Vaccinations in the Pediatric Transplant Population

Vanderbilt Transplant
Advanced Practice Provider Symposium
October 15, 2024

Stacee Lerret PhD, RN, CPNP-AC/PC, CCTC, FAAN
Professor, Medical College of Wisconsin
Pediatric Nurse Practitioner, Children's Hospital of Wisconsin

Vaccines and Solid Organ Transplant Patients

WHAT DO WE KNOW?

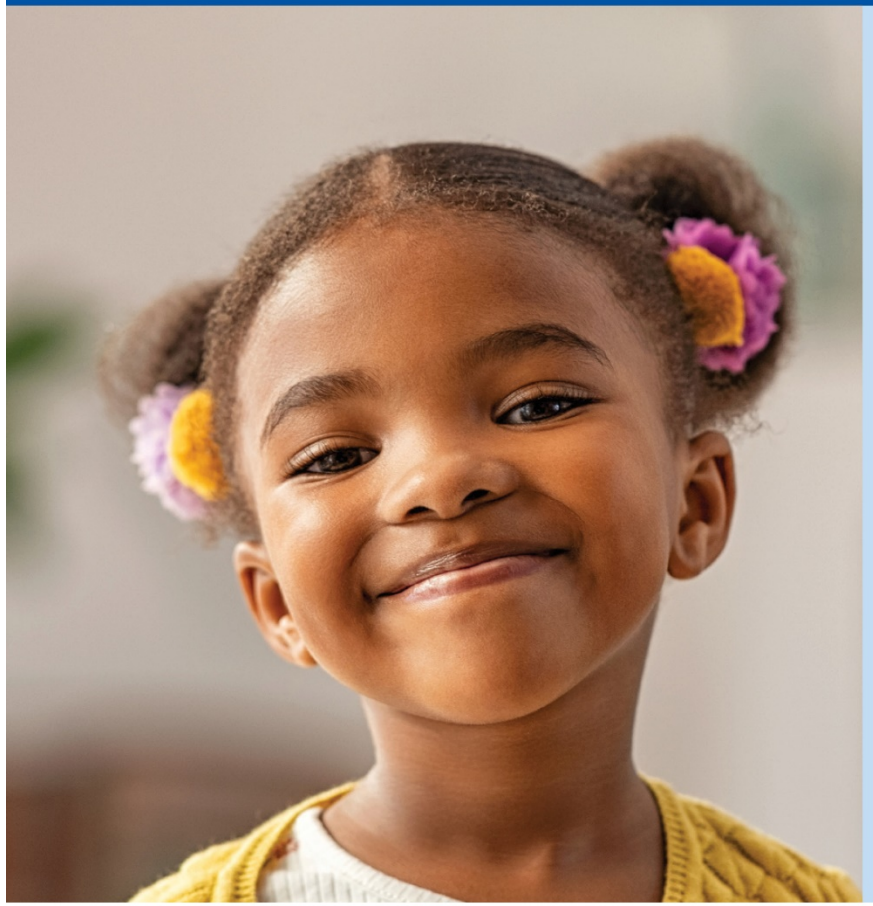
WHAT DOES THIS MEAN FOR OUR PATIENTS?

HOW CAN WE MAKE A DIFFERENCE?

Vaccines for Children

Protecting America's children every day

The Vaccines for Children (VFC) program helps ensure that all children have a better chance of getting their recommended vaccines. VFC has helped prevent disease and save lives.



CDC estimates that vaccination of children born between 1994 and 2021 will:

prevent **472 million** illnesses
(29.8 million hospitalizations)

more than the current population of the entire U.S.A.

help avoid **1,052,000** deaths

greater than the population of Seattle, WA

save nearly **$2.2 trillion** in total societal costs
(that includes $479 billion in direct costs)

more than $5,000 for each American

Updated 2021 analysis using methods from "Benefits from Immunization during the Vaccines for Children Program Era—United States, 1994-2021."

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

www.cdc.gov/features/vfcprogram

NCIRDWTLC | 10/28/22

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Why is This Important?

Healthy children

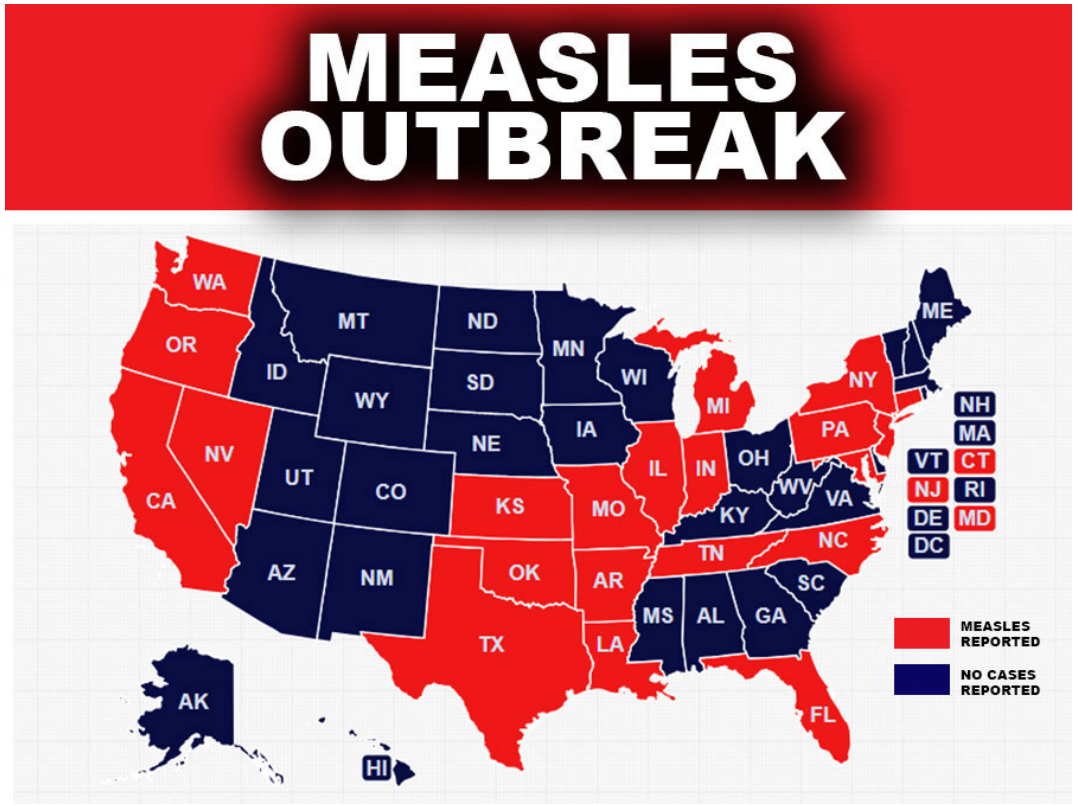
- Reduced herd immunity

Measles

- 2000 = declared eliminated in US
- 2019 = measles outbreak, over 1200 cases

January to August 2024

- 219 measles cases



Vaccines and Solid Organ Transplant Patients

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WHAT DOES THIS MEAN FOR OUR PATIENTS?

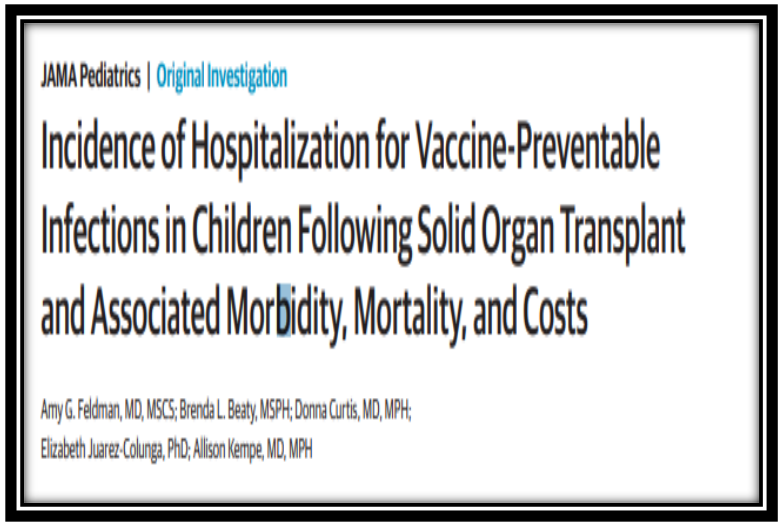
Many pediatric liver transplant patients do not complete their childhood immunization series.

