short-term (10 weeks) seroconversion rate** single dose/ double dose/ p-value A/H1N1 33% 47% <0.05 A/H3N2 30% 39% - B-strain. 64% 76% - **Long-term (12 months) seroconversion rate** single dose/ double dose/ p-value A/H1N1 20% 21% - A/H3N2 45% 41% - B-strain. 51% 64% - **Short-term (10 weeks) seroprotection rate** single dose/ double dose/ p-value A/H1N1 43% 54% <0.05 A/H3N2 46% 57% <0.05 B-strain. 72% 84% <0.01 **Long-term (12 months) seroprotection rate** single dose/ double dose/ p-value A/H1N1 33% 27% - A/H3N2 54% 48% - B-strain. 69% 74% -	Clinical efficacy of vaccination was very high, nearly 100% Booster strategy induces an increased antibody response.	1% (n = 5) patients diagnosed with influenza during follow-up 35 SAEs – 3 possibly related to influenza

(*Continued*)

Table 1. (Continued).

Author	Vaccine Formulation	Group	Administration	Results	Conclusion	Safety and adverse effects
Manuel et al., 2007	2 doses (n = 57) given 4 weeks apart TIV (Vaxigrip, Sanofi-Pasteur)	57 SOTR after lung transplant >3 months after transplant Country: Canada	1st dose Intramuscular 0,5 ml (15 µg antigen from each strain) + 2nd Intradermal 0,1 ml (3 µg antigen from each strain)	** **Seroconversion rate after** 1st dose/2nd dose (intradermal) A/H1N1 52% 46% A/H3N2 50% 49% B-strain 42% 37% **Seroprotection rate after** Baseline/1st dose/2nd dose (intradermal) A/H1N1 72% **90%*** 95% A/H3N2 52% **87%*** 88% B-strain. 52% **92%*** 88% * $p < 0.001$ between baseline and 1st dose Other comparisons not statistically significant	Intradermal booster dose did not significantly improve overall immunogenicity.	Vaccine was well tolerated. None of the patients developed influenza during follow-up (6 months)

(*Continued*)

Table 1. (Continued).

Author	Vaccine Formulation	Group	Administration	Results	Conclusion	Safety and adverse effects
Manuel et al., 2011	Low-dose Intradermal (n = 41) vs standard-dose intramuscular (n = 44) TIV (Vaxigrip, Sanofi-Pasteur)	85 SOTR after lung transplant >3 months after transplant Country: Canada	0,2 ml Intradermal (6 µg from each strain) vs 0,5 ml intramuscular (15 µg of each strain)	*** **Seroconversion rate** intradermal/ intramuscular/ p-value A/H1N1 7.3% 7.0% 1.00 A/H3N2 4.9% 7.0% 1.00 B-strain 7.3% 11.6% 0.71 **Seroprotection rate** intradermal/ intramuscular/ p-value H1N1 39% 28% 0.36 H3N2 83% 98% 0.02 B-strain 29% 58% <0.01	Seroconversion rate was low, but it was similar between groups.	Adverse events were seen in 44% of patients in the intradermal group vs 34% in the intramuscular group (p = 0.38).Two patients in the intradermal group developed influenza (2 of 41, 4.8%), compared with none in the intramuscular group (p = 0.23)
Baluch et al. 2013	HD id. (n = 107) vs SD im. (n = 105) SD im. Vaccine – TIV Vaxigrip, Sanofi-Pasteur) HD id. Vaccine – TIV Intanza (Sanofi-Pasteur)	212 SOTR after lung, heart, liver and kidney transplant >3 months after transplant Country: Canada	0,1 ml Intradermal (9 µg from each strain) vs. 0,5 ml Intramuscular (15 µg from each strain)	** **Seroconversion rate** intradermal/ intramuscular/ p-value A/H1N1 37% 34% 0.64 A/H3N2 29% 30% 0.81 Influenza B. 21% 17% 0.42 **Seroprotection rate** intradermal/ intramuscular/ p-value H1N1 71% 70% 0.93 H3N2 70% 63% 0.33 B-strain 63% 52% .099	Overall seroconversion and seroprotection rates to both vaccines were low, and there were no significant differences in vaccine response.	Vaccines were well tolerated. Increased adverse effect ratio on intradermal group. Three patients developed influenza.

(*Continued*)

Table 1. (Continued).

Author	Vaccine Formulation	Group	Administration	Results	Conclusion	Safety and adverse effects
Kumar et al. 2016	MF59 adjuvanted (n = 31) vs. nonadjuvanted (n = 29) standard TIV Adjuvanted – TIV Fluad (Novartis) Nonadjuvanted – TIV Agriflu (Novartis)	60 SOTR after kidney transplant >3 months after transplant Country: Canada	0,5 ml intramuscular (15 µg from each strain)	** **Seroconversion rate** nonadjuvanted/ adjuvanted/ p-value A/H1N1 48% 45% 0.81 A/H3N2 34% 48% 0.28 Influenza B. 24% 32% 0.49 **Seroprotection rate** nonadjuvanted/ adjuvanted/ p-value H1N1 86% 83% 0.80 H3N2 93% 100% 0.23 B-strain 65% 61% 0.73	No significant differences in immunogenicity between the 2 cohorts were seen.	No patient with documented influenza infection within follow-up time.
Natori et al. 2017	High dose (n = 84) vs standard dose (n = 77) HD – TIV FluzoneHD (Sanofi) SD – TIV Fluviral (GSK)	161 SOTR after kidney, liver, heart, lung and pancreas, or combined organs transplant >3 months after transplant Country: Canada	Intramuscular 60 µg (high dose) 15 µg (standard dose)	* **Seroconversion rate** High dose/ standard dose / p-value A/H1N1 40% 21% .007 A/H3N2 57% 32% .002 B- strain 58% 42% .033 **Seroprotection rate** High dose/ standard dose / p-value H1N1 83% 83% 0.97 H3N2 80% 74% 0.39 B-strain 94% 91% 0.55	Seroconversion to all three strains were higher in HD vs. SD vaccine. Differences in seroprotection rate were not statistically significant.	Greater adverse effects in HD group, although no statistical significance. Influenza infection was diagnosed in 2 (2.4%) patients in SD group and 1 (1.1%) in HD group (P = 0.62)

(*Continued*)

Table 1. (Continued).

Author	Vaccine Formulation	Group	Administration	Results	Conclusion	Safety and adverse effects
Perez-Romero et al. 2015	Vaccination within 6 months after transplantation vs vaccination more than 6 months after transplantation depends on vaccination year: 2009–2010: monovalent MF-59 adjuvanted vaccine Focetria (Novartis) 2010–2012: nonadjuvanted TIV Gripvac (Sanofi-Pasteur) 2012–2013: nonadjuvanted TIV Mutagrip (Sanofi-Pasteur)	798 (>15 yr) SOTR after kidney, heart and liver transplant Country: Spain	Intramuscular *exact amount of injected vaccine was not specified by authors	** **Seroconversion rate** Early group/late group/p-value A/H1N1 52% 57% .352 A/H3N2 47% 47% .936 B- strain 40% 51% .030 **Seroprotection rate** Early group/late group/p-value A/H1N1 73% 77% .494 A/H3N2 67% 74% .171 B- strain 84% 85% .800	Rate of seroprotection <6 months is similar to that obtained in patients vaccinated >6 months since transplantation.	1 patient was diagnosed with chronic graft rejection – not related to vaccination

all preparations where 'adjuvanted' was not indicated – were not-adjuvanted
SOTR – solid organ transplant recipients
TIV – trivalent inactivated influenza vaccine
HD- high dose
SD – standard dose
* Seroconversion rate was defined by the percentage of patients with a 4-fold increase in HIA titer after vaccination or negative prevaccination serum that reached postvaccination titers >1:40. Seroprotection was defined as an HIA titer of ≥1:40.
** Seroconversion rate was defined by the percentage of patients with a 4-fold increase in HIA titer after vaccination. Seroprotection was defined as an HIA titer of ≥1:40.
*** Seroconversion rate was defined by the percentage of patients with a 4-fold increase in HIA titer after vaccination. Seroprotection was defined as an HIA titer of ≥1:32.

Table 2. Summary of the results of studies evaluating the immunogenicity of hepatitis A vaccines in organ transplant recipients.

Author	Vaccine Formulation	Group	Administration	Results	Conclusion	Safety and adverse effects
Jeon et al. 2014	2 doses of inactivated anti-HAV vaccine at interval of 6 months Inactivated vaccine Havrix (GSK)	416 kidney transplant recipients >6 month after transplant Country: Korea	1 ml (1440 ELISA units) Intramuscular	* 338 of 416 patients screened before vaccination were seropositive. In group of 52 seronegative patients SR was 26.9%.	Seroconversion was low. Data suggests that the vaccine response is inversely associated with strength of immunosuppression.	Vaccination was well tolerated by all KTRs. Anti-HAV vaccination had no effect on the graft function.
Arslan et al. 2001	2 doses of inactivated anti-HAV vaccine at interval of 6 months Inactivated vaccine Havrix (GSK)	37 seronegative liver transplant recipients >12 month after transplant Country: United States	1 ml (1440 ELISA units) Intramuscular	* 8% of patients had seroconversion at 1 month after full course of vaccination, 19% at 6 month and 26% at 7 month time point.	SR was significantly lower than that reported in healthy individuals.	Vaccine was well tolerated by all patients.
Stark et al. 1999	2 doses of inactivated anti-HAV vaccine at interval of 6 months Inactivated vaccine Havrix (GSK)	Liver (n = 39) or kidney (n = 39) transplant recipients + control group (n = 29) >3 months after transplant Country: Germany	1 ml (1440 ELISA units) Intramuscular	** **Seroconversion rate** LTRs/ KTRs/ control/ p-value After 1st dose 41% 24% 90% <.0001 After 2nd dose 97% 72% 100% <.001	The differences in vaccine immunogenicity between LTRs and the KTRs may be due to differences in immunosuppressive therapy regimens. (higher degree of immunosuppression in the KTRs group)	No serious adverse events were observed.

KTRs – kidney transplant recipients
LTRs – liver transplant recipients
*Seroconversion was defined as appearance of anti-HAV IgG in seronegative patients.
** Seroconversion was defined as appearance of anti-HAV IgG in seronegative patients. Subjects with titers <33 mIU/mL were considered seronegative.

Table 3. Summary of the results of studies evaluating the immunogenicity of hepatitis B vaccines in organ transplant recipients.

Author	Vaccine Formulation	Group	Administration	Results	Conclusion	Safety and adverse effects
Lindemann et al. 2017	1 dose of Inactivated, adjuvanted HBV vaccine- Fendrix (GSK)	17 KTRs non responders for standard vaccines - vaccinated at least 3 times >6 month after transplant Country: Germany	intramuscular 20 µg of recombinant hepatitis B surface antigen 50 µg of MPL adjuvant	* Humoral immunity: 41% of KTRs displayed anti-HBs Ab > 10IU/l Overal increase in anti-HBs titers (p = 0.02) Cellular immunity: 4 patients displayed HBV-specific lymphocyte proliferation and 1 patient displayed HBV-specific IFN-γ response	Single vaccination with MPL adjuvanted vaccine induced humoral or cellular response in more than half KTRs.	No adverse effect have been observed
Fakhrousavi et al. 2016	4 doses of inactivated HBV vaccine Euvax B (LG life science) 0,1-,2-,6- month schedule	49 KTRs negative history of HBV vaccination >6 month after transplant Country: Iran	intramuscular Each dose: 40 µg of recombinant hepatitis B surface antigen	* Humoral immunity: Seroconversion rate was 44,89% after 3rd dose 57.14% after 4th dose Cellular immunity: no data	Four double-strength doses can lead to proper protection in patients that did not respond for other vaccination scheme.	No adverse effect have been observed
Friedrich et al. 2015	No data	51 kidney transplant recipients with documented HBV vaccination (mean from vaccination 1.9 ±1 years) 22 healthy controls with documented HBV vaccination (mean from vaccination 3 ±2.9 years) Mean time from transplantation 7,5 years Country: Germany	No data	** In studied population of LTRs: 29% Non-responders 33% Low-responedrs 38% High-responders In 50% of non-responders, HBsAg-specific CD4 + T cells were found. No significant differences in the frequency of HBsAg-specific T cells between healthy individuals and KTRs was seen.	KTRs are able to mount HBV- specific T cell responses irrespective of their humoral status.	No data
Weber et al. 2010	3 doses of inactivated HBV vaccine in 0,1-,6- month schedule Twinrix (GSK) Engerix (GSK) Recombivax (Merck) Or combination of more than one agent	12 LTRs after HBV related cirrhosis Median time from transplantation 14 months All patients having lamivudine 100–150 mg/day and low dose HBIG (keeping anti-HBsAg >200IU/l) as prophylactic regimen.	HBV vaccination was initiated prior to HBIg discontinuation. (patients maintained oral anti-viral agents) Twinrix 20 µg im. Engerix 40 µg im. Recombivax 20 µg im.	*** None of the patients maintained anti-HBsAg >10 IU/l at most recent follow-up. Mean follow-time 16.3 months (range 7.8–32).	HBV vaccination followed by HBIg discontinuation is inefficient and not provide sustainable protection.	No data
Karasu et al. 2004	2 doses of inactivated HBV vaccine Genhavac B Pasteur (Aventis Pasteur) 0,1-,6- month schedule + second course of 2 dose vaccination for non-responders in 0,1-,2- month schedule Vaccination started 1 month HBIg discontinuation	14 LTRs after HBV related cirrhosis Median time from transplantation 14 months All patients having lamivudine and low dose HBIG as prophylactic regimen. Country: Turkey	intramuscular Each dose: 40 µg of recombinant hepatitis B surface antigen	**** Only one (7%) patient seroconverted (an anti-HBs titer of 37 IU/L) after the first cycle. After booster dose he developed an anti-HBs titer of 80 IU/L, but needed revaccination every 2–3 months to maintain anti-HBs titer >10 IU/L	Double dose, double course of HBV vaccination is not effective in LTRs after HBV related cirrhosis.	No data

(*Continued*)

Table 3. (Continued).

Author	Vaccine Formulation	Group	Administration	Results	Conclusion	Safety and adverse effects
Choy et al. 2002	8 doses of inactivated, HBV vaccine Engerix (GSK) in 2 weeks intervals + booster dose for non-responders after 8 dose id. scheme in 12 month	24 KTRs who did not respond for four or more double-strength doses of HBV vaccine Country: China	Intradermal 5 µg of recombinant hepatitis B surface antigen 40 µg im. booster dose for non-responders	***** Humoral immunity: 37,5% of KTRs displayed anti-HBs Ab > 10IU/l 8% of KTRs displayed anti-HBs AB at level 4–6IU/l after 8 id. doses In group of 13 non-responders, 30% of them seroconverted after 40 µg im. booster	Combination of id. vaccine with double-strength im. booster achieve response rate of 62,5%	Vaccine was well tolerated by patients

SOTR – solid organ transplant recipient
KTRs – kidney transplant recipients
LTRs – liver transplant recipients
Id. – intradermal
Im. – intramuscular
* Patients with titers of anti-HBs > 10IU/l were considered as responders/anti-HBs < 10IU/l were considered as non-responders.
** Patients with an antibody titer above 100IE/mL were classified as High-Responders, with an antibody titer between 11 and 100IE/mL as Low-Responders, with titers below 11 IE/mL as No-Responders.
*** Anti-HBs >10 mIU/ml indicated seroconversion when determined after the last vaccine dose and at least 7.5 months post-HBIg
**** Seroconversion was defined as anti-HBs titer >10 IU/L at 3 months after the third dose of vaccine.
***** Patients with titers of anti-HBs > 10IU/l were considered as responders/anti-HBs 4–10IU/l were considered as initial responders/anti-HBs < 4IU/l were considered as non-responders.

the influenza, the researchers failed to prove any significant differences in seroconversion rates and seroprotection rates between groups. (Table 1) None of the patients developed influenza.

Attempts were also made to improve SR by increasing the single dose of the vaccine. Natori et al. [18] compared the SR using SD (*standard dose*) and HD (*high dose*) vaccine doses in a group of 172 patients over 18 years of age after organ transplantation using routine post-transplantation immunosuppression. They showed that seroconversion for at least one of the three influenza virus serotypes was higher in patients who received HD compared to SD (78.6% vs. 55.8%, p = 0.002). According to the study of Natori et al. [18] seroconversion for serotypes: A/H1N1, A/H3N2 and B for patients who were vaccinated with HD and SD, was respectively: 40.5% vs 20.8%, 57.1% vs 32.5%, and 58.3% vs 41.6% (p = 0.007, p = 0.002, p = 0.033). In contrast, GiaQuinta et al. [19], who conducted a similar study in 37 pediatric solid organ recipients, despite showing trends indicating higher immunogenicity of the higher-dose vaccine, obtained results which were statistically significant only for one of the three serotypes: A (H3N2). A higher dose correlates with an increased frequency of mild adverse vaccine reactions in the children studied. At the same time, no severe VAE (*vaccine adverse event*) was observed in the study group.

Another factor that may potentially affect the effectiveness of the influenza vaccination in transplant patients is the time between transplantation and vaccination. There is a small number of publications available in literature that analyze this issue [20]. According to the analysis of Perez-Romero et al. [21], there is no statistically significant difference in the immune response to the influenza vaccination, in solid organ transplant patients vaccinated up to 6 months and more than 6 months after transplantation, respectively (73.1% vs. 76.5% for A/(H1N1) pdm (p 0.49), 67.5% vs. 74.1% for A/H3N2 (p 0.17) and 84.2% vs. 85.2% for influenza B (p 0.80). No vaccine-associated graft dysfunction or severe VAE was observed in either group. Despite a lack of sufficient evidence, the guidelines of transplant societies recommend vaccinations outside the periods of HD of immunosuppression, which is particularly common in the early post-transplantation period [3].

Immunosuppressive drugs used in solid organ transplantation patients are combined in differentiated regimens to prevent graft rejection most effectively by inhibiting the immune response. Pharmaceuticals such as azathioprine, tacrolimus, cyclosporine, sirolimus, mycophenolate mofetil, steroid drugs or biologics are among the most commonly used. In view of the known mechanisms of action of the above-mentioned drugs, there is concern whether their use will not lower the SR after influenza vaccination. A meta-analysis by Karbasi-Afshar et al. [22], which analyzed 15 studies (a total of 947 solid organ transplant recipients) comparing the SR in groups of transplant patients using different immunosuppression regimens, showed that only MMF (*mofetil mycophenolate*) has an effect of lowering SR (p = 0.001). The analyses of other immunosuppressants showed no statistically significant differences. The conclusions of Karbasi-Afshar et al. [22] are

based on a comparison of the SR between immunosuppressed patients on different therapeutic regimens, without considering patients from the general population. A certain limitation of meta-analysis is the fact that in transplantology two- or three-drug regimens are commonly used, which makes it impossible to directly assess the effect of a particular drug in relation to the others. In literature, there are papers indicating the beneficial effect of regimens containing sirolimus. According to the studies of Hayney et al. [23] and Wilcocks et al. [24], sirolimus can increase the seroprotection and immune response to a greater number of influenza virus antigens relative to regimens that do not contain this pharmaceutical. However, these data are limited due to the small sample size and lack of significant statistical differences.

4.2. Hepatitis A (HAV)

Hepatitis A is one of the most common acute liver diseases mainly affecting people in developing countries, and in developed countries it particularly affects travelers. The increased incidence is mainly associated with poor hygiene as well as risky sexual behavior, especially among MSM (*men who have sex with men*). The course of the disease can vary. In some patients, mainly pediatric, it is asymptomatic or mild and self-limiting. In adult patients, the course is often severe, requiring hospitalization. The rare (0,015–0,5%), but most severe complication of HAV is *fulminant hepatitis*, which often leads to death [25].

The recommended form of prophylaxis is the use of an inactivated vaccine in a two-dose schedule. While data are well established for patients with chronic liver disease, there are limited results in literature for patients taking chronic immunosuppressive therapy to maintain the graft function, making this group an important focus of research for the implementation of recommendations.

In contrast to influenza discussed above, literature data on the effectiveness of the HAV vaccination in solid organ recipients are limited. Jeon et al. [26] evaluated the efficacy and safety of the HAV vaccination in KTRs from the South Korean population. In their study, they examined anti-HAV IgG seroconversion 1 month apart after the 2nd dose of the vaccine. They showed that, in the studied group of 52 seronegative KTRs, the percentage of seroconversion was only 26.9%. Similar results were obtained by Arslan et al. [27] studying 37 LTRs from the United States of America (SR = 26%). Contrary to the results of Arslan et al. [27] and Jeon et al. [26] are the results of Stark et al. [28] who studied the immunogenicity and safety of the HAV vaccine in liver and kidney recipients from a German population. In contrast to previously cited studies, they obtained high SRs in both groups studied after the second dose of the vaccine; 97.4% and 71.8%, respectively. Due to a limited number of studies, it is not possible to draw firm conclusions regarding the effectiveness of the HAV vaccination in organ recipients. At the same time, the papers analyzed relatively small study groups included. One should note the marked discrepancy in the SR values in the studies of Jeon et al. [26] and Arslan et al. [27] which indicated a low post-vaccination response in recipients, versus the work of Stark et al. [28] who showed a very high SR in their results. It is worth mentioning that this work was conducted on different ethnic groups; Asian and Caucasian populations, respectively. However, in literature, articles, which confirmed the hypothesis that the HAV immune response would be different between Asians and Caucasians were not found.

It is also noteworthy that the authors consistently point out the dependence of SR on the immunosuppressive treatment regimen used. According to Jeon's study [26], the use of tacrolimus was associated with a worse post-vaccination response. In turn, Stark et al. [28] pointed to the comparison of seroconversion among LTRs and KTRs groups in terms of the immunosuppressive treatment used. In this study, LTRs received tacrolimus or cyclosporine A in monotherapy, while KTRs received a two- or three-drug regimen. More intensive immunosuppressive treatment was associated with poorer post-vaccination responses and lower mean immune antibody concentrations.

It is worth noting that renal or hepatic insufficiency alone are independent factors of a worse postvaccination response [29], so when considering the efficacy of the vaccination, the initial cause that led to the transplantation should be considered as well as the graft function at the time of vaccination.

4.3. Hepatitis B (HBV)

HBV infection, despite available vaccine and antiviral protocols, remains a significant cause of death in transplant recipients. An important aspect of post-transplantation care is the prevention of HBV infection in organ recipients [3,30]. As Moal et al. proved [31] in the post-transplantation period, a reduced anti-HbsAg count can be observed, which was proven in the 12-month monitoring of kidney transplant patients. 141 patients divided into 3 groups, according to their base levels of anti-HbsAg, were monitored and it was concluded that only the group with a level of anti-HbsAg>100 IU/L 93% kept their level of protection (>10IU/L), whereas in patients with base levels of 10–100 IU/L the level of protection was kept by only 33%. At the same time, it is estimated that 90% of patients in the population of healthy people produce anti-HBs [32]. As recommended by KDIGO, it is considered the best practice to immunize patients prior to transplantation and assess their levels of anti-HbsAg within 6–12 weeks after the complete inoculation protocol. In the case of anti-HbsAg levels <10 IU/L, it is recommended to administer a booster dose [3]. Medical databases were researched and only few studies were found on the analysis of the impact of immunosuppression induced due to transplantations on HBV vaccination immunogenicity.

The analyzed studies discuss the immunogenicity of HBV vaccination in patients after organ transplantation differently. There is no methodological consistency between the studies, which makes it impossible to directly compare their results. However, it is worth mentioning the studies available in literature that indicate the possible factors increasing the immunogenicity of HBV vaccination.

Di Paolo et al. [33] studied eighteen patients after liver transplantation due to HBV related cirrhosis of the liver treated with lamivudine and immunoglobulin HBIg prior to

transplantation. Patients received twelve doses of Fendrix vaccination (containing 20 µg of recombinant HBsAg and 50 µg of 3-O-desacyl-40-monophosphoryl lipid A (MPL) adiuvant) at monthly intervals. The first six doses of the vaccination were administered in combination with lamivudine (100 mg/day) and immunoglobulin (2000 IU/month) -The subsequent six doses were administered with lamivudine alone. Then the patients were followed up for twelve months. Antibody titers were assessed at three time intervals: 6, 12 and 24 months after the commencement of immunization. It was shown that all patients had anti-HBsAg titers above 100IU/L after six months. After 12 and 24 months of follow-up, 55% and 44% of patients retained their antibody titers above 100IU/L, respectively. In the final phase of the follow-up, 39% of patients had anti-HBsAg titers <10 IU/L. Researchers have shown that, using the described immunization regimen, it is possible to maintain the antibody titers enabling seroprotection in half of the patients. This regimen is more effective than the standard vaccination used in patients after liver transplantation due to HBV related cirrhosis, where the seroprotection rate is 20–25% (34–38 according to the paper by Di Paolo et al. [33])

Lindemann et al. [34] analyzed the use of Fendrix containing 3-O-desacyl-40-monophosphoryl lipid A (MPL) as an adjuvant in kidney transplant patients who had not responded to standard HBV vaccination. The study included 35 kidney transplant recipients who did not develop anti-HBs after being vaccinated three times against HBV. Seventeen patients did not show a cellular or humoral response to vaccination. This group showed an increased representation of HLA antigens associated with a lack of response to HBV vaccination. One month after the vaccination of patients using HBV vaccine, a statistically significant ($p = 0.02$) increase in anti-HBs titer was observed. 41% of patients included in the study had an anti-HBs titer > 10IU/L, and in 24% an increase in the proliferation of HBV-specific lymphocytes was observed. On the basis of the conducted studies, researchers showed that a single dose of Fendrix activates the cellular and/or humoral response to HBV. At the same time, no side effects of the vaccine were observed in the study group. Considering the correlations demonstrated by Lindemann et al. [34], it may be concluded that the use of Fendrix vaccination may provide more effective protection against HBV in kidney transplant patients.

A different strategy was used by Fakhrousavi et al. [35], including forty-nine KTRs never vaccinated against HBV in their study. Six months after transplantation, they performed the four-dose vaccination regimen using Euvax (0, 1, 2, 6 months), but with a double dose (40 µg). Anti-HBs titers were assessed at intervals of eight weeks after the third and fourth doses of the vaccine. The anti-HBs titer > 10IU/L was assumed as the seroprotective value. Seroprotection was shown in nearly 45% of people after the 3rd dose and about 57% after the 4th dose of Euvax administered in the described regimen. Based on the results of researchers in Iran, the 4-dose regimen of a double dose of Euvax vaccine may be effective in kidney transplant patients never vaccinated against HBV. The approach of Fakhrousavi et al. [35] may therefore be another form of an effective, modified on the basis of a proprietary regimen, anti-HBV vaccination strategy that can be used in patients after kidney transplantation. It is worth noting, however, that the authors did not address the safety issue of the proposed regimen, which should be examined before possible future implementation.