Some patients received the accelerated vaccination schedule in preparation for transplant.

Immunosuppression medications following a liver transplant can impact the efficacy of vaccines in this population.

Lower immunity and lack of immunization increases risk of acquired infections.

Background


JAMA Pediatrics | Original Investigation

Incidence of Hospitalization for Vaccine-Preventable Infections in Children Following Solid Organ Transplant and Associated Morbidity, Mortality, and Costs

Amy G. Feldman, MD, MSCS; Brenda L. Beaty, MSPH; Donna Curtis, MD, MPH; Elizabeth Juarez-Colunga, PhD; Allison Kempe, MD, MPH

Hospitalization for vaccine-preventable infections

- 16% of pediatric transplant patients are in the first 5 years after transplant

Prolonged hospitalization for vaccine preventable infection **costs** approximately $120,498

- Influenza = 7.2%
- Rotavirus = 3.7%
- Varicella = 2.1%

Vaccination administration

- Less invasive and less expensive option to reduce infections for children before and after transplant

Maximum effort indicated

- Ensure complete immunization of transplant candidates and recipients

Inactivated and Live Vaccines

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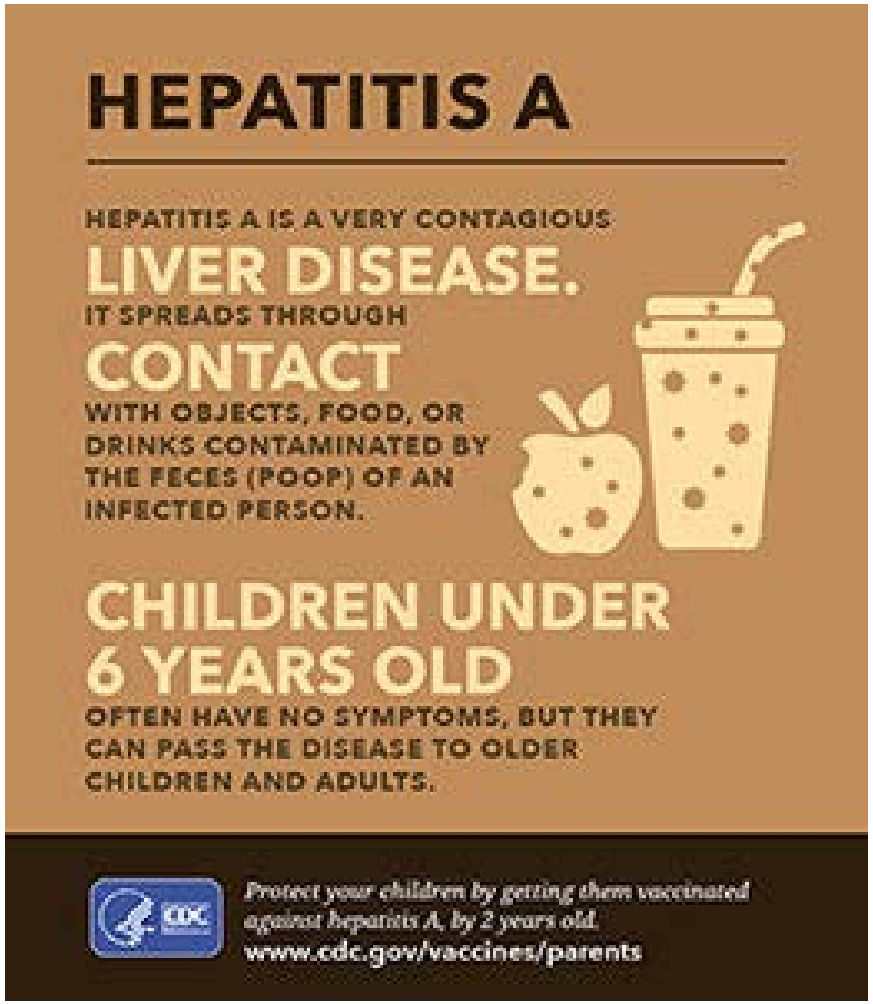


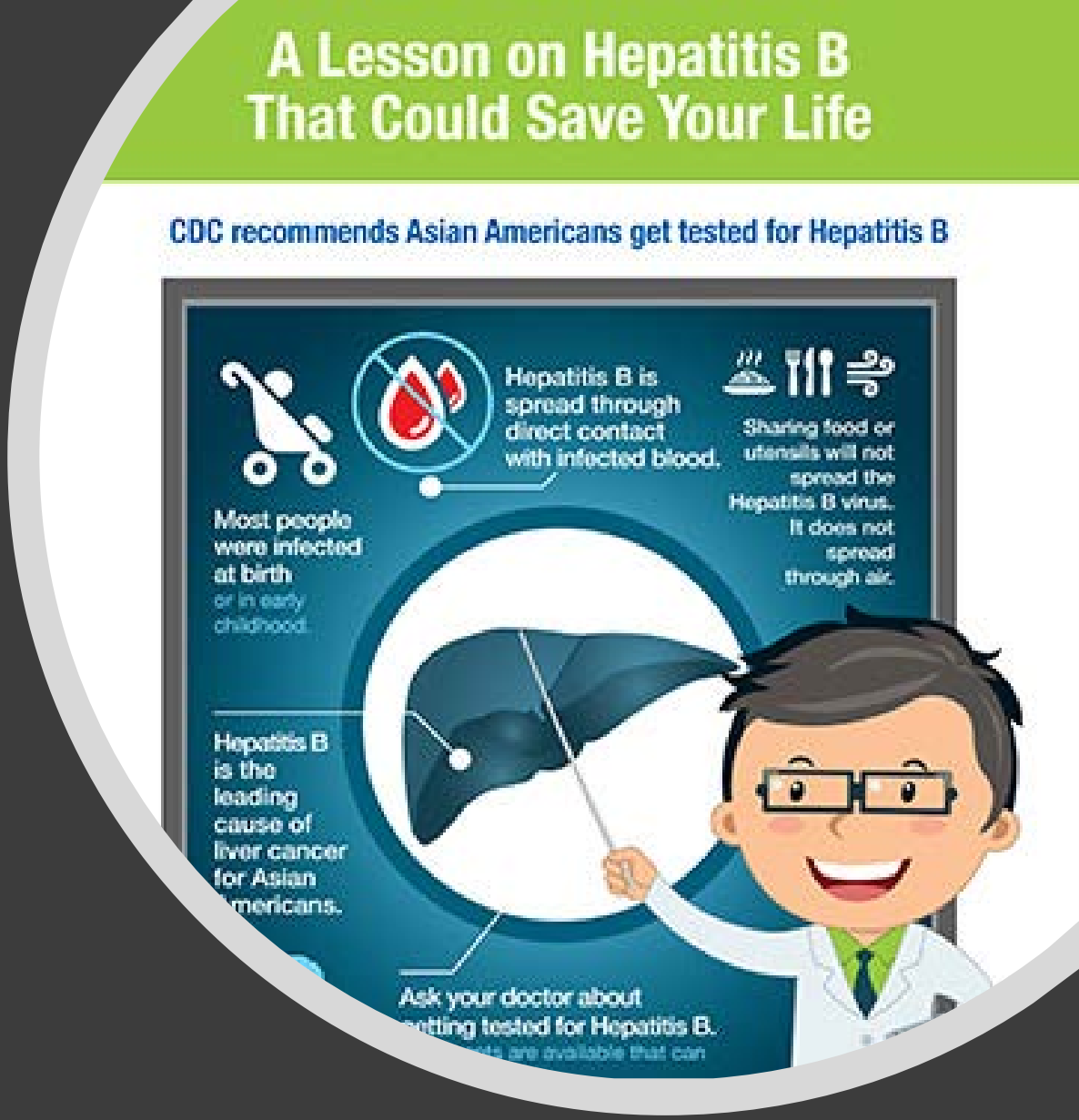
Inactivated: Hepatitis A

- Important to protect patients with liver disease from other infectious hepatotrophic viruses when possible
- Hepatitis A vaccine has good immunogenicity in children with chronic liver disease with detectable Ab
  - HBV pts - 87% at 1 mos, 88% at 6 mos
  - HCV pts – 92% at 1 mos, 75% at 6 mos