Yet another approach was proposed by Weber et al. [36], who studied patients after liver transplantation performed due to liver failure caused by hepatitis B. Although the study included a small group of patients (n = 12), the study is worth considering because liver failure after hepatitis B is a rare indication for this organ transplant (5% of cases). Patients were subjected to a three-dose HBV vaccination regimen with monovaccinations using the following products: Twinrix, Engerix, Recombivax or a combination of these products at intervals of 0, 1 and 6 months. Immunization was performed prior to discontinuation of HBIg, or on the day of the last dose of HBIg. The mean seroprotection monitoring period was 16.3 months. Contrary to the results of other researchers, the observation showed no anti-HBs titers at the seroprotective level (anti-HBs> 10IU/L). On this basis, it was concluded that vaccination against HBs is ineffective in the group of patients after liver transplantation due to own liver failure in the course of hepatitis B. However, the study protocol should be slightly criticized, because the influence of vaccination on cellular immunity has not been investigated and the applied vaccination regimens in the study conducted by Weber et al. [36] were heterogeneous. However, the conclusions of Weber et al. [36] are confirmed in the studies conducted by Karasu et al. [37], who studied the effectiveness of vaccinations in the prevention of HBV recurrence in patients after liver transplantation in a similar number (n = 14) of patients. In the regimen adopted by the researchers, one type of product (Genhavac B) was used in all patients included in the study. Three doses of the vaccine were administered at the same time intervals as those administered by Weber et al. [36] (0, 1, 6 months). In addition, in patients who did not respond to vaccination, this process was intensified by adding a second three-dose vaccination course (0, 1, 2 months). It was shown that the antibodies titer at the level of seroprotection was obtained only in one patient, which was not statistically significant ($p > 0.05$). In light of the research conducted by Karasu et al and Weber et al. [36,37] in the absence of other literature data, it should be concluded that vaccinations do not constitute an effective form of prevention of HBV recurrence in patients after liver transplantation due to own liver failure caused by hepatitis B, and the currently used immunoglobulin and antiviral treatment regimen should remain in the post-transplant care regimen in this group of patients.

Choy et al. [38] included twenty-four KTRs in their study who did not develop anti-HBs in response to four or more double doses of recombinant vaccine (40 µg) administered intramuscularly after transplantation. Patients included in the group were administered eight doses of Engerix 5 µg intradermally at two-week intervals. Two weeks after the

administration of the last eighth dose of the vaccine, anti-HBs titers were tested. As the protective level, as in other analyzed studies, Choy et al. assumed an anti-HBs titer > 10 UI/ml. In this way, patients who initially responded to vaccination were singled out. Patients whose antibody titers at month 12 had decreased to < 10 UI/ml were administered a 40 µg booster intramuscularly. As a result of the applied regimen, the protective level of anti-HBs was observed in nine patients, low level (4–9 IU/L) in two patients; thirteen patients did not respond to vaccination. Summarizing the authors' results, the anti-HBs response to vaccination was achieved in fifteen patients, which shows that the overall response rate of KTRs to vaccination administered intramuscularly and intradermally was 62.5%. It is worth adding that no significant side effects were observed, and the only observed side effects were local skin reactions. This speaks to the safety of the regimen proposed by Choy et al. The combination of HBV vaccine administered intramuscularly and intradermally may be effective in KTRs initially not responding to vaccination, but further studies in a representative group of patients are required to confirm the appropriateness of this approach.

Friedrich et al. [39] demonstrated the correlation of HBs-specific T cells with the humoral response to HBV vaccination in fifty-one patients receiving immunosuppressive therapy for kidney transplantation compared to twenty-two healthy patients (control group). Patients included in the analysis were also divided into three groups: non responders (NRs, n = 15), low responders (LRs, n = 17) and high responders (HRs, n = 19), and the division criterion was based on the determined titer of vaccine antibodies (average time since vaccination 1.9 years). There were no significant differences in the concentration of HBsAg-specific lymphocytes between HRs and the control group ($p > 0.05$). Lymphocyte concentrations in the HRs group were significantly higher compared to LRs (0.009), as in the comparison of LRs to NRs ($p = 0.043$). Of the fifty-one patients included in the study, within 2 years of vaccination, antibodies were detected in thirty-six patients (70%).

An interesting result of the study conducted by Friedrich et al. [39] is the finding that 50% of patients not producing anti-HBs have HBsAg-specific Th cells. As the authors of this study conclude, it may be the basis for further research on the cellular mechanism of the immune response against HBV in a group of patients after transplantation that may increase their immunity despite the inability to produce antibodies. However, this study does not answer the question concerning the comparison of seroconversion and seroprotection rates in patients after organ transplantation with the general population.

4.4. Safety of vaccination in KTRs and LTRs

In all researched articles, the frequency of AEFI occurrence in post-liver or kidney transplantation patients vaccinated with influenza or HAV vaccines was analyzed. Reported AEFIs were typically rated mild or rarely moderate. With regard to influenza, mild AEFIs were reported in 25–77% of cases [8,11–13,17–19,22,23]. This is comparable to the general population. Authors, thus, indicate the safety of vaccinations. As far as HAV vaccine data is concerned, the data is quite limited. In 3 papers that were included in the study, only in one did the authors report AEFIs [26] of 2%. In other papers researchers indicated that the vaccination was safe with no SAEs reports. Apart from AEFIs, which are typical in transplantations, there is a risk of organ rejection. With regard to the flu vaccine there was a 0% –7% rejection rate [8,9,11–13,17,18], whereas no organ rejections were reported for HAV vaccinations. However, due to the small sample studied, these were statistically insignificant, as illustrated in Table 1, Table 2 and Table 3.

5. Conclusions

- The vaccine response to viral disease vaccines in organ recipients using immunosuppressive drugs is worse compared to the general population
- This response varies depending on the treatment regimen used
- MMF has the greatest effect on lowering SR compared to other immunosuppressive drugs for the influenza vaccination.
- This response also depends on the type of vaccine
- Interestingly, the modification of the vaccination schedule may improve SR in organ recipients on immunosuppressive therapy
- The objective may also be achieved by increasing the dose of the vaccine or administering a booster
- Perhaps finding new adjuvants will bring benefits in the future, such as increasing SR in non-immunocompetent individuals
- A thorough understanding of this issue requires studies on a larger group of patients
- The vaccination impact on anti-HLA de novo creation cannot be ruled out and, thus, consequently on organ transplant rejection.
- In patients after kidney transplantation, well-documented effectiveness of immunization ensuring HBV seroprotection based on modified vaccination regimens was demonstrated.
- Vaccination using Fendrix containing an MPL adjuvant is an effective form of active prevention of HBV infection in kidney transplant patients.
- A double dose of Euvax seems to be a good form of active immunization against HBV in patients after kidney transplantation, but studies assessing the safety profile of such treatment are recommended.
- In the assessment of the protective role of immunization in patients after organ transplantation, apart from humoral immunity, further studies to consider the role of cellular immunity in the process of immunization against HBV seem justified.

6. Expert opinion

The effect of chronic immunosuppressive therapy on the immunogenicity of vaccines has not thoroughly been studied.

The cited studies include relatively small groups of patients and cannot form a basis for drawing clear conclusions. The multitude of immunosuppressive regimens used in post-transplantation care makes it difficult to compare the results of individual studies as well as determine the effect of individual immunosuppressive drugs on the immunogenicity of vaccinations.

Among immunosuppressive drugs used in post-transplantation care, MMF has been identified as a drug negatively influencing the immunogenicity of the influenza vaccination. Confirmation of this hypothesis on a more representative group of patients could form a basis for the modification of immunosuppressive treatment regimens in organ transplant patients burdened with additional risk factors for severe infections.

At the same time, the influence of other, commonly used drugs on the maintenance of the vaccination response was not determined, which requires further studies.

A positive effect of an increased vaccine dose and the use of adjuvants (MF-59 for influenza and MPL for the HBV vaccine) on the immunogenicity of the vaccination was demonstrated. Transplant patients are particularly vulnerable to severe infections. Efforts should be made to modify the rules of immunization in this particular group of patients. The measure with the lowest risk combined with a beneficial effect of increased SR appears to be the use of an additional dose of the influenza vaccine.

In the case of transplantation after HBV related cirrhosis, vaccinations do not provide adequate levels of seroprotection. The use of immunoglobulin and antiviral drugs remains the method of effective prevention of HBV recurrence.

AEFIs cases in post-transplantation patients correspond with general population levels. As some cases of kidney and liver transplant rejections were reported post flu vaccination, there is a need to monitor such patients for risk of severe adverse events (SAEs). There is some vague proof [40] of an increase in the s-HLA count in post-transplantation patients after the flu vaccination, so the possible impact of the vaccination on transplant rejections cannot be excluded. There is a need for further research to assess the safety of the flu vaccination with regard to anti-HLA *de novo* creation to further optimize vaccination recommendations in this group of patients.

Currently, due to the prevailing COVID-19 pandemic worldwide, the highest possible seroconversion rate and the longest possible persistence of effective antibodies are desirable. Universal immunization programs against COVID-19 are used. The vaccination rate of the population, especially in societies of highly developed countries, is now the highest it has been for many years. It is equally high in transplant patients. This provides a unique potential to conduct multicenter studies on a representative group of patients in which the SR will be evaluated after the use of particular types of vaccines depending on the immunosuppressive treatment used in post-transplant care.

Clinical centers that care for post-transplant patients should be motivated to conduct collaborative studies to evaluate the effectiveness of the COVID-19 vaccination depending on the immunosuppressive drugs used. This will allow to supplement current knowledge and implement action to increase the survival of post-transplant patients during the COVID-19 pandemic as well as reduce the incidence of other viral infectious diseases.

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Abbreviations

HAV- hepatitis A virusHBV – hepatitis B virusHD- high doseKTRs – kidney transplant recipientsLD- low doseLTRs- liver transplant recipientsMMF- mycophenolate mofetilMSM- men who have sex with menSR - seroconversion rateTIV- Trivalent Influenza VaccineVAE- vaccine adverse eventWHO – World Health Organization

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Does Intrauterine Exposure of the Foetus to Immunosuppressive Drugs Used by the Mother—The Organ Recipient—Affect the Development of Post-Vaccination Immunity against Selected Viral Diseases in Children of These Mothers in Postnatal Life?

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Abstract: Background: Pregnancy in women who are organ recipients has long been a controversial issue due to the lack of data on the safety of immunosuppressive drugs for the developing foetus. Scientific data show that the effect of immunosuppressants on the foetus causes an impairment of T and B lymphocyte function and a reduction in their total number. For this reason, some authors recommend delaying the obligatory immunization of infants. The aim of the study is to analyse the impact of chronic immunosuppressive therapy used during pregnancy by women after organ transplantation on the effectiveness of anti-viral vaccinations in the children of these women. Methods: Concentrations of post-vaccination IgG antibodies (measles, HBV, polio) in 18 children of post-transplant mothers (9KTRs; 9LTRs) were determined using the ELISA method. The results were compared with the control group (n = 21). The incidence of vaccination AEs was also analysed. Results: There were no significant differences between the analysed groups in the concentrations of antibodies against HBV, measles and polio ($p > 0.05$). Conclusions: No difference was observed in the immunogenicity of HBV, polio and measles vaccinations between children of post-transplant mothers and the general population. The immunization of children of post-transplant mothers is safe, and the percentage of adverse post-vaccination events does not differ from the general population. The obtained study results do not indicate the necessity for modifying the vaccination program for HBV, measles, and polio in this group of patients.

Keywords: immunogenicity; immunosuppressive drugs in pregnancy; transplantation; safety of vaccination; anti-viral vaccination; children

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1. Introduction

Transplantology is one of the most intensively developing fields of medicine. The constantly growing number of transplantations creates additional tasks during the period of broadly understood post-transplantation care. Both in the case of liver and kidney transplantation, organ recipients comprise patients in various age groups, including people of childbearing age. For a long time, pregnancy in female transplant recipients was a controversial issue due to the lack of data on the safety of immunosuppressive drugs for the developing foetus [1–3].

The first birth of a woman after an organ transplant took place in 1958. The patient's pregnancy occurred after the transplant of a kidney, which the recipient received from

her twin sister [4]. With the development of transplantology, immunology, perinatology, neonatology and other fields of medicine, pregnancy after organ transplantation became more common over the years, allowing women to enjoy the motherhood they always wanted [5–7].

Immunosuppressive drugs used after organ transplantation are known to have numerous side effects. Some are contraindicated for use in pregnant women due to the proven harmful effects on the developing foetus or even the teratogenic effects. All of these issues are significant in this group of patients, and therefore, it is extremely important to carry out a comprehensive analysis of the state of health and try to detect early on the risks that may occur in the children of post-transplant mothers not only for the mothers of these children and their families, but above all for the fates of the children themselves. In a group of newborns of post-transplant mothers, prematurity, low birth weight, or delivery of a wasted foetus are most frequently observed. When compared to newborns in the general population, these findings are confirmed by the literature.