Majda-Stanislawska E, et al. *Pediatr Infect Dis*. 2004

Hepatitis B

- Hepatitis B in liver transplant patients is more severe and damages the liver more rapidly than healthy patients
- Like HAV, important to protect liver patients from this virus pre- and post-transplant



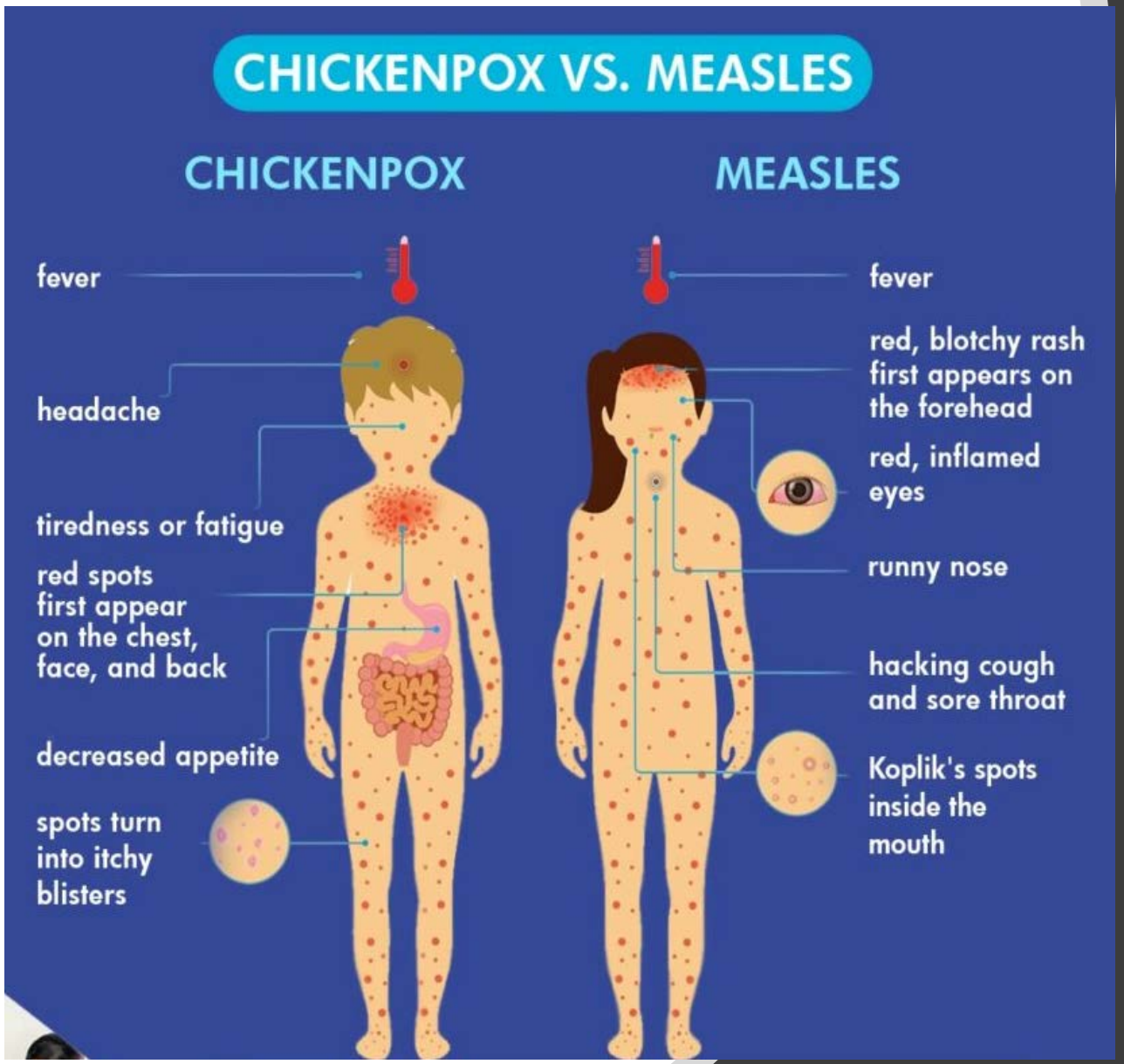
Hepatitis B

Ni, Y. et al.
Transplantation, 2008

Response to Booster Hepatitis B Vaccines in Liver-Transplanted Children Primarily Vaccinated in Infancy

Yen-Hsuan Ni,[1] Ming-Chih Ho,[2] Jia-Feng Wu,[1] Huey-Ling Chen,[1] Yao-Ming Wu,[2] Rey-Heng Hu,[2] Po-Huang Lee,[2,3] and Mei-Hwei Chang[1]

- 31 patients from Taiwan
- Stable >1 year post liver transplant
- All patients completed primary HBV series before transplant
- 65% (n = 20) had immunity post-transplant
- Booster shots to remaining 35% (n = 11)
  - 2/3 seroconverted after 1 booster dose
  - Remaining seroconverted after 2nd booster dose



Live Vaccines

- Varicella
  - Varicella outbreaks have drastically declined in the last 20 years
  - Early 1990s an average of 4 million people had varicella
  - <150,000 annually per CDC
- Measles
  - Officially declared eliminated in the United States in 2000
  - It's back

CASE REPORT OPEN ACCESS

Fatal Hyperacute Liver Failure due to Varicella Zoster Virus Immediately After Living-Donor Liver Transplantation: A Case Report and Review of the Literature

Takeo Toda[1] | Junichi Kaneko[1] | Masako Ikemura[2] | Mariko Tanaka[2] | Akinori Miyata[1] | Yujiro Nishioka[1] | Akihiko Ichida[1] | Yoshikuni Kawaguchi[1] | Nobuhisa Akamatsu[1] | Kiyoshi Hasegawa[1]

[1]Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan | [2]Department of Pathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

ABSTRACT

Background: Although acute hepatitis caused by varicella zoster virus mostly develops in immunocompromised patients, hyperacute liver failure is very rare. To our knowledge, there are no previous reports on liver transplant patients.

Methods: We report the first case of fatal hyperacute liver failure due to varicella zoster virus immediately after living-donor liver transplantation without cutaneous lesions and review the literature.

Result: The present case exhibited rapid development and progression of acute liver failure from postoperative days 11–13, despite being seropositive for varicella zoster virus but unvaccinated and on immunosuppression before transplantation. Especially in solid organ transplantation, only six cases of severe acute liver failure that included hepatic encephalopathy and/or impaired consciousness and sudden extremely high (> 4000 U/L) serum aspartate aminotransferase levels have been reported in heart, lung, and kidney transplant patients.

Conclusions: Early diagnosis of hyperacute liver failure due to varicella zoster virus is challenging because the disease progresses rapidly and skin lesions are absent.

TABLE 1 | Summary of severe[a] acute liver failure due to varicella zoster virus after solid organ transplantation in the literature.