Researchers focus on the multifactorial and long-term follow-up of children of post-transplant mothers. Several registries have been established worldwide to collect clinical data on these children's development and potential health problems. The Transplant Pregnancy Registry International, which is the largest international database of publications on the course of pregnancies in women after organ transplantation and the postnatal life of their children, contains data on over 3000 pregnancies of women after organ transplantation. The registry is based on the principles of Evidence-Based Medicine. The aim of the registry is to provide comprehensive recommendations on aspects of pregnancy management to recipients and to provide guidelines for the postnatal care of their children [8]. Despite the presence of important clinical issues in the care of children of post-transplant mothers, the topic of preventive vaccination has not been discussed so far, and it remains open to researchers.

Vaccines are a cornerstone in the long and challenging construction of better global health. Neonatologists and paediatricians who take care of children of post-transplant mothers often wonder whether—due to the higher percentage of prematurity, obstetric complications, and impaired development of leukocytes in the first months of life [4]—a different (deferred) vaccination program should be used. The issue of preventive vaccinations, including specific recommendations regarding vaccinations of children of mothers that are recipients, has not been widely discussed so far. Therefore, there are no unequivocal recommendations from specialists regarding the course of vaccination in this particular group of patients.

Taking into account the fact that obligatory vaccination schedules vary from country to country, the vaccination schedule in Poland, which was implemented equally by all study participants, is presented below.

Hepatitis B Virus vaccine: the first dose up to 24 h after birth, the second dose 3 months after birth, the third dose 7 months after birth. Polio vaccine: the first dose (IPV—Inactivated Poliovirus Vaccine) 3–4 months after birth, the second dose (IPV) 5–6 months after birth, the third dose (IPV) 16–18 months after birth, and the fourth dose (OPV—Oral Poliovirus Vaccine) at the age of 6. Measles vaccine (MMR—Measles, Mumps, Rubella vaccine): the first dose 13–14 months after birth, the second dose at the age of 10.

The aim of this study is to compare the immunogenicity of vaccination against selected childhood infectious diseases of viral aetiology (hepatitis B, polio, measles) based on the assessment of post-vaccination IgG antibodies from long-term follow-up in children of post-transplant mothers and children not exposed to immunosuppressive drugs in the prenatal period (from the general population).

In addition, the aim is to determine whether the type of transplanted organ (liver or kidney) from a mother and the subsequent immunosuppressive treatment regimen used prenatally influences the immunogenicity of vaccination in the child.

2. Materials and Methods

The study group consisted of 18 children aged 6–16 (born in 2008–2014) whose mothers during pregnancy took immunosuppressive drugs due to liver or kidney transplantation. The most commonly used immunosuppression regimen in renal recipients was cyclosporine + azathioprine + steroid, and in the liver recipient group, tacrolimus + azathioprine + steroid.

The control group consisted of 21 children recruited from the general paediatric population who were without exposure to immunosuppressive treatment in the prenatal period. The children were matched to the study group in terms of age. Three of the children in the control group were under 10 years of age (2 girls aged 6 years, 1 boy aged 7 years). Thus, the size of the control group for measles was correspondingly smaller and consisted of 18 children. They received only one dose of MMR vaccination (a booster dose is given at 10 years of age). These children were not included in the statistical analysis for measles. They had the same doses of the other vaccines (HBV, polio) as the rest of the children.

The inclusion and exclusion criteria are presented in Table 1. A detailed description of the groups is shown in Table 2. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Medical University of Warsaw Bioethics Committee (Approval no. KB/161/2021).

All children were vaccinated against hepatitis B, polio, and measles on schedule, in accordance with the immunization program applicable for their birth year.

A measure of 3 mL of venous blood was collected from each patient into a clot tube. The material was centrifuged 1.5 h after being collected in a centrifuge (10,000 rpm, 5 min). Then, the material was frozen at −80 degrees Celsius. The material had been stored until ELISA tests were performed.

ELISA tests were performed using standardized kits by Alpha Diagnostic Intl., Inc. San Antonio, Texas, USA. The tests for each sample were performed twice. The tests were performed in accordance with the manufacturer's instructions [9–11].

Absorbance readings were performed using a UVM340 plate reader (ASYS, Biogenet), and the results were analysed using MikroWin2000 v4 software (Mikrotek Laborsysteme GmbH, Biogenet, Overath, Germany). Antibody concentrations are expressed in conventional units (U/mL), which are defined by the manufacturers for each test as appropriate. The details are presented in Table 3.

A survey was conducted on the children's general health, past illnesses, hospitalizations, and adverse post-vaccination events. The questions that were included in the form along with the results are presented in Table 2. Data on vaccination adverse events were obtained through a questionnaire for the parents of the children.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• Age: 6–16 • Maternal immunosuppression during pregnancy due to organ transplantation • Non-use of long-term pharmacotherapy • Immunization in accordance with the Protective Immunization Program applicable in Poland for this year of birth • Informed consent to participate in the study	• Active infection of the respiratory tract, digestive system, and urinary tract within 30 days prior to sample collection (existence of symptoms such as runny nose, cough, body temperature above 38 degrees Celsius, acute diarrhoea) • Chronic diseases of the digestive system (e.g., Crohn's disease), respiratory system (e.g., cystic fibrosis), in particular autoimmune diseases, systemic connective tissue diseases, congenital and acquired immunodeficiencies, cancer

Table 2. Detailed description of the study and control groups.

Parameters	Transplant n = 18	Control n = 21	p Value (Mann-Whitney U Test)
Children			
Male	7 (39%)	9 (43%)	$p > 0.05$
Female	11 (61%)	12 (57%)	$p > 0.05$
Mean ± SD age	12.11 ± 3.16	9.05 ± 3.07	$p > 0.05$
Chronic diseases	2 (11%)	3 (14%)	$p > 0.05$
History of hospitalization	0 (0%)	1 (5%)	$p > 0.05$
History of vaccination AEs			
Mild	3 (17%)	5 (24%)	$p > 0.05$
Moderate	0 (0%)	0 (0%)	$p > 0.05$
Severe	0 (0%)	0 (0%)	$p > 0.05$
Type of Tx			
Kidney	9		
Liver	9		
Immunosuppressive schemes during pregnancy	Children of KTRs	Children of LTRs	
Cyclosporine + azathioprine + steroid	6 (67%)	0	
Tacrolimus + azathioprine + steroid	3 (33%)	3 (33%)	
Tacrolimus + steroid	0	1 (11%)	
Tacrolimus	0	2 (22%)	
Azathioprine + steroid	0	1 (11%)	
Tacrolimus + azathioprine	0	2 (22%)	

KTRs—kidney transplant recipients, LTRs—liver transplant recipients, Tx—transplantation AEs—adverse events.

Table 3. Interpretation of the results of ELISA tests concerning Anti-Poliomyelitis virus 1–3 IgG, Anti-HBsAg IgG, and Anti-Measles IgG, according to manufacturers' recommendations.

	Anti-Poliomyelitis Virus 1–3 IgG	Anti-HBsAg IgG	Anti-Measles IgG
Interpretation:	Positive > 10 U/mL Negative < 10 U/mL	Positive > 10 U/mL Negative < 10 U/mL	Positive 12 U/mL Not conclusive 8–12 U/mL Negative < 8 U/mL

Statistical Analysis

Mean concentrations of post-vaccination IgG antibodies against the following viruses were analysed: hepatitis B, measles and polio. Mean antibody concentrations were the arithmetic mean of antibodies calculated from two independent absorbance readings for individual patient sera.

For the parameters analysed (separately for the control and study groups and the subgroups of the study group: LTRs and KTRs), the conditions for parametric tests were verified. The normality of distribution was assessed using the Shapiro–Wilk test. The homogeneity of variance was tested using the Levene's test.

For each of the three analysed tests (polio, hepatitis B, measles), the data did not meet the assumptions for parametric tests (the null hypothesis of normal distributions had to be rejected, $p < 0.05$).

In view of the above, the results were subjected to non-parametric analysis. Two separate statistical analyses were performed. The significance of differences in antibody titres between the control and study groups was analysed using the Kolmogorov–Smirnov test for two independent samples. The ANOVA signed rank Kruskal–Wallis test was used to investigate the significance of differences in antibody titres between the groups, taking into account the type of mother's organ transplantation. The Kolmogorov–Smirnov test is based on the maximum absolute difference between the observed cumulative distribution functions for both samples. Kruskal's test is the most powerful non-parametric equivalent to the parametric analysis of variance. The choice of the tests was attributed to the small

size of the control and study groups, which resulted from the unique nature of the group of patients, which included children of post-transplant mothers.

3. Results

The statistical analysis results are presented in Table 4 and Figures 1–3. The median concentration of anti-HBV antibodies (Anti-HBsAg), anti-poliovirus antibodies and anti-Measles antibodies are presented. These results, however, are not statistically significant ($p > 0.05$). The Anti-Poliomyelitis virus 1–3 IgG and anti-measles virus antibodies (Anti-Measles IgG) in the group of children of post-transplant mothers was higher compared to the control group. The differences expressed by the Kolmogorov–Smirnov test were not statistically significant ($p > 0.1$). The obtained concentrations of post-vaccination immune antibodies (Anti-Poliomyelitis virus 1–3 IgG, Anti-HBsAg IgG, Anti-Measles IgG) were interpreted according to the recommendations of the manufacturer of the ELISA tests (details in Table 3).

Table 4. Median and IQR (*Interquartile range*) of post-vaccination antibody concentrations (Anti-Poliomyelitis virus 1–3 IgG, Anti-HBsAg IgG, Anti-Measles IgG) in children of post-transplant mothers and in children from the general population.

	Children of Post-Transplant Mothers		Children from the Control Group		Results of the Analysis Using the Kolmogorov–Smirnov Test		
	Median Concentration of Antibodies IgG [U/mL]	IQR [U/mL]	Median Concentration of Antibodies IgG [U/mL]	IQR [U/mL]	Maximum Negative Difference	Maximum Positive Difference	*p*
HBV	2306.04	1546.34	2130.93	2109.38	−0.14	+0.21	$p > 0.1$
Polio	30.84	33.41	23.21	20.48	0.00	+0.30	$p > 0.1$
Measles	3052.66	3736.53	3020.19	2173.48	−0.06	+0.26	$p > 0.1$

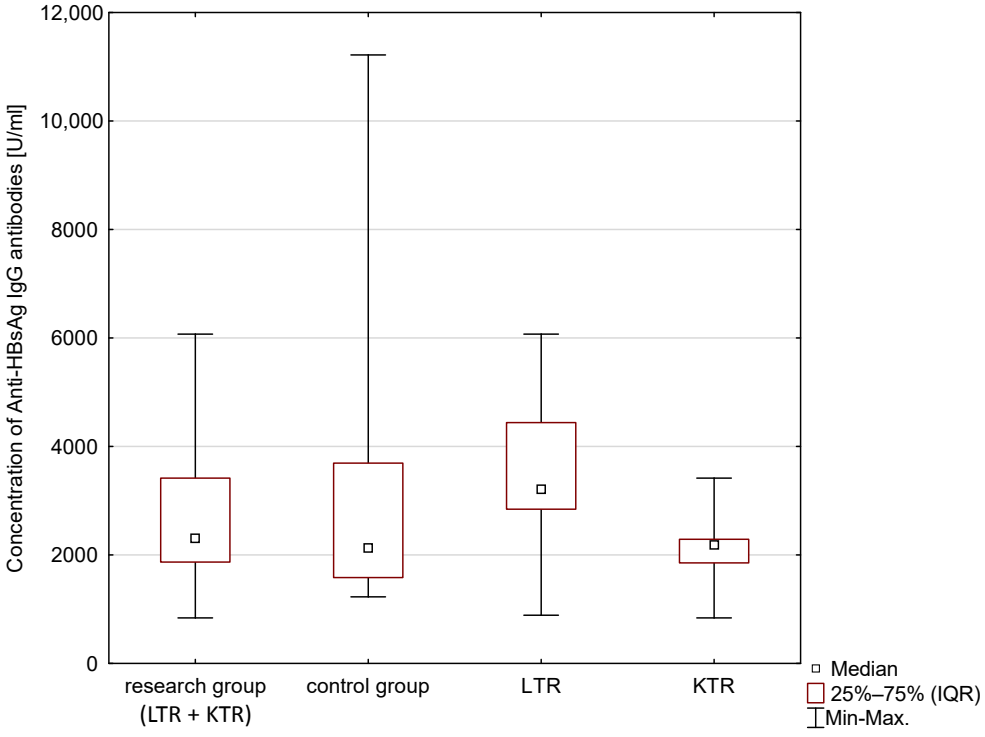

Figure 1. Concentration of Anti-HBsAg IgG antibodies in blood serum.

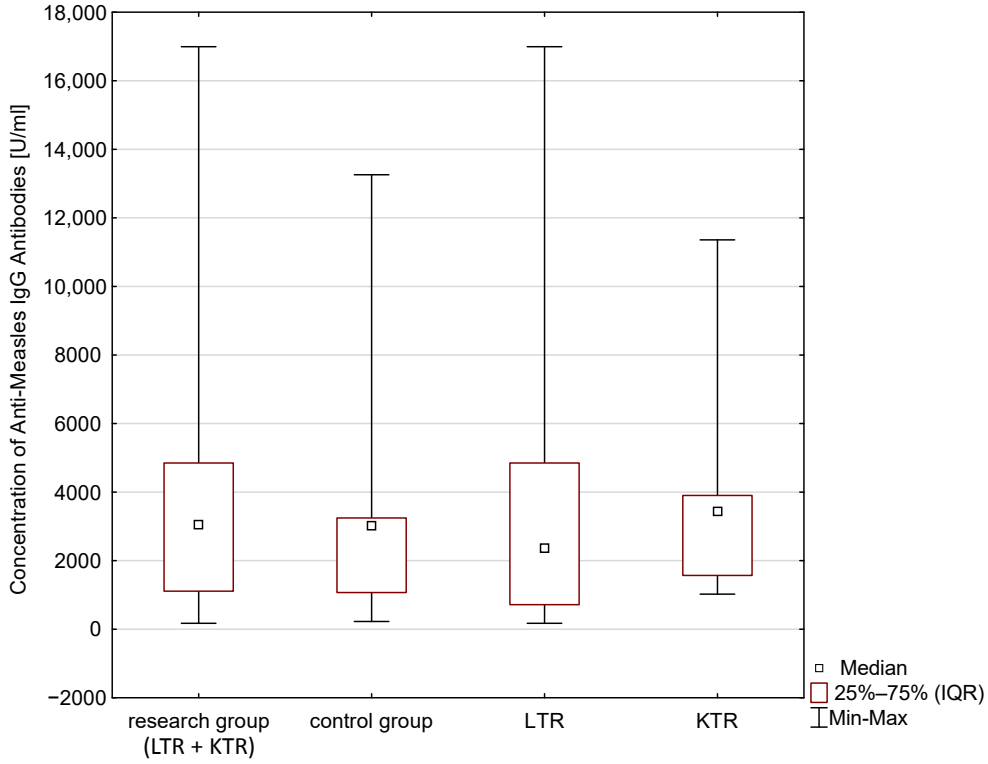

Figure 2. Concentration of Anti-Measles IgG antibodies in blood serum.

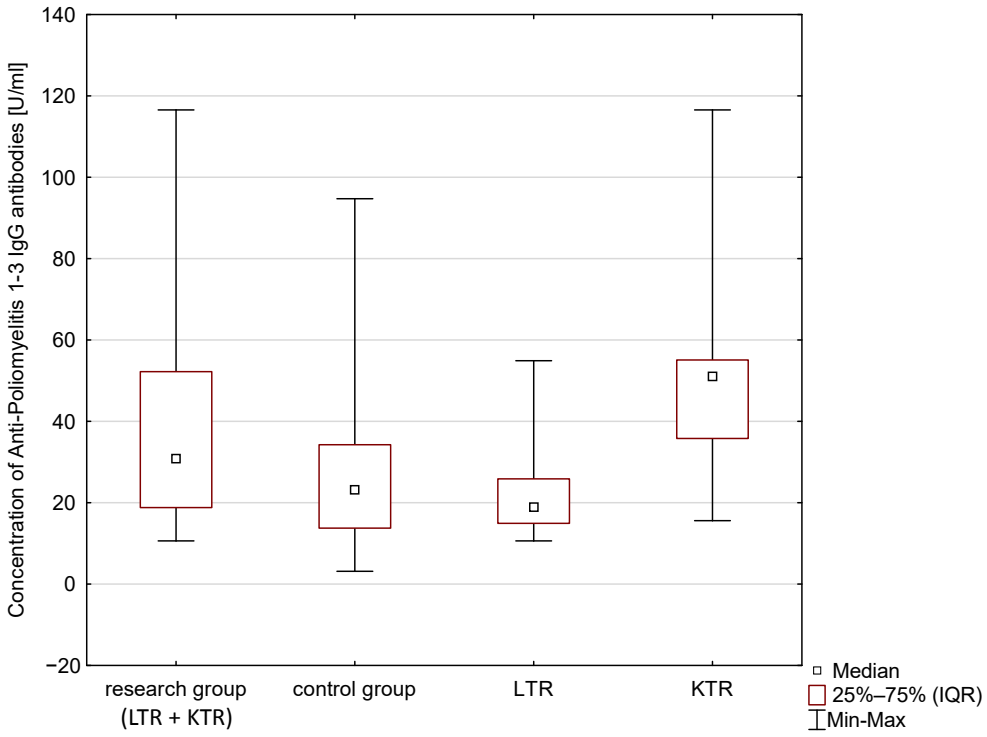

Figure 3. Concentration of Anti-Poliomyelitis Virus 1-3 IgG antibodies in blood serum.

As presented in Table 5, all children obtained protective levels of post-vaccination antibodies against HBV and measles. The exception is the Anti-Poliomyelitis virus 1–3 IgG antibodies, in the case of which nearly 10% of the cases from the general paediatric popula-

tion were seronegative after vaccination. The result is interesting because it only applies to the general population. However, these results are not statistically significant ($p > 0.05$).

Table 5. Seropositivity after vaccination against hepatitis B, polio, and measles in children of post-transplant mothers (study group) and children from the general paediatric population (control group).

	Anti-HBsAg IgG		Anti-Measles IgG		Anti-Poliomyelitis Virus 1–3 IgG	
	Study Group	Control Group	Study Group	Control Group	Study Group	Control Group
Seropositivity	100%	100%	100%	100%	100%	90.5%

The ANOVA signed rank Kruskal–Wallis test was used to analyse the concentrations of immune antibodies in children of mother recipients. It took into account the type of transplantation. The detailed results are presented in Table 6. No statistically significant differences were found, despite the differences in the median concentrations of the tested antibodies between the groups ($p > 0.05$).

Table 6. Median and IQR of post-vaccination antibody concentrations (Anti-Poliomyelitis virus 1–3 IgG, Anti-HBsAg IgG, Anti-Measles IgG), taking into account the type of transplantation.

	Children of Mothers after Kidney Transplantation		Children of Mothers after Liver Transplantation		Control Group	
	Median Concentration of Antibodies IgG [U/mL]	IQR [U/mL]	Median Concentration of Antibodies IgG [U/mL]	IQR [U/mL]	Median Concentration of Antibodies IgG [U/mL]	IQR [U/mL]
HBV	2187.50 *	436.42	3211.21 *	1594.83	2130.93 *	2109.38
Polio	51.11 *	19.31	18.97 *	10.94	23.21 *	20.48
Measles	3440.09 *	2335.51	2362.43 *	4133.18	3020.19 *	2173.48

* differences between the individual groups were not statistically significant ($p > 0.05$).

4. Discussion

The results of our study showed no statistically significant differences in the concentrations of post-vaccination antibodies against the HBV virus, measles virus, and poliovirus between children of mothers who were liver and kidney recipients and those from the general population. It is very tough to compare the results with other researchers due to the limited number of publications on the health of children of mothers who had received liver and kidney transplantation.

Due to the relatively rare occurrence of HBV, polio, and measles in modern Europe, the contribution of patient contact with these viruses to immunity is insignificant. Consequently, the results obtained primarily illustrate the effect of the vaccine response.

As mentioned in the introduction, there are only a few centres that keep records of the development of children of post-transplant mothers. Follow-ups in our centre are carried out from the moment a child is born to an organ recipient to when they reach the age of majority, and sometimes also after reaching the age of majority. The long-term specialist care of children (0–18 years) by our team means that the follow-up data on the health problems of the patients is constantly recorded, and it becomes possible to detect clinically interesting differences in the development of this group of children in relation to the general population.

An extensive analysis of the worldwide literature published in the last thirty years was carried out (1992–2022) during the search for research on the development and function of the immune system in children of post-transplant mothers. This research included the comparison of the titres of post-vaccination antibodies against viruses such as HBV, measles, and polio in the indicated group with the general paediatric population.

One study was found that evaluated post-vaccination responses in children of mother-recipients that were immunized against bacterial diseases, but not viral diseases as was the case of our study. Dinelli et al. [12] examined humoral response after vaccination against Haemophilus influenzae, S. pneumoniae, and M. tuberculosis in 24 children of mother-recipients and found no differences in the immune response compared to the control group ($p > 0.05$). These results were consistent with our observations, suggesting an adequate immune response in children of post-transplant mothers to preventive vaccinations. However, this team's research results cannot be directly compared with ours because both groups tested the response against different vaccines.

No article was found that compared post-vaccination antibody titres against HBV virus, measles virus, and poliovirus in the indicated group compared to the general paediatric population. Consequently, the results of this study are pioneering on a global scale. At the same time, due to the lack of studies available for comparison, it is not possible to relate the obtained results directly to the results of other researchers.

In the data bases of medical publications, a few articles were found whose authors examined the function and development of the immune system in newborns and infants of post-transplant mothers. Schen et al. [13], in a 12-month follow-up period, showed a reduced number of T lymphocytes (CD3+, CD4+, CD8+) and B lymphocytes (CD19+) in a white blood cell smear in 11 children of mothers who had undergone kidney transplantation compared to children of mothers who had not been exposed to immunosuppressive drugs in the prenatal period. Moreover, Schen et al. [13] found reduced levels of immunoglobulins in the same group of children. E. Ono et al. [14] examined 28 children after delivery and in the 8th month of life and showed a similar dependence on a lower number of lymphocytes to that of Schen et al. [13]. They also pointed out the necessity of the close monitoring of infants of mothers after organ transplantation who may be at higher risk of hospitalization not only due to prematurity, but also due to the fact they were born to female organ recipients. Due to the lack of studies on this issue in the literature, studies conducted on very small groups of patients, as in the case of Di Paolo et al. [15] and Takahashi et al. [16] (in both studies, groups of six newborns), who confirm this correlation, cannot be omitted. Based on the results, some researchers draw conclusions in which they recommend delaying mandatory vaccinations in this group of infants [4]. Some authors suggest that the first doses of vaccine should be administered after the 6th month of life and not after the 6th week of life [4], as in the case of the general population of children. They present the problem of both the possibility of a suboptimal immune response and the increased risk of vaccine adverse events.

The data presented above is most likely the result of immunosuppressive treatment used during pregnancy. Freriksen et al. [17] showed that tacrolimus, which is widely used in transplantation, may accumulate in the tissues of the foetal placenta. All immunosuppressive drugs used after kidney and liver transplantation cross the placental barrier and can be detected in foetal blood [17].

Taking into account our results, it seems that alterations to the white blood cell line of the immune system occurring in the first months of life do not affect the ability to develop long-term, specific post-vaccination immunity against viral diseases.

Our study did not record an increased percentage of adverse post-vaccination events compared to the general population for the analysed vaccinations. This analysis proves the safety of vaccinations that are carried out according to the standard program in children of mothers who undergo organ transplantation.

To date, no studies have been conducted that could provide the basis for creating recommendations regarding vaccinations in children of post-transplant mothers. Currently, immunization in this group is the same as that in the general population. There is no argument as to whether such a procedure is correct or involves an increased risk for children of mothers that are organ recipients. Taking into account our results, it seems reasonable to maintain a standard vaccination protocol in the group of children of post-transplant mothers that would be the same as for the general population. Due to the

known mechanisms of transfer of immune antibodies through the placenta and breast milk, active screening of antibody levels in organ recipients who plan to become pregnant should be considered in order to possibly administer an additional dose of the vaccination. Such actions may provide better protection in the early postnatal period when children of post-transplant mothers have reduced lymphocyte counts.

The obtained conclusions require confirmation through studies conducted on more numerous groups of children of post-transplant mothers.

The results of studies of other clinical parameters in children of mothers after transplantation published in recent years mostly show no differences in the parameters studied when compared to children from the general paediatric population. Such findings were observed in papers in relation to lipid profile, biochemical parameters, and neurological development of these children [18–20].

These data indicate that there is a non-existent or insignificant impact of the immunosuppression used during pregnancy on the long-term development of their children. The number of pregnancies of post-transplant mothers is successively increasing, and these mothers can enjoy the motherhood that they longed for.

5. Limitations of the Study

This study analysed post-vaccination antibody titres against HBV, polio, and measles in subjects aged 6–16 years. This study does not allow us to determine whether the immunological response in the earlier years of life (under 6 years) is comparable. The study assessed only the humoral response. On its basis, it is impossible to determine the role of the cellular response in developing post-vaccination immunity against virus diseases. The objective of the study was to determine immunogenicity. Still, it is difficult to assess the real effectiveness of vaccination because of the low incidence of hepatitis B, poliomyelitis, and measles in Europe due to collective immunity caused by the high vaccination coverage of Europeans. Antibody titres are not the only measure of post-vaccination protection. The immune memory response as measured by an increase in antibody titres after a booster dose may be an equally important factor in protection against disease when compared to baseline titres alone. The statistical analysis of the effect of specific immunosuppressive drugs used during pregnancy on postvaccination antibody concentrations was not conducted. This was due to the large variation in immunosuppressive therapy regimens, which, with a small sample size, would have made it impossible to obtain objective results and thus statistical inference.

6. Conclusions

No difference was observed in the immunogenicity of hepatitis B, polio, and measles vaccinations between children of post-transplant mothers and those of the general population. Based on the study, there are no differences in the immunogenicity of vaccinations in the child and the type of organ transplanted to the mother.

The immunization of children of mothers that have had organ transplantation is safe, and the percentage of adverse post-vaccination events does not differ from the general population.

The obtained results do not indicate the need for modification of the vaccination program against HBV, measles, and polio in this group of patients.