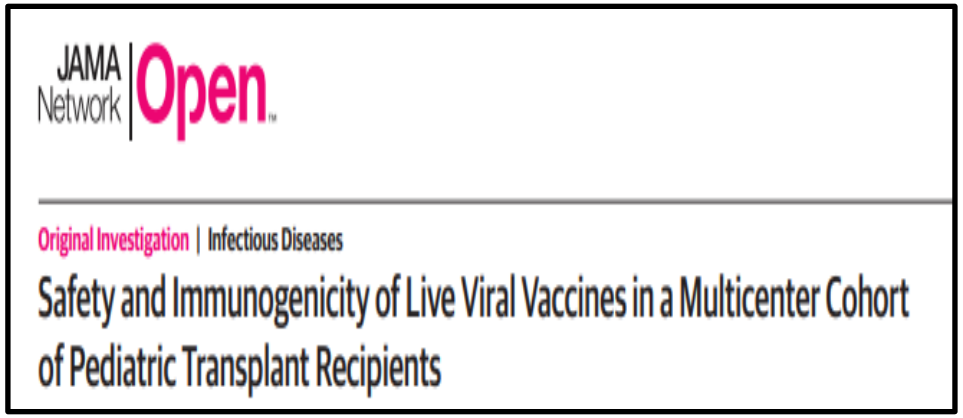
Author	Year	Age/ gender	Tx organ	VZV-IgG	Skin involvement	Abdominal pain	Fever	Time between SOT to ALF	Hepatic encephalopathy	Peak AST level (U/L)	Aciclovir	LTx	Survival
Patti [14]	1990	29 F	Kidney	N/A	+	+	+	5 years	+	7770	+	−	Dead
Dits [9]	1998	30 M	Kidney	Negative	+	+	+	7 years	+	4520	+	−	Dead
Alvite [10]	2009	43 M	Heart	N/A	+	+	−	9 months	+	18 599	+	+	Alive
Verleden [13]	2012	28 M	Lung	N/A	+	+	+	1 months	N/A	6000	+	−	Dead
Wang [15]	2021	33 M	Kidney	Negative	−	+	−	6 months	N/A	4814	+	−	Dead
Park [12]	2022	39 M	Kidney	Positive	+	+	−	3 weeks	N/A	5276	+	−	Alive
Present	2023	17 F	Liver	Positive	−	−	+	10 days	+	8851	−	−	Dead

5 males
2 females

4 kidney
1 heart
1 lung
1 liver

2 seropositive pre-transplant

Median time
0.75 years



281 pediatric kidney and liver transplant recipients

18 US transplant centers

Individual transplant center protocols

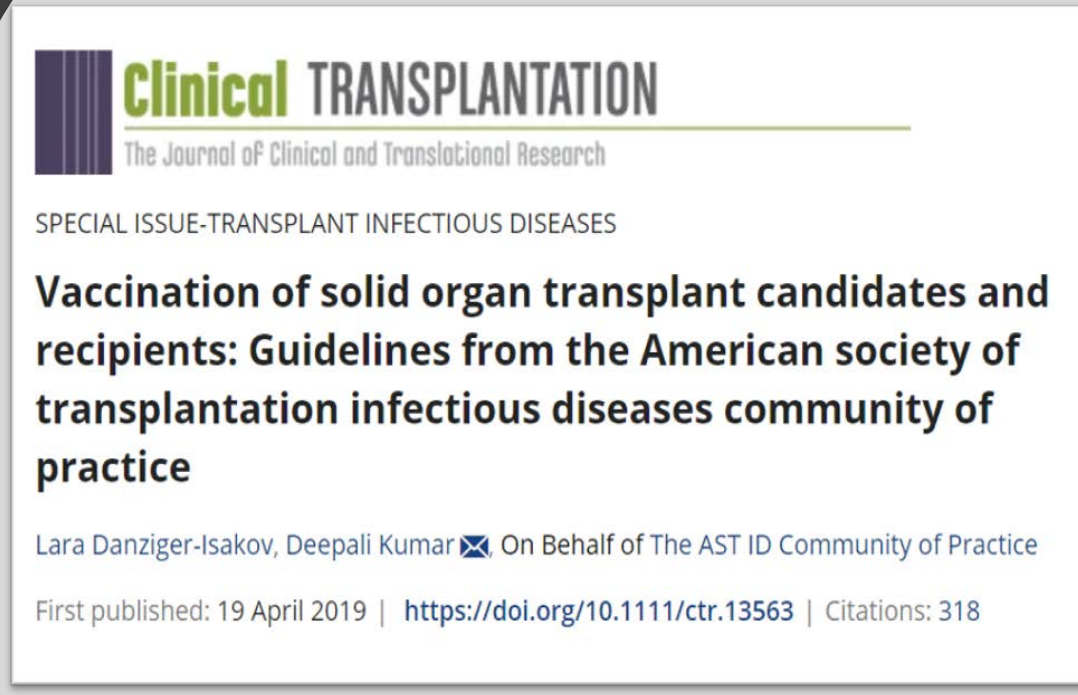
Majority of children developed protective antibodies

- Varicella = 72%
- Measles = 86%
- Mumps = 83%
- Rubella = 99%

No serious adverse events

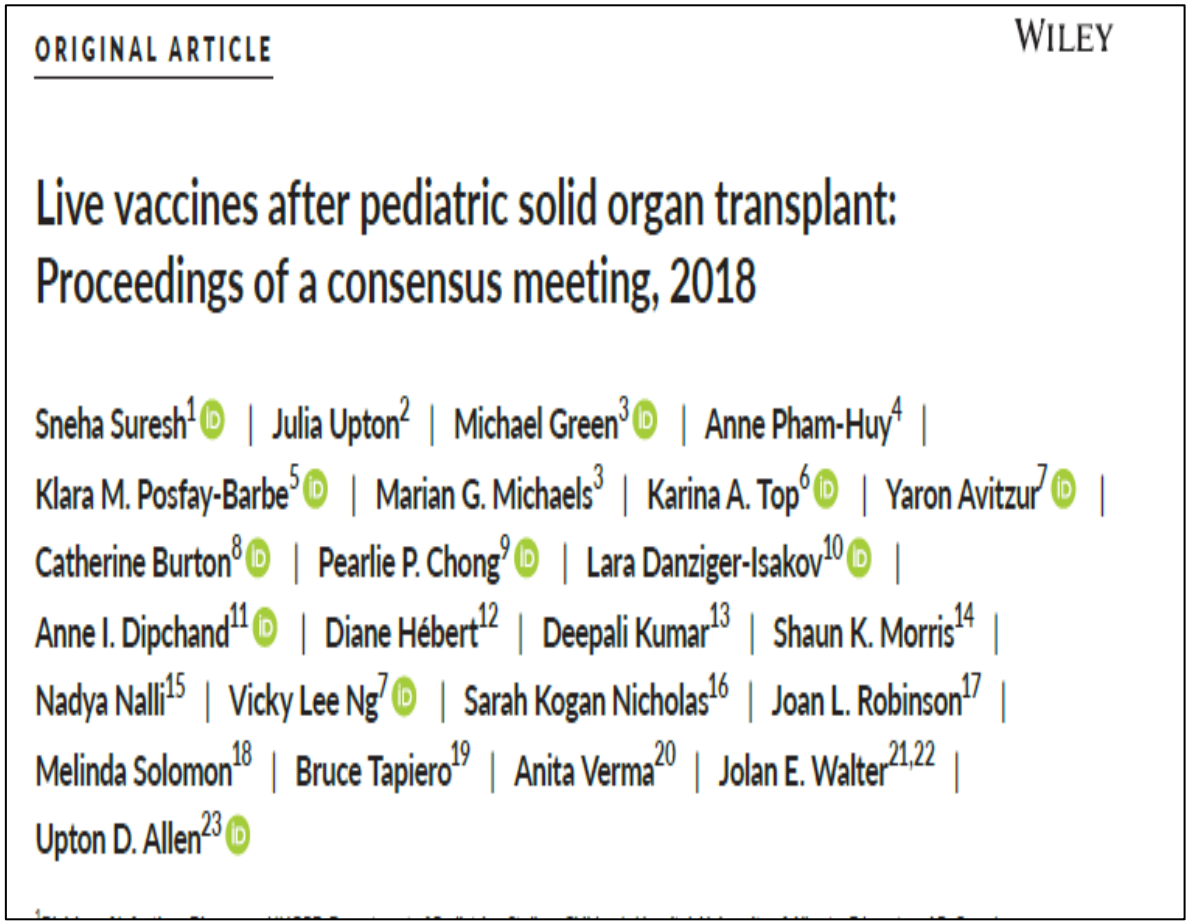
What is Current Practice?