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Article

Evaluation of the Development of Post-Vaccination Immunity against Selected Bacterial Diseases in Children of Post-Solid-Organ-Transplant Mothers

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Abstract: Pregnancy after organ transplantation is considered high-risk and requires supervision in specialized centers. The impact of immunosuppression on the developing fetus is still the subject of research. It has been shown that it affects lymphocyte populations in the first year of life. For this reason, researchers suggest postponing mandatory infant vaccinations. The aim of the study was to analyze the influence of intrauterine exposure of the fetus to immunosuppression on the immunogenicity of protective vaccinations against selected bacterial pathogens. The ELISA method was used to determine the concentration of post-vaccination IgG antibodies against diphtheria, tetanus, pertussis, tuberculosis, *H. influenzae* type B, and *S. pneumoniae* in 18 children of mothers who underwent organ transplantation. The results were compared with the control group (n = 21). A comparison of the incidence of adverse post-vaccination reactions between the analyzed groups was also performed. There were no statistically significant differences in the immunogenicity of the analyzed vaccines between children of mothers who underwent organ transplantation and the age-matched general pediatric population. There were no differences in the incidence of adverse post-vaccination reactions between the analyzed groups. The obtained results do not indicate the need to modify the current protective vaccination schemes against bacterial pathogens in children of mothers who underwent organ transplantation.

Keywords: immunogenicity; immunosuppressive drugs in pregnancy; transplantation; safety of vaccination; anti-bacterial vaccination; children

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1. Introduction

Transplantology is one of the fastest growing fields of medicine. Due to the development of this field, there is a steadily increasing age of survival after transplantation, sometimes comparable to the general population. Thus, the development of peri-transplantation knowledge, focused not so much on maintaining the function of the transplanted organ, but also holistic measures aimed at improving the quality of life, is becoming more important. One of the most important aspects of social life, as well as human physiology, is reproduction and the desire to have offspring. In the past, pregnancy in solid-organ transplant patients was a debatable issue. Initially, the relatively short survival period of patients after transplantation surgery due to the imperfection of surgical techniques, as well as post-transplantation care, meant that pregnancy in organ recipients was not recommended. The first full-term pregnancy of a transplant patient was described in 1963 by Murray et al. [1]. It was a patient after a kidney transplant. It is now known that

pregnancy after organ transplantation is possible. Current immunosuppressive regimens in pregnancy allow one to maintain the function of the transplanted organ and to carry to term. However, each pregnancy in an post-organ-transplant patient is considered a high-risk pregnancy. Patients should be monitored by a multidisciplinary team with relevant experience in managing pregnancies of post-transplant patients, preferably in higher-level referral facilities. Pregnancy in post-organ-transplant patients has been shown to have an increased risk of maternal–fetal complications. Despite the available knowledge and experience of clinicians, pregnancy after organ transplantation is associated with a 10-fold lower probability of giving a birth to a live baby than that in the general population [2]. An increased risk of hypertension, preeclampsia, and eclampsia has been observed in pregnant post-transplant women. Fetal complications include growth restriction, preterm delivery, and increased incidence of cesarean section [3–8]. Knowledge of the long-term effects of intrauterine fetal exposure to immunosuppressive drugs is incomplete. Few papers are available in the literature assessing, among other things, the development of children of post-transplant mothers in the context of selected biochemical parameters [9], lipid metabolism [10], immune system development [11], neurological system [12], birth parameters, and the course of pregnancy and delivery [3–8]. Intrauterine fetal exposure to immunosuppressive drugs has an impact on the development of the child's immune system. It has been shown that during the first year of life, children of post-transplant mothers show a reduced number of T and B lymphocytes compared to the general population [13–15]. For this reason, it seems to be important to assess whether children from this population also show a different post-vaccination response to the general pediatric population. Vaccination is an important aspect for the proper development of a child, preventing life-threatening infectious diseases. Therefore, knowing whether vaccination schedules in this group of children should be implemented the same or differently from the common immunization calendar is essential. In the literature so far, only a few papers have been published comparing the immunogenicity of vaccination in children of organ recipient mothers which concerned the response to vaccination against selected viral and bacterial diseases [16,17]. The conclusions of the papers were based on studies conducted on small groups of patients, and each time the authors stressed the need for expanded studies on larger, more representative groups of patients. Significant pathogens in both childhood and adulthood include pathogens against which there are immunizations. Assessing the impact of intrauterine fetal exposure on the long-term response to vaccination directed against bacterial diseases has not yet been analyzed by researchers. In view of the fact that this issue appears to have significant clinical relevance it has become the subject of this paper.

The aim of the study was to evaluate the immunogenicity of immunization against diphtheria, tetanus, pertussis, tuberculosis, *Hemophilus influenzae* type b, and *Streptococcus pneumoniae* in children of mothers after liver or kidney transplantation and its comparison to children from the general population. An additional aim was to assess the incidence of adverse reactions after vaccination in the groups analyzed.

2. Material and Methods

The study was conducted in 2021–2022. The study included two groups of children between the ages of 6 and 16 born between 2008 and 2014. The study group consisted of 18 children of post-solid-organ-transplant mothers: 9 children of liver recipient mothers and 9 children of kidney recipient mothers. The children's mothers took immunosuppressive drugs during pregnancy in accordance with current standards of post-transplant care. The control group consisted of 21 healthy, gender-matched children from the general pediatric population. All children were vaccinated in accordance with the immunization calendar in effect in Poland. In order to ensure the greatest homogeneity of the groups in terms of the number of immunization doses received, children between the ages of 6 and 16 were selected, since vaccination against bacterial diseases, the subject of this study, is not performed during this age range. All children received 1 dose of BCG (Bacillus Calmette–Guérin) tuberculosis vaccine, 4 doses of DTP (Diphtheria, Tetanus, Pertussis),

4 doses of Hib (*Hemophilus influenzae* type b) vaccine, and 3 doses of 13-valent pneumococcal vaccine (PCV-13)

Detailed characteristics of the groups, including the inclusion and exclusion criteria, as well as the regimens of immunosuppressive treatment used are summarized in Tables 1 and 2.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• Age: 6–16. • Maternal immunosuppression during pregnancy due to organ transplantation. • Non-use of long-term pharmacotherapy. • Immunization in accordance with the Protective Immunization Program applicable in Poland for this year of birth. • Informed consent to participate in the study.	• Active infection of the respiratory tract, digestive system, and urinary tract within 30 days prior to sample collection (existence of symptoms such as runny nose, cough, body temperature above 38 degrees Celsius, acute diarrhea). • Chronic diseases of the digestive system (e.g., Crohn's disease), respiratory system (e.g., cystic fibrosis), in particular autoimmune diseases, systemic connective tissue diseases, congenital and acquired immunodeficiencies, cancer.

Table 2. Detailed description of the study and control groups.

Parameters	Transplant n = 18	Control n = 21	*p* Value (Mann–Whitney U Test)
Children			
Male	7 (+39%)	9 (+43%)	$p > 0.05$
Female	11 (61%)	12 (57%)	$p > 0.05$
Mean ± SD age	12.11 ± 3.16	9.05 ± 3.07	$p > 0.05$
Chronic diseases	2 (11%)	3 (14%)	$p > 0.05$
History of hospitalization	0 (0%)	1 (5%)	$p > 0.05$
History of vaccination AEs			
Mild (grade 1)	4 (+22%)	6 (+28%)	$p > 0.05$
Moderate (grade 2)	0 (0%)	0 (0%)	$p > 0.05$
Severe (grade 3)	0 (0%)	0 (0%)	$p > 0.05$
Potentially life threatening (grade 4)	0 (0%)	0 (0%)	$p > 0.05$
Type of Tx			
Kidney	9		
Liver	9		
Immunosuppressive schemes during pregnancy	**Children of KTRs**	**Children of LTRs**	
Cyclosporine + azathioprine + steroid	6 (+67%)	0	
Tacrolimus + azathioprine + steroid	3 (+33%)	3 (+33%)	
Tacrolimus + steroid	0	1 (+11%)	
Tacrolimus	0	2 (+22%)	
Azathioprine + steroid	0	1 (+11%)	
Tacrolimus + azathioprine	0	2 (+22%)	

Data on the occurrence of adverse events related to vaccinations were collected from analyses of patients' medical records as well as on the basis of questionnaires completed by parents regarding the medical history of children. The severity of the local and systemic AEFIs was graded on a scale of 1 to 4 based on the guidelines of the U.S. Food and Drug Administration [18].

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Medical University of Warsaw Bioethics Committee (Approval no. KB/161/2021).

A sample of 3 mL of venous blood was taken from each child into a clot activator tube. The material was then centrifuged (10,000 rpm, 5 min). The separated blood plasma was frozen at −80 degrees C. After obtaining a set of samples, the material was thawed and analyzed by ELISA. The following antibodies were analyzed: anti-tuberculosis BCG IgG, anti-*Hemophilus influenzae* B IgG, anti-*S. pneumococcal* vaccine IgG, anti-Tetanus Toxoid IgG. Standardized reagent kits from Alpha Diagnostic Intel were used for ELISA testing. Each sample was tested twice. The tests were performed according to the manufacturer's instructions. Absorbance was read using a UVM340 plate reader (ASYS, Biogenet, Santa Clara, CA, USA). The results were then analyzed using MikroWin2000 v4 software (Mikrotek La-borsysteme GmbH, Biogenet, Overath, Germany). Absorbance results were converted to antibody concentrations in units (U/mL) as defined by the manufacturer. An average was calculated from the two measurements for each sample, which was used for further statistical analysis. Details are shown in Table 3.

Table 3. Medians with quartile ranges and means with standard deviations of immune antibody concentrations in the children in study and control groups.

	Study Group						**Control Group**	
	Children of Mothers Who underwent Organ Transplantation in Total (LTR + KTR)		**Children of Mothers Who underwent Kidney Transplantation (KTR)**		**Children of Mothers Who underwent Liver Transplantation (LTR)**		**Children from the Control Group**	
	Median Concentration of Antibodies IgG (IQR) [U/mL]	**Mean Concentration of Antibodies IgG +/− SD [U/mL]**	**Median Concentration of Antibodies IgG (IQR) [U/mL]**	**Mean Concentration of Antibodies IgG +/− SD [U/mL]**	**Median Concentration of Antibodies IgG (IQR) [U/mL]**	**Mean Concentration of Antibodies IgG +/− SD [U/mL]**	**Median Concentration of Antibodies IgG (IQR) [U/mL]**	**Mean Concentration of Antibodies IgG +/− SD [U/mL]**
C. diphteriae	24.6 (39.85)	40.07 +/− 37.30	26.63 (39.34)	39.19 +/− 29.33	19.07 (21.64)	40.94 +/− 45.76	20.92 (32.22)	35.33 +/− 33.28
B. pertusis	2580.24 (10,800.29)	46,769.97 +/− 84,326.64	3983.48 (9566.65)	47,827.15 +/− 86,349.95	2110.48 (1589.01)	45,712.79 +/− 87,475.77	13,490.10 (198,515.70)	93,800.13 +/− 105,233.80
M. tuberculosis	321.85 (132.60)	350.37 +/− 175.22	379.15 (154.18)	443.51 +/− 193.07	277.90 (109.47)	257.23 +/− 91.94	254.77 (122.32)	273.67 +/− 80.88
H. influenzae	546.10 (1848.57)	839.57 +/− 685.17	678.33 (1761.52)	1022.39 +/− 672.41	332.39 (1775.40)	656.75 +/− 685.76	890.50 (1838.62)	951.82 +/− 612.24
N. meningitidis	0 (395.15)	261.37 +/− 435.98	143.05 (706.38)	409.64 +/− 548.63	0 (0.82)	113.09 +/− 231.22	0 (339.45)	203.29 +/− 300.65
S. pneumoniae	1254.26 (54.93)	1144.69 +/− 287.02	1267.05 (18.00)	1262.42 +/− 33.84	1231.06 (386.36)	1026.95 +/− 377.79	1259.47 (30.30)	1133.42 +/− 302.02
C. tetani	80.76 (94.98)	123.05 +/− 119.32	140.81 (217.10)	183.49 +/− 139.12	53.52 (82.02)	62.61 +/− 51.77	49.60 (132.80)	83.31 +/− 79.12

Statistical analysis was performed using StatSoft Statistica 13.1 software. A verification of assumptions for the use of parametric tests was carried out. The normality of the distributions was tested using the Shapiro–Wilk test. Homogeneity of variance was assessed using the Leaven test. In each case, the distributions analyzed did not meet the criteria for parametric tests. In view of the above, a proper statistical analysis was carried out using non-parametric tests. The strongest equivalent of one-way analysis of variance, the Kruskal–Wallis test, was used. Relative to the correlations for which statistically significant differences were shown, a post hoc analysis was performed using the Dunn test with Bonferroni correction. The test was chosen because of the small size of the control and study groups, which is due to the specific nature of the patient group, which includes children of post-transplant mothers.

The median concentrations of immune antibodies were analyzed by the Kruskal–Wallis test, followed by post hoc analysis, separately for each type, i.e., anti-tuberculosis BCG IgG, anti-*Hemophilus influenzae* B IgG, anti-*S. pneumococcal* vaccine IgG, anti-Tetanus

Toxoid IgG between children of mothers after organ transplant (liver and kidney combined–LTR + KTR), kidney and liver (subgroups, respectively: KTR and LTR) and children from the control group (no intrauterine exposure to immunosuppressive drugs—Control). A significance level of $\alpha = 0.05$ was adopted, below which the results were statistically significant. The results of the analyses are summarized in Tables 4–7 and discussed in Section 3.

Table 4. Results of statistical analysis of Anti-tuberculosis BCG IgG antibody concentrations.

***Anti-tuberculosis* BCG IgG—the Kruskal–Wallis *p*-Value Test**				
	LTR	**KTR**	**Control**	**LTR + KTR**
LTR		0.05	1.00	0.79
KTR	0.05		0.03	0.79
Control	1.00	0.03		0.72
LTR + KTR	0.79	0.79	0.72	

Table 5. Results of statistical analysis of anti-*Hemophilus influenzae* B IgG antibody concentrations.

Anti-*Hemophilus influenzae* B IgG—the Kruskal–Wallis *p*-Value Test				
	LTR	**KTR**	**Control**	**LTR + KTR**
LTR		0.26	0.28	1.00
KTR	0.26		1.00	1.00
Control	0.28	1.00		1.00
LTR + KTR	1.00	1.00	1.00	

Table 6. Results of statistical analysis of anti-*S. pneumococcal* vaccine IgG antibody concentrations.

Anti-*S. pneumococcal* Vaccine IgG—the Kruskal–Wallis *p*-Value Test				
	LTR	**KTR**	**Control**	**LTR + KTR**
LTR		0.43	1.00	1.00
KTR	0.43		1.00	1.00
Control	1.00	1.00		1.00
LTR + KTR	1.00	1.00	1.00	

Table 7. Results of statistical analysis of anti-Tetanus Toxoid IgG antibody concentrations.

Anti-Tetanus Toxoid IgG—The Kruskal–Wallis *p*-Value Test				
	LTR	**KTR**	**Control**	**LTR + KTR**
LTR		0.16	1.00	1.00
KTR	0.16		0.17	1.00
Control	1.00	0.17		1.00
LTR + KTR	1.00	1.00	1.00	

3. Results

Table 3 shows the detailed results of concentrations for each type of immune antibody.

Tables 4–7 show the results of the analysis of Dunn's post hoc test with Bonferroni correction for each type of antibody. The tables do not include the results of analyses for C. Diphteriae and B. Pertusis for which no statistical relationships were shown.

Table 4 shows the results of post hoc analysis of anti-tuberculosis BCG IgG antibodies. According to the analysis, the median concentration of anti-tuberculosis BCG IgG antibodies

in children of post-organ-transplant mothers (both children of liver or kidney recipients and regardless of the type of transplanted organ) was higher than in the control group, in which it amounted to 254.77 U/mL (IQR = 122.32 U/mL). However, only in children of renal transplant mothers (379.15 U/mL; IQR = 154.18 U/mL) statistically significant differences ($p = 0.03 < \alpha$) were shown. In the other subgroups, despite finding a higher median value, the results were not statistically significant ($p > 0.05$). The results are illustrated in Figure 1 in the form of "box-and-whisker" diagrams.

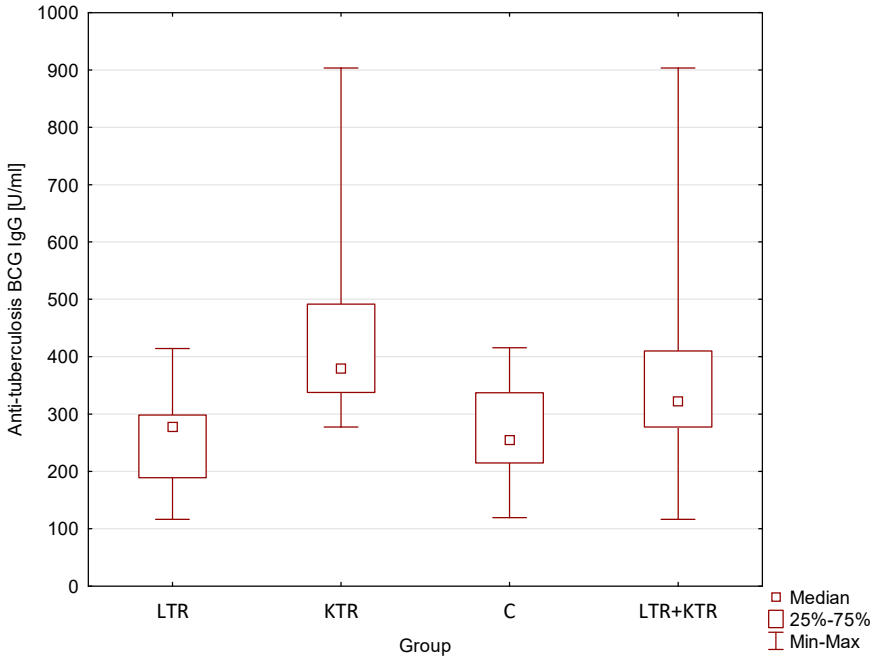

Figure 1. Medians of anti-tuberculosis BCG IgG antibody concentrations.

Tables 5–7 show the results of post hoc analyses, respectively, for anti-*Hemophilus influenzae* B IgG, anti-*S. pneumococcal* vaccine IgG, *anti-Tetanus* Toxoid IgG. On the basis of Dunn's post hoc analysis with Bonferroni correction for each of the analyzed antibody types, there were no statistically significant differences between the analyzed subgroups ($p > 0.05$).

A comparative analysis of the incidence of adverse vaccine reactions was also conducted. The incidence of serious and severe vaccine reactions was not observed in the study populations. Among the most common were malaise and redness at the injection site. The incidence of mild vaccine reactions was analyzed using the Mann–Whitney U-test. No differences in their incidence were observed between the study group (KTR + LTR) and the control group were observed (22% vs. 28% $p > 0.05$).

4. Discussion

The analysis showed no statistically significant differences in post-vaccination antibodies to diphtheria, tetanus, pertussis, tuberculosis, and pneumococcus between children of liver and kidney recipient mothers and those of the general population. Chronic maternal immunosuppression also applied during pregnancy is not indifferent to the developing fetal immune system. As shown in numerous publications, children of post-solid-organ-transplant mothers in the first 12 months of life have reduced numbers of T lymphocytes (CD3+, CD4+, CD8+) and B lymphocytes (CD19+) compared to children not exposed to immunosuppression during fetal life [13–15]. After the first year of life, the white blood cell smear normalizes and no longer shows differences from the general population.

The abnormalities found in the development of the immune system in the first months of life may suggest a poorer response to vaccination in children of post-transplant mothers. The analysis of immunization immunogenicity is a clinically important aspect of interdisciplinary care for this special group of patients.

The topic of the health of children of post-transplant mothers has been covered quite extensively in the works of other researchers. However, the body of work evaluating the immunogenicity and safety of immunization in this patient group available in medical publication databases is limited. For this reason, each newly published work analyzing this issue represents a significant development of the current state of knowledge.

Dinelli et al. [17] conducted a study on a group of 24 children of kidney post-transplant mothers at 7–8 months of age. They showed that median concentrations of antibodies to tetanus, *H. influenzae* type B, and pneumococcus were comparable to the general population ($p > 0.05$). There were also no differences in the incidence of vaccine side effects between the groups. The results were therefore comparable to those obtained by our team.

Baarsma et al. [19] described a clinical case of the child of a post-liver-transplant mother. Antibody concentrations against diphtheria, tetanus, and poliomyelitis in the second year of life were analyzed. Again, the post-vaccination response was adequate.

In our study, we found higher median anti-tuberculosis BCG IgG antibody concentrations in the children of kidney recipient mothers compared to children from the general population ($p < 0.05$). Given the lack of differences for all other vaccine antibodies, the reason for the relationship obtained is unknown. Based on current medical knowledge, it is difficult to explain the reason for the obtained correlation and this needs to be verified in further studies.

As is known, there are many other factors that influence the development of the newborn's immune system. One of them is breastfeeding and the moment of introducing complementary foods [20]. Breastfeeding, especially in the first period of life, has a positive impact on the development of the newborn's immunity [20–23]. The analysis of the impact of these factors was not the subject of our study.

The literature contains the results of few studies assessing the concentration of immunosuppressive drugs used in post-transplantation care in human milk [24–30]. The results of the analyzed studies clearly indicated that the concentration of cyclosporine in colostrum and mature milk is significantly below the therapeutic level (approx. 1% of the maintenance dose for adults), and the bioavailability after oral ingestion is approximately 28% [24]. Despite the low level of transmission of cyclosporine and its metabolites into breast milk, the benefits of breastfeeding by mothers—organ recipients—is debatable. Clinicians involved in post-transplantation care inform women about the possible positive and negative effects of breastfeeding while receiving immunosuppressive therapy. The choice is left to the mother's discretion. Perhaps future studies conducted on larger groups of patients will contribute to changing the current recommendations.

The current state of knowledge on the immunogenicity of immunization against bacterial diseases in children of post-transplant mothers is incomplete. The few studies that have been conducted on this issue cannot be the basis for formulating separate guidelines for the vaccination of children of post-organ-transplant mothers. Currently, vaccination schedules for children of recipient mothers are implemented according to the vaccination calendar for children in the general population. The results of the conducted work, as well as the available literature data, do not indicate the need to modify this procedure. Given our results, it seems reasonable to maintain a standard vaccination protocol against bacterial diseases in the group of children of post-transplant mothers, the same as in the general population.

5. Conclusions

1. No difference in the immunogenicity of immunization against selected childhood infectious diseases of bacterial etiology (diphtheria, tetanus, pertussis, tuberculosis,

pneumococcus) has been found in children of post-solid-organ-transplant mothers compared to the general pediatric population.
2. Increased immunogenicity of the BCG (Bacillus Calmette–Guérin) vaccine has been demonstrated in children of kidney-recipient mothers compared to children of the general population. However, the reason for this relationship is unclear and requires further research on larger patient populations.
3. The safety profile of the bacterial vaccinations analyzed in children of post-solid-organ-transplant mothers is comparable to that in the general pediatric population.
4. Based on the analysis, there is no evidence for the validity of modifying childhood bacterial vaccination schedules in children of post-transplant mothers.
5. It is suggested that existing vaccinations schedules be maintained and that children of organ recipient mothers be vaccinated in accordance with the immunization calendar in effect for children in the general population.
6. Due to the limited number of patients and the small number of publications available in the literature, it is suggested to continue studies on a larger population based on multicenter studies.

6. Limitations of the Study

This study analyzes post-vaccination antibody concentrations against diphtheria, tetanus, pertussis, tuberculosis, *Hemophilus influenzae* type b, and *Streptococcus pneumoniae* in children of post-liver/kidney-transplant mothers and in a control group aged 6 to 16 years. The study does not evaluate the post-vaccination response in younger children (under 6 years of age) or older children and adults (over 16 years of age). The test evaluates only the humoral response. The methodology adopted in the study, which relies on the evaluation of post-vaccination antibodies, does not allow for the determination of the cellular response in children of post-transplant mothers. The vaccination rate for the infectious diseases studied in the European Union is high; thus, there is high herd immunity in the area of patient residence and migration. For this reason, it is not possible to infer the effectiveness of immunization (determined as the effectiveness of protection against the occurrence of an infectious disease) only by assessing immunogenicity, both in the population of children of post-transplant mothers and children of the general population from Poland.

In our study a small number of patients were examined (research group—18; control group—21). This results in suboptimal power of the study. The rare group of patients, such as children of mothers after organ transplantation, makes it difficult to conduct research on a larger group of patients. Considering the fact that no other research on this topic, conducted on a larger population, has been published so far, each new study expands the available knowledge about the health of children of mothers after organ transplantation. No statistical analysis of the effect of individual immunosuppressive drugs used by mothers during pregnancy on the immunogenicity of their children's immunizations was performed in this study. Six independent immunosuppression regimens (cyclosporine + azathioprine + corticosteroid, tacrolimus + azathioprine + corticosteroid, tacrolimus + corticosteroid, tacrolimus in monotherapy, azathioprine + corticosteroid, tacrolimus + azathioprine) were used in the analyzed groups of female liver and kidney recipients. Conducting an analysis of differences would require dividing the 18 patients into six subgroups, and such small groups cannot be the basis for statistical inference. For such an analysis to be carried out, a much larger group of patients would need to be included in the study. To this end, it would be beneficial to carry out a multicenter study conducted in collaboration of centers dealing with the health of children of organ recipient mothers.

Author Contributions: Conceptualization, K.T. and B.K.-N.; Methodology, T.G., K.T., O.T. and A.S.-E.; Software, A.S.-E.; Validation, O.T.; Formal analysis, O.T.; Investigation, T.G., K.T. and A.S.-E.; Writing—original draft, T.G. and K.T.; Writing—review & editing, B.K.-N.; Supervision, B.K.-N.; Project administration, T.G. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee) of Medical University of Warsaw (protocol code: KB/161/2021, date of approval: 4 October 2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

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

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11. Podsumowanie i wnioski

Zdrowie dzieci matek po transplantacji narządu pozostaje przedmiotem zainteresowania wielu badaczy. W ostatnich dekadach obserwuje się wzrastającą liczbę ciąż kobiet po transplantacji narządu. Wyniki przeprowadzonych dotychczas analiz wskazują, że dzieci narażone na działanie leków immunosupresyjnych *in utero* rozwijają się podobnie jak dzieci z populacji ogólnej. Nie opisywano do tej pory zwiększonej chorobowości w tej grupie pacjentów lub częstszego występowania określonych problemów zdrowotnych. Mimo to, wiedza medyczna dotycząca zdrowia tej szczególnej grupy pacjentów pozostaje niepełna i uważa się, że z tego powodu dzieci powinny pozostać pod zwiększonym nadzorem interdyscyplinarnego zespołu specjalistów. W niniejszej dysertacji skupiono się na szczegółowej ocenie wpływu leków immunosupresyjnych stosowanych w ciąży na immunogenność wybranych szczepień u dzieci w obserwacji długoterminowej.