- Inactivated vaccines safe to use starting at approximately 3 months after transplant
  - Baseline immunosuppression
- Live vaccines avoided
  - 4 week before transplant
  - After transplant
- Avoid live vaccines until further studies are available



International Multispecialty Expert Consortium in 2018

- Pediatric transplantation
- Immunology
- Pharmacy
- Infectious Disease



ORIGINAL ARTICLE

WILEY

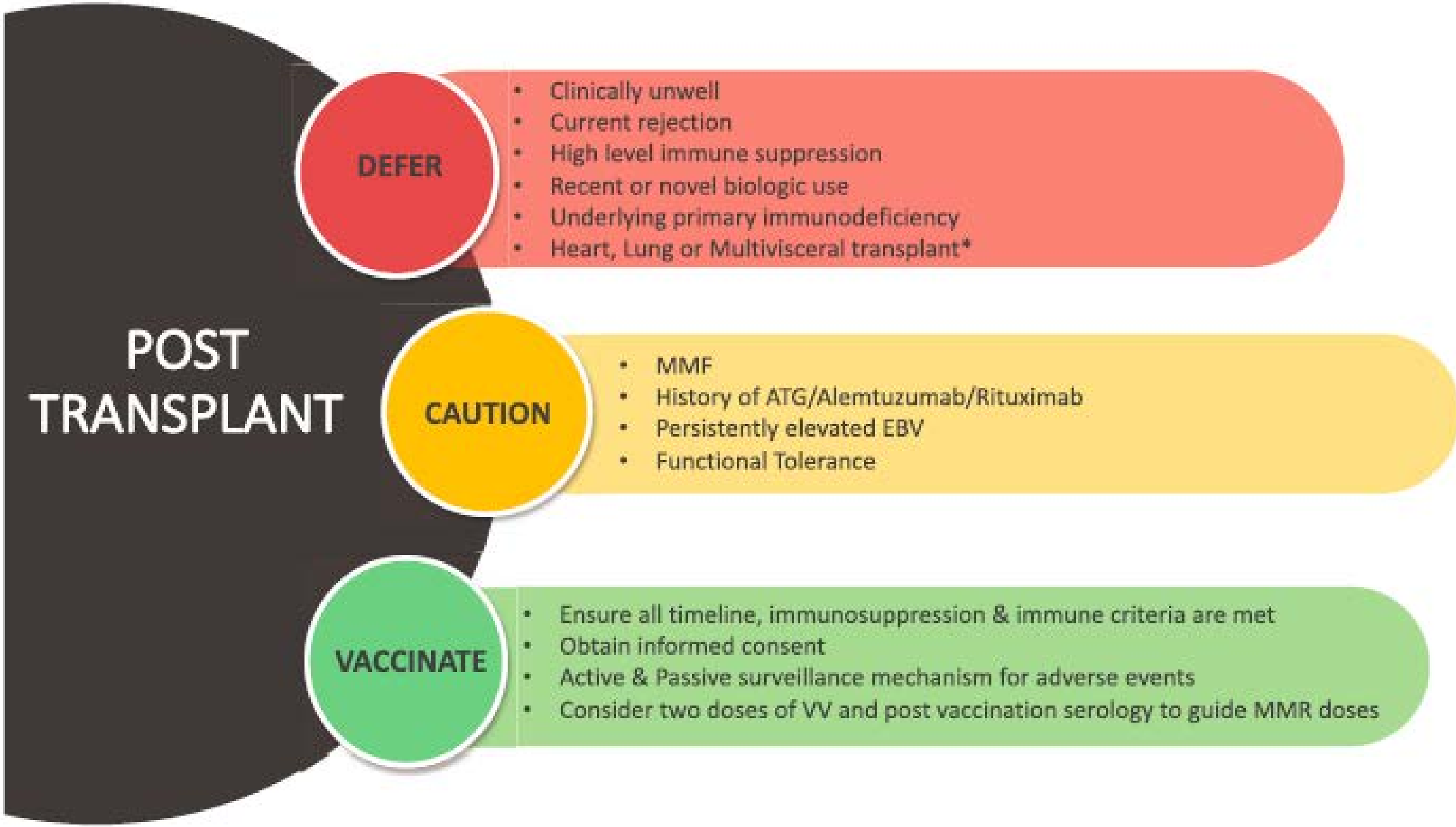
Live vaccines after pediatric solid organ transplant: Proceedings of a consensus meeting, 2018

Sneha Suresh[1] | Julia Upton[2] | Michael Green[3] | Anne Pham-Huy[4] | Klara M. Posfay-Barbe[5] | Marian G. Michaels[3] | Karina A. Top[6] | Yaron Avitzur[7] | Catherine Burton[8] | Pearlie P. Chong[9] | Lara Danziger-Isakov[10] | Anne I. Dipchand[11] | Diane Hébert[12] | Deepali Kumar[13] | Shaun K. Morris[14] | Nadya Nalli[15] | Vicky Lee Ng[7] | Sarah Kogan Nicholas[16] | Joan L. Robinson[17] | Melinda Solomon[18] | Bruce Tapiero[19] | Anita Verma[20] | Jolan E. Walter[21,22] | Upton D. Allen[23]

Consensus Meeting: Live Vaccine Recommendations
(Suresh et al., 2019)

Declining concerns for low vaccine efficacy and adverse effects from live vaccines following liver transplants.

Live vaccines can be administered to selected post-transplant patients meeting certain criteria.


POST TRANSPLANT
DEFER
Clinically unwell
Current rejection
High level immune suppression
Recent or novel biologic use
Underlying primary immunodeficiency
Heart, Lung or Multivisceral transplant*
CAUTION
MMF
History of ATG/Alemtuzumab/Rituximab
Persistently elevated EBV
Functional Tolerance
VACCINATE
Ensure all timeline, immunosuppression & immune criteria are met
Obtain informed consent
Active & Passive surveillance mechanism for adverse events
Consider two doses of VV and post vaccination serology to guide MMR doses

Vaccines and Solid Organ Transplant Patients

WHAT DO WE KNOW?

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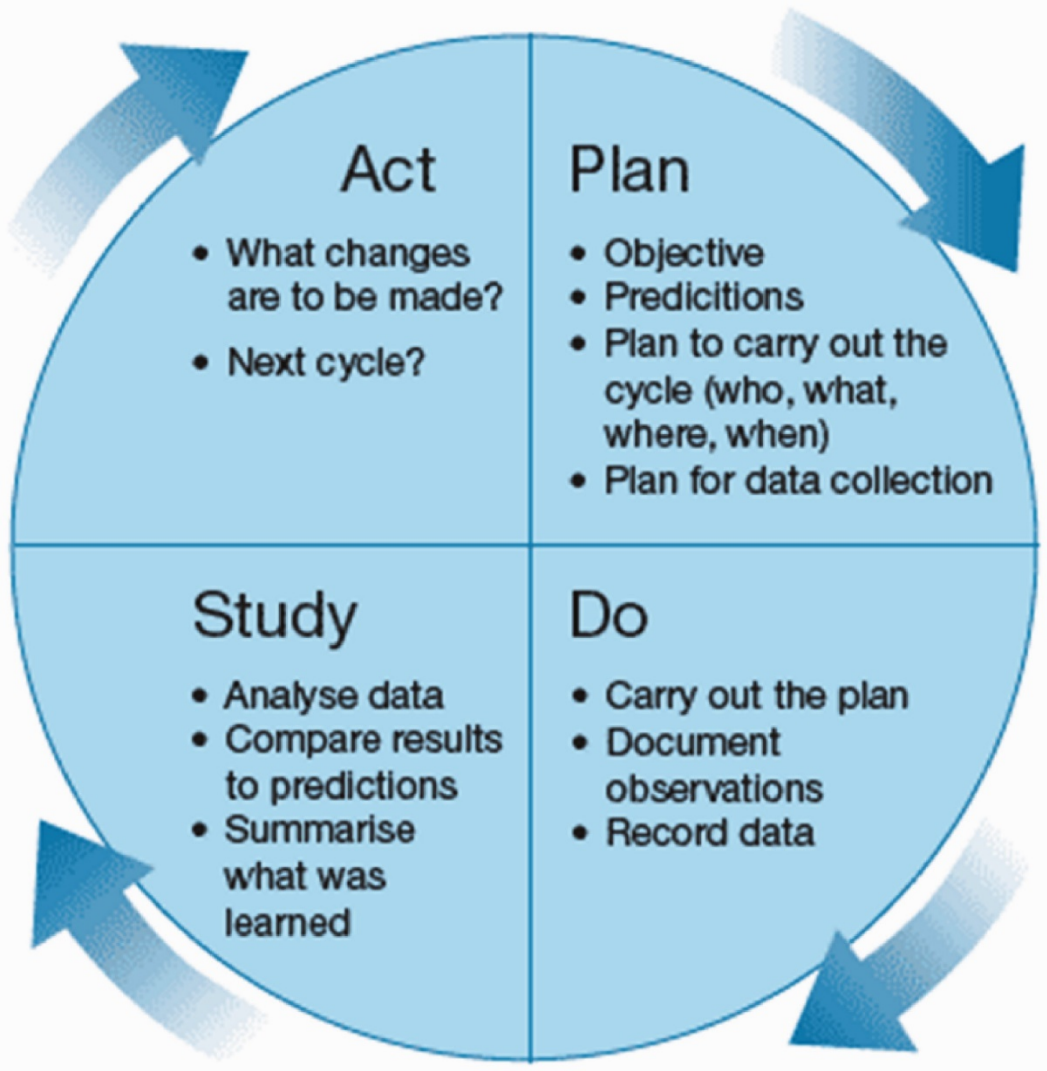
HOW CAN WE MAKE A DIFFERENCE?

Starting the Conversation…

- Avoiding live vaccines following liver transplant is standard practice for most centers due to concern for active infections
- But…this can increase morbidity and mortality in adulthood from infections like measles and varicella
- Several single center studies have shown administering live vaccines post-transplant is safe and effective in select patients
- Booster immunization in these patients demonstrate a good response

Quality Assurance and Performance Improvement

Inactive and Live Vaccines for Pediatric Liver Transplant Patients



Purpose

1	2	3	4
Achieve an immunity rate of 95% among pediatric liver transplant patients.	Monitor titers in 100% of pediatric liver transplant patients annually to ensure ongoing immunity. • Varicella, measles, mumps, Haemophilus influenzae B, hepatitis A and hepatitis B	Administer boosters or primary immunizations to ≥ 95% of patients with low titers.	Assess duration of immunity.

Methods

Setting

- Children's Wisconsin by the Division of Pediatric Gastroenterology, Hepatology and Nutrition in Milwaukee
- Plan-Do-Study-Act (PDSA) cycles

Team

- Hepatologists, infectious disease physician, nurse practitioner, pharmacist, transplant coordinators, GI fellow

Methods

Family Education	The importance of immunization and the new protocol was provided by the nurse practitioner seeing all post-transplant patients in the outpatient setting.
Titer Analysis	Antibody titers for varicella, measles, mumps, rubella, HiB, HAV, and HBV were obtained annually during the post-transplant visit.
Vaccine Recommendations	The team met biweekly to review titers. Families were subsequently contacted by the transplant coordinator to share vaccine recommendations.
Vaccine Administration	Primary care providers (PCP) were sent a letter with vaccine recommendations for each patient. Vaccines were given at PCP office.
Follow-up	The Wisconsin Immunization Record (WIR) was utilized to track patients received vaccines. Titers were recommended and ordered at least 4 weeks post-vaccine administration.

Immunization Criteria

Live Vaccines	Inactive Vaccines
o ≥1-year post-transplant	o ≥1-year post-transplant
o Low titers for varicella, measles, mumps, or rubella	o Low titers for Haemophilus influenzae B, hepatitis A, and hepatitis B
o Monotherapy immunosuppression with tacrolimus, sirolimus, or everolimus with target trough level ≤8	o No Rituximab within 12 months
o No steroids within 3 months	
o No rejection or serious infection within 6 months	
o No Rituximab within 12 months	
o No chemotherapy within 1 year	

Liver Transplant Immunization Titers

Patient: _____

Transplant date: _____

Labs drawn: _____

Titer	Vaccine/booster indicated		Date Given	Repeat Titer
Hepatitis A: _____	Yes	NO	_____	_____
Hepatitis B: _____	Yes	NO	_____	_____
HiB: _____	Yes	NO	_____	_____
Measles: _____	Yes	NO	_____	_____
Mumps: _____	Yes	NO	_____	_____
Rubella: _____	Yes	NO	_____	_____
Varicella: _____	Yes	NO	_____	_____

Criteria:

One year post transplant	YES	NO	N/A
Monotherapy:	YES	NO	N/A
No rejection in 6 months:	YES	NO	N/A
No steroid in 3 months:	YES	NO	N/A
No serious infection in 6 months	YES	NO	N/A
No Rituximab given in 6 months	YES	NO	

Date Reviewed: _____

Patient DOES or DOES NOT meet criteria for live immunizations. N/A

Recommended vaccines: _____

Follow up:

Call to family with results and recommendation: _____

Letter to PCP: _____

Immunizations administered: _____

Follow up phone call post administration: _____

Titer	Vaccine/booster indicated	Date Given	Repeat Titer
Hepatitis A: non-reactive	(Yes) NO		
Hepatitis B: negative	(Yes) NO		
HiB: <0.15	(Yes) NO		
Measles: 1.70 (+)	Yes (NO)		
Mumps: 0.72 (−)	(Yes) NO		
Rubella: positive	Yes (NO)		
Varicella: 0.49 (−)	(Yes) NO		

Criteria:

One year post transplant	(YES)	NO	N/A
Monotherapy:	(YES)	NO	N/A
No rejection in 6 months:	(YES)	NO	N/A
No steroid in 3 months:	(YES)	NO	N/A
No serious infection in 6 months	(YES)	NO	N/A
No Rituximab given in 6 months	(YES)	NO	

Date Reviewed: 2/14/19

Patient (DOES) or DOES NOT meet criteria for live immunizations

Recommended vaccines: Hep A, Hep B, HiB, MMR, Varicella

Titer	Vaccine/booster indicated	Date Given	Repeat Titer
✓ Hepatitis A: reactive	Yes (NO)		
✓ Hepatitis B: INP	(Yes) NO	9/9/19	
✓ HiB: <0.51	(Yes) NO	9/9/19	
✓ Measles: 4.97 (+)	Yes (NO)		
✓ Mumps: 5.00 (+)	Yes (NO)		
✓ Rubella: POS	Yes (NO)		
✓ Varicella: 0.55 (-)	(Yes) NO		

Criteria:

One year post transplant	(YES)	NO	N/A
Monotherapy:	YES	(NO)	N/A
No rejection in 6 months:	YES	(NO)	N/A
No steroid in 3 months:	YES	(NO)	N/A
No serious infection in 6 months	(YES)	NO	N/A
No Rituximab given in 6 months	(YES)	NO	

Date Reviewed: 8/29/2019

Patient (DOES) or DOES NOT meet criteria for live immunizations

Recommended vaccines: Hepatitis B and HiB

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Children's Specialty Group

We ask that you partner with us to administer any recommended vaccinations based on titer results. If you have questions or concerns, we are happy to discuss this with you further.

Many thanks,

The Pediatric Liver Transplant Team at Children's Hospital of Wisconsin

Bernadette Vitola, MD, MPH Grzegorz Telega, MD Stacee Lerret, PhD, CPNP

Janelle Hogan, RN Matt Zeman, RN

Immunizations recommended for patient name (DOB: *******) by the Team include:

Hep B booster, HiB, MMR

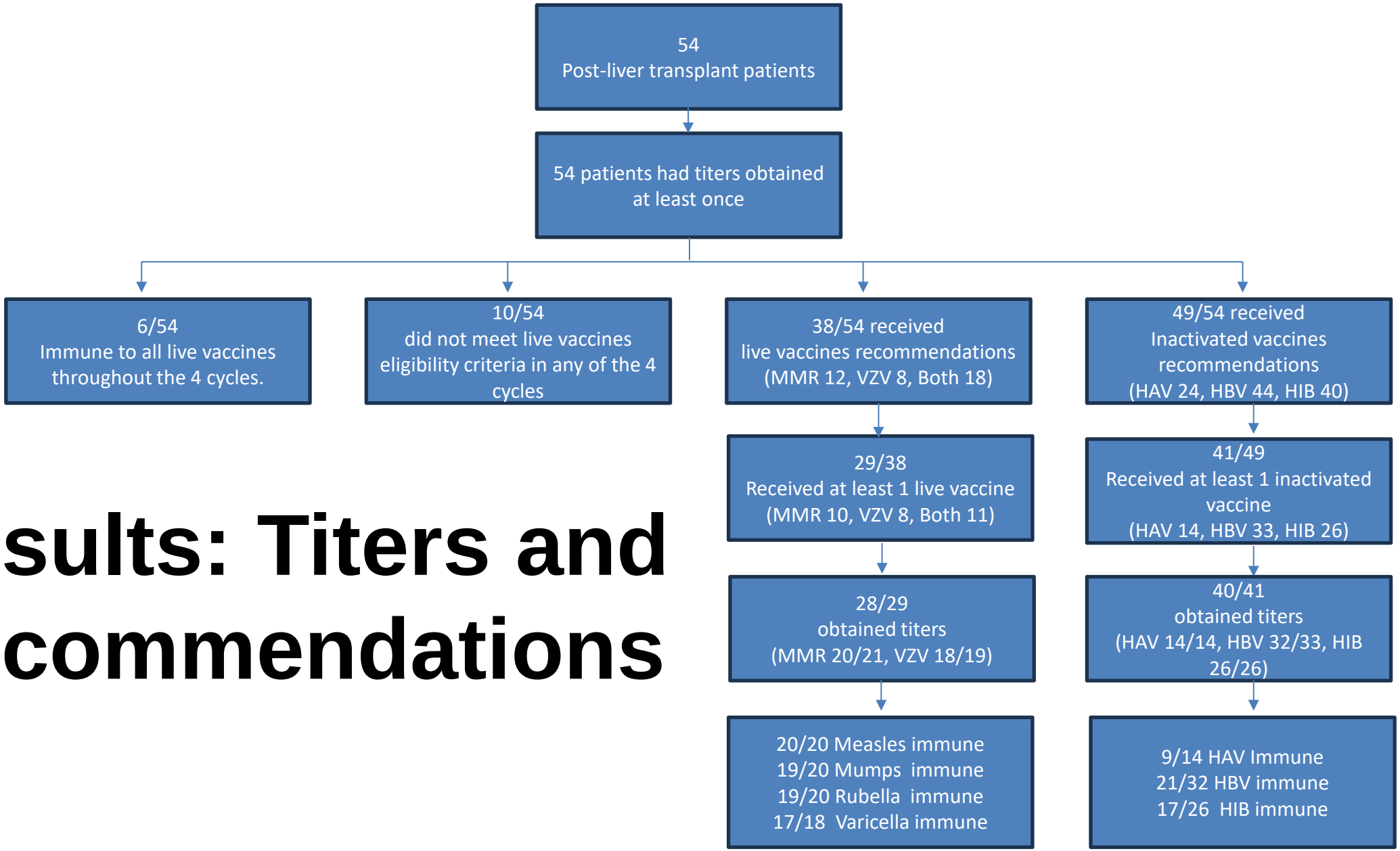
Demographics: Cycles 1 to 4

Liver Transplant Patients	n = 54
Age at the end of cycle 4	**Age in Years** Median: 13 Range: 5-21
Sex • Female • Male	**n (%)** 24 (44%) 30 (56%)
Race • Caucasian • African American • Asian • Native American	**n (%)** 37 (68%) 12 (22%) 3 (6%) 2 (4%)

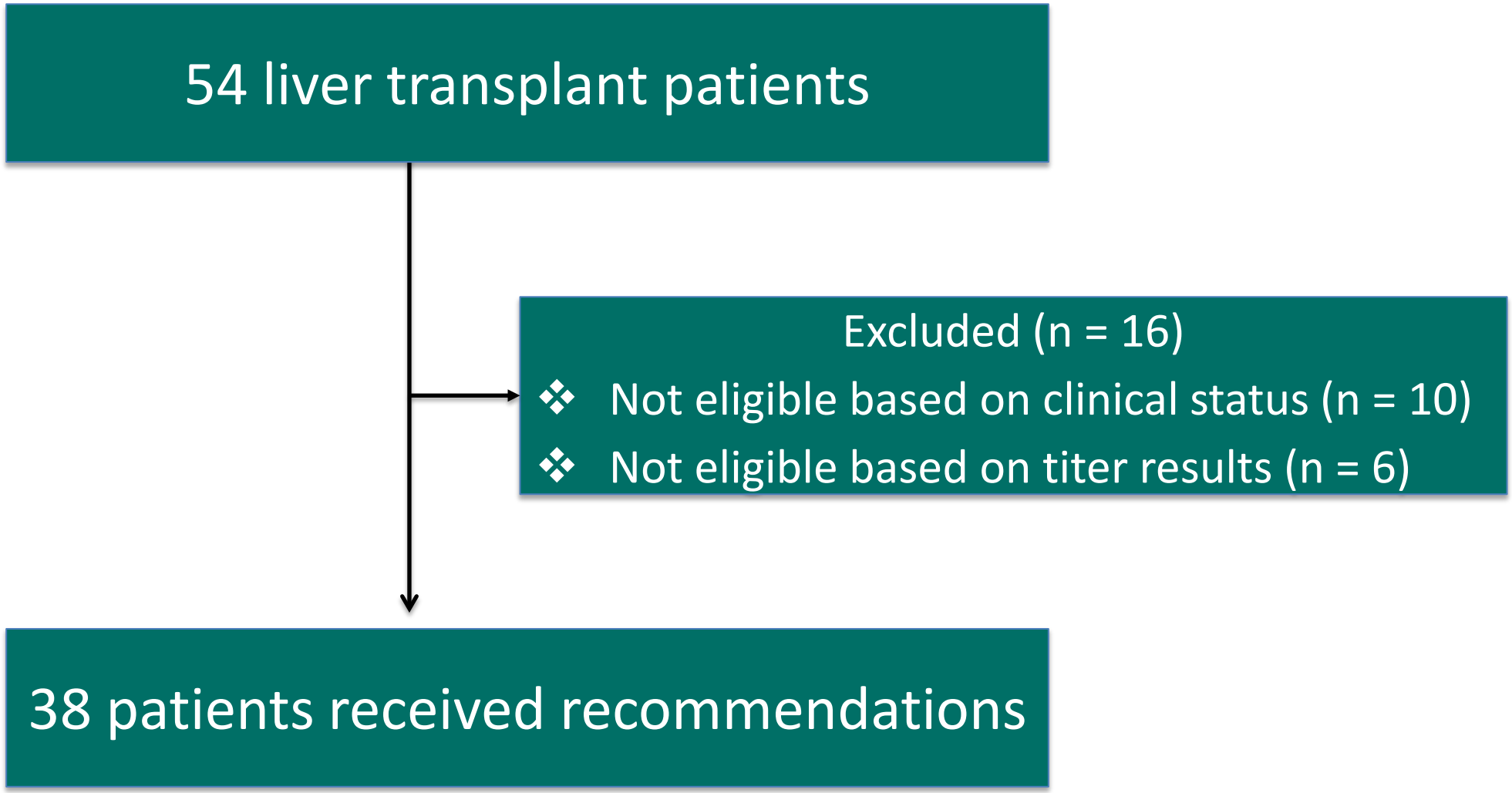
Demographics

Liver Transplant Patients	n = 54
Indication for Liver Transplant	**n (%)**
• Biliary Atresia	20 (37%)
• Hepatoblastoma	9 (17%)
• Genetic	8 (15%)
• Acute Liver Failure of Unknown Etiology	6 (11%)
• Metabolic	6 (11%)
• Anatomical	3 (6%)
• Other	2 (3%)
Years from transplant	**n (%)**
• < 5	34 (63%)
• 5-10	12 (22%)
• > 10	8 (15%)

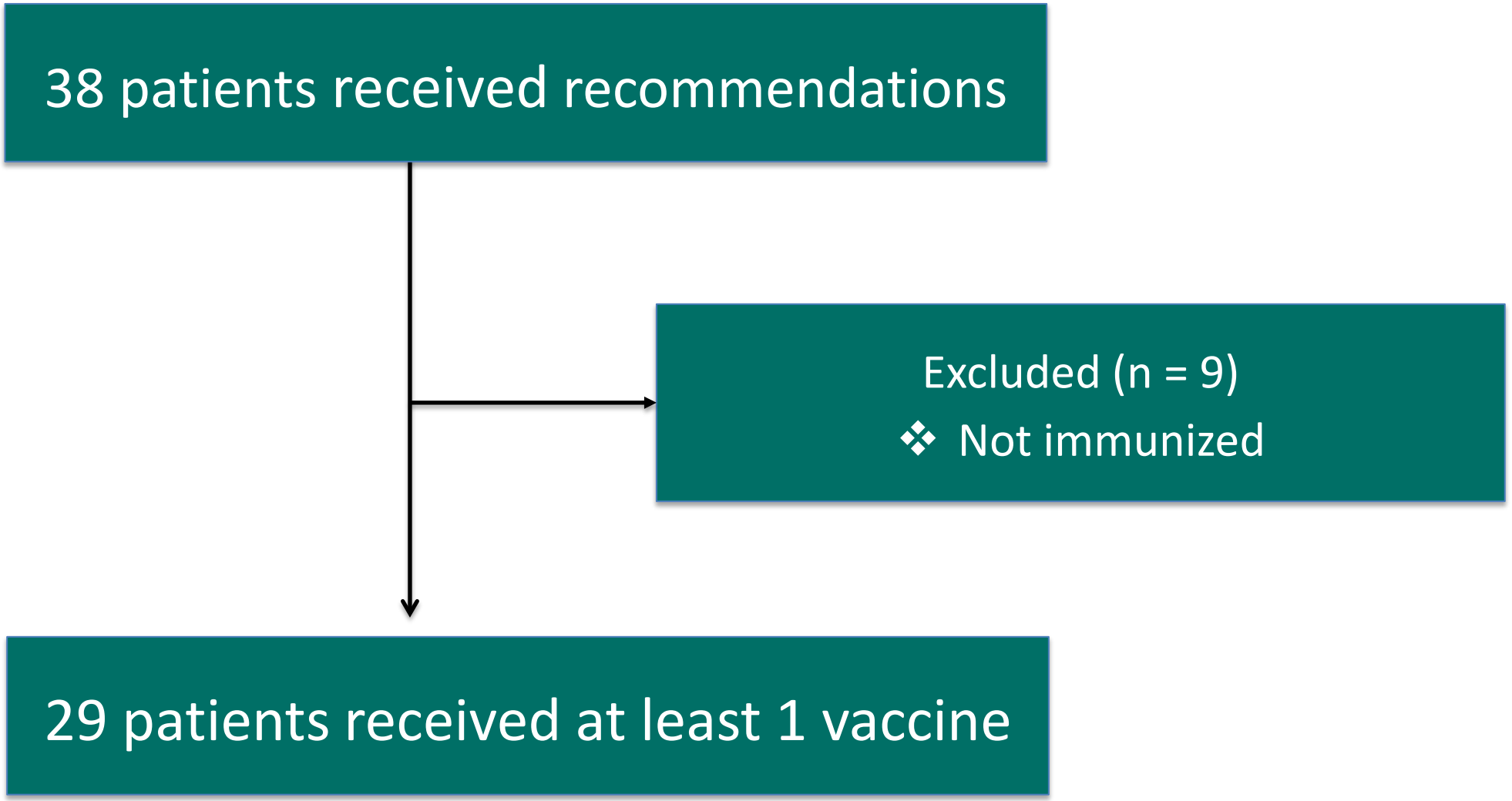
Results: Titers and Recommendations



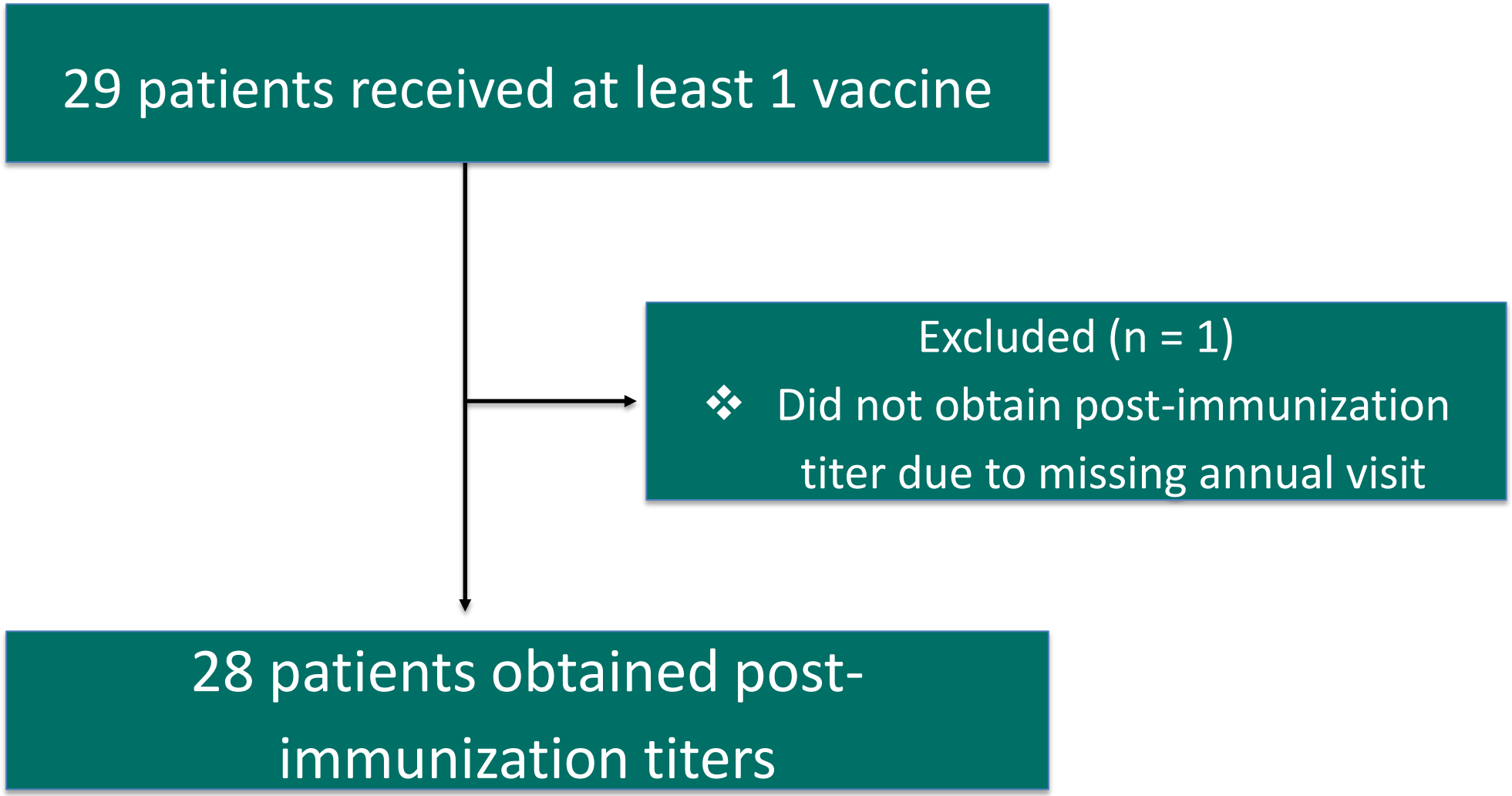
Results: Live Vaccine Recommendations



Results: Live Vaccine Administration



Results: Live Vaccine Post-Immunization Titers



Results: Live Vaccine Immunity

28 patients obtained post-immunization titers