Na podstawie przedstawionego cyklu publikacji można wnioskować, że ekspozycja płodu *in utero* na leki immunosupresyjne stosowane przez matki biorczynie narządu nie wpływa na odpowiedź poszczepienną ich dzieci, zarówno przeciwko patogenom bakteryjnym, jak i wirusowym. W badaniu nie wykazano różnic w mianach przeciwciał poszczepiennych pomiędzy grupą badawczą i kontrolną. Przeprowadzona analiza częstości występowania niepożądanych odczynów poszczepiennych, również nie wykazała różnic pomiędzy grupami. Wydaje się, że szczepienia w tej grupie pacjentów, które aktualnie wykonywane są zgodnie z powszechnym programem szczepień tożsamym dla dzieci z populacji ogólnej powinny zostać utrzymane. Nie wykazano podstaw do modyfikacji schematów szczepień w grupie dzieci matek po transplantacji narządu.

Wyniki rozprawy otwierają również nowe perspektywy badawcze. Przede wszystkim wskazują na potrzebę prowadzenia dalszych, wieloośrodkowych badań obejmujących większe populacje dzieci matek biorczyń narządu, aby umożliwić dalszą analizę wpływu poszczególnych schematów immunosupresji na odpowiedź poszczepienną. Wskazane byłoby również rozszerzenie obserwacji o dodatkowe aspekty funkcjonowania układu immunologicznego, takie jak odpowiedź komórkowa czy długoterminowe utrzymywanie się pamięci immunologicznej.

Podsumowując, analiza przedstawionego cyklu publikacji doprowadziła do wypracowania następujących konkluzji:

- Terapia immunosupresyjna zmniejsza immunogenność szczepień u biorców graftów. Celem poprawy efektywności szczepień stosowane są różne modyfikacje, takie jak zwiększenie liczby dawek szczepionki, zmiana drogi jej podania czy wykorzystywanie preparatów zawierających adiuwanty.

- Gorsza odpowiedź poszczepienna kobiet po przeszczepieniu narządu nie przekłada się w sposób bezpośredni na pogorszenie immunogenności u ich dzieci, pomimo ich narażenia na wpływ immunosupresji w okresie prenatalnym.

- W odniesieniu do szczepionek przeciwko patogenom wirusowym, jak również większości patogenów bakteryjnych nie stwierdza się istotnych statystycznie różnic w immunogenności zarówno pomiędzy grupą dzieci matek po transplantacji wątroby a grupą kobiet po przeszczepieniu nerki jak i w porównaniu do populacji ogólnej.

- Dzieci biorczyń po przeszczepieniu nerki wykazują wyższe stężenie przeciwciał anty – BCG przeciwko *Mycobacterium tuberculosis complex*, niż dzieci matek po przeszczepieniu wątroby oraz dzieci zdrowe jednak przyczyna tej zależności na chwilę obecna jest niejasna i wymaga przeprowadzenia dalszych badań.

- Częstość występowania niepożądanych odczynów poszczepiennych u dzieci matek po transplantacji narządu nie odbiega od ogólnej populacji pediatrycznej.

- Ze względu na brak różnic w immunogenności i tożsamy dla populacji ogólnej profil bezpieczeństwa, w odniesieniu do analizowanych szczepień sugeruje się stosowanie ogólnie obowiązującego Programu Szczepień Ochronnych u dzieci matek po transplantacji narządu.

- Uzyskanie pełnej wiedzy na temat funkcji układu odpornościowego dzieci matek po transplantacji narządu wymaga przeprowadzenia badań wieloośrodkowych, na większej liczebnie grupie pacjentów z poszerzeniem analizy o parametry determinujące odpowiedź humoralną i komórkową.

12. Opinia Komisji Bioetycznej

Komisja Bioetyczna
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KB/161/2021

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 04 października 2021 r. po zapoznaniu się z wnioskiem:

Lek. Tomasz Ginda
Klinika Neonatologii,
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dotyczącym: wyrażenia opinii w sprawie badania pt. „Czy wewnątrzmaciczna ekspozycja płodu na leki immunosupresyjne stosowane w czasie ciąży przez kobiety po transplantacji narządu ma wpływ na miana przeciwciał odpornościowych przeciwko chorobom zakaźnym u dzieci w obserwacji długoterminowej w porównaniu do populacji ogólnej?"

- Badanie może być prowadzone wyłącznie w okresie obowiązywania polisy ubezpieczeniowej.

wyraża następującą
o p i n i ę

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma-Kozakiewicz

*niepotrzebne skreślić

strona podpisowa do uchwały Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym nr KB/.....161..... z dnia 04 października 2021r.

1. Prof. dr hab. n.med. Magdalena Kuźma –Kozakiewicz .....
2. Dr hab. n. med. Tomasz Grzela .....
3. Dr hab. n. med. Andrea Horvath-Stolarczyk .....
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5. Dr hab. n.med. Maciej Siński .....
6. Dr hab. n. farm. Sylwia Flis .....
7. Prof. dr hab.n.med Tomasz Jakimowicz .....
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11. Dr hab. n.med. Barbara Grzechocińska .....
12. Dr n. med. Artur Hącia OP .....
13. Mgr Anna Jasińska .....

Warszawa, 06.05.2025
(miejscowość, data)

Prof. dr hab. n.med. Bożena Kociszewska-Najman
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

The influence of selected factors on the immunogenicity of preventive vaccinations against hepatitis A, B and influenza in solid organ transplant recipients undergoing immunosuppressive therapy - a review,

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

nadzór merytoryczny w trakcie przygotowywania publikacji, korekta manuskryptu

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

stworzenie koncepcji publikacji, analiza piśmiennictwa, przygotowanie manuskryptu, wprowadzanie poprawek edytorskich.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

KIEROWNIK
Kliniki Neonatologii i Chorób Rzadkich
prof. dr. hab. n. med. Bożena Kociszewska-Najman

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 06.05.2025
(miejscowość, data)

Dr n.med. Karol Taradaj
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

The influence of selected factors on the immunogenicity of preventive vaccinations against hepatitis A, B and influenza in solid organ transplant recipients undergoing immunosuppressive therapy - a review,

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

współudział w analizie piśmiennictwa, współudział w przygotowaniu manuskryptu.

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

stworzenie koncepcji publikacji, analiza piśmiennictwa, przygotowanie manuskryptu, wprowadzanie poprawek edytorskich.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 05.05.2025
(miejscowość, data)

Prof. dr hab. n.med. Bożena Kociszewska-Najman
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

Does Intrauterine Exposure of the Foetus to Immunosuppressive Drugs Used by the Mother-The Organ Recipient-Affect the Development of Post-Vaccination Immunity against Selected Viral Diseases in Children of These Mothers in Postnatal Life?

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

nadzór merytoryczny w trakcie przygotowywania publikacji, rekrutacja grupy badawczej, korekta manuskryptu

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

stworzenie koncepcji publikacji, analiza piśmiennictwa, rekrutacja pacjentów, samodzielne wykonanie oznaczeń laboratoryjnych, analiza statystyczna, opracowanie wniosków, przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

KIEROWNIK
Kliniki Neonatologii i Chorób Rzadkich
prof. dr. hab. n. med. Bożena Kociszewska-Najman

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 05.05.2025r.
(miejscowość, data)

Dr n.med. Karol Taradaj
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

Does Intrauterine Exposure of the Foetus to Immunosuppressive Drugs Used by the Mother-The Organ Recipient-Affect the Development of Post-Vaccination Immunity against Selected Viral Diseases in Children of These Mothers in Postnatal Life?

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współudział w części badawczej, analiza statystyczna, współudział w przygotowaniu manuskryptu

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

stworzenie koncepcji publikacji, analiza piśmiennictwa, rekrutacja pacjentów, samodzielne wykonanie oznaczeń laboratoryjnych, analiza statystyczna, opracowanie wniosków, przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 05.05.2025r.
(miejscowość, data)

Lek. Patrycja Kociołek
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

Does Intrauterine Exposure of the Foetus to Immunosuppressive Drugs Used by the Mother-The Organ Recipient-Affect the Development of Post-Vaccination Immunity against Selected Viral Diseases in Children of These Mothers in Postnatal Life?

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

udział w przygotowaniu manuskryptu, graficzne opracowanie wyników badania

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

stworzenie koncepcji publikacji, analiza piśmiennictwa, rekrutacja pacjentów, samodzielne wykonanie oznaczeń laboratoryjnych, analiza statystyczna, opracowanie wniosków, przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

Patrycja Kociołek
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 05.05.2025r.
(miejscowość, data)

Lek. Oliver Jendro
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

Does Intrauterine Exposure of the Foetus to Immunosuppressive Drugs Used by the Mother-The Organ Recipient-Affect the Development of Post-Vaccination Immunity against Selected Viral Diseases in Children of These Mothers in Postnatal Life?

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

rekrutacja pacjentów, współudział w części badawczej projektu

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

stworzenie koncepcji publikacji, analiza piśmiennictwa, rekrutacja pacjentów, samodzielne wykonanie oznaczeń laboratoryjnych, analiza statystyczna, opracowanie wniosków, przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 05.05.2025
(miejscowość, data)

Dr hab. n.med. Olga Tronina
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

Does Intrauterine Exposure of the Foetus to Immunosuppressive Drugs Used by the Mother-The Organ Recipient-Affect the Development of Post-Vaccination Immunity against Selected Viral Diseases in Children of These Mothers in Postnatal Life?

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

rekrutacja grupy badawczej, logistyka projektu, udział w części badawczej, korekta manuskryptu

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

stworzenie koncepcji publikacji, analiza piśmiennictwa, rekrutacja pacjentów, samodzielne wykonanie oznaczeń laboratoryjnych, analiza statystyczna, opracowanie wniosków, przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

W-wa 7.05.2025
(miejscowość, data)

Dr hab. n.med. Anna Stelmaszczyk-Emmel
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

Does Intrauterine Exposure of the Foetus to Immunosuppressive Drugs Used by the Mother-The Organ Recipient-Affect the Development of Post-Vaccination Immunity against Selected Viral Diseases in Children of These Mothers in Postnatal Life?

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

nadzór merytoryczny nad częścią badawczą, współudział w analizie i interpretacji wyników

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

stworzenie koncepcji publikacji, analiza piśmiennictwa, rekrutacja pacjentów, samodzielne wykonanie oznaczeń laboratoryjnych, analiza statystyczna, opracowanie wniosków, przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

A. Stelmaszczyk-Emmel
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 07.05.2025
(miejscowość, data)

Prof. dr hab. n.med. Bożena Kociszewska-Najman
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

Evaluation of the Development of Post-Vaccination Immunity against Selected Bacterial Diseases in Children of Post-Solid-Organ-Transplant Mothers.

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

nadzór merytoryczny w trakcie przygotowywania publikacji, rekrutacja grupy badawczej, korekta manuskryptu

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

stworzenie koncepcji publikacji, analiza piśmiennictwa, rekrutacja pacjentów, samodzielne wykonanie oznaczeń laboratoryjnych, analiza statystyczna, opracowanie wniosków, przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

KIEROWNIK
Kliniki Neonatologii i Chorób Rzadkich
.... prof. dr. hab. n. med. Bożena Kociszewska-Najman
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 07.05.2025r.
(miejscowość, data)

Dr n.med. Karol Taradaj
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

Evaluation of the Development of Post-Vaccination Immunity against Selected Bacterial Diseases in Children of Post-Solid-Organ-Transplant Mothers.

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

współudział w części badawczej, analiza statystyczna, współudział w przygotowaniu manuskryptu

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

stworzenie koncepcji publikacji, analiza piśmiennictwa, rekrutacja pacjentów, samodzielne wykonanie oznaczeń laboratoryjnych, analiza statystyczna, opracowanie wniosków, przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 05.05.2025
(miejscowość, data)

Dr hab. n.med. Olga Tronina
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

Evaluation of the Development of Post-Vaccination Immunity against Selected Bacterial Diseases in Children of Post-Solid-Organ-Transplant Mothers.

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

rekrutacja grupy badawczej, logistyka projektu, udział w części badawczej, korekta manuskryptu

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

stworzenie koncepcji publikacji, analiza piśmiennictwa, rekrutacja pacjentów, samodzielne wykonanie oznaczeń laboratoryjnych, analiza statystyczna, opracowanie wniosków, przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

Olga Tronina

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Wwa, 7.05.2025
(miejscowość, data)

Dr hab. n.med. Anna Stelmaszczyk-Emmel
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt.

Evaluation of the Development of Post-Vaccination Immunity against Selected Bacterial Diseases in Children of Post-Solid-Organ-Transplant Mothers.

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

nadzór merytoryczny nad częścią badawczą, współudział w analizie i interpretacji wyników

Wkład *lek. Tomasza Gindy* w powstawanie publikacji obejmował:
(imię i nazwisko kandydata do stopnia)

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Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej *lek. Tomasza Gindy*
(imię i nazwisko kandydata do stopnia)

A. Stelmaszczyk-Emmel
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników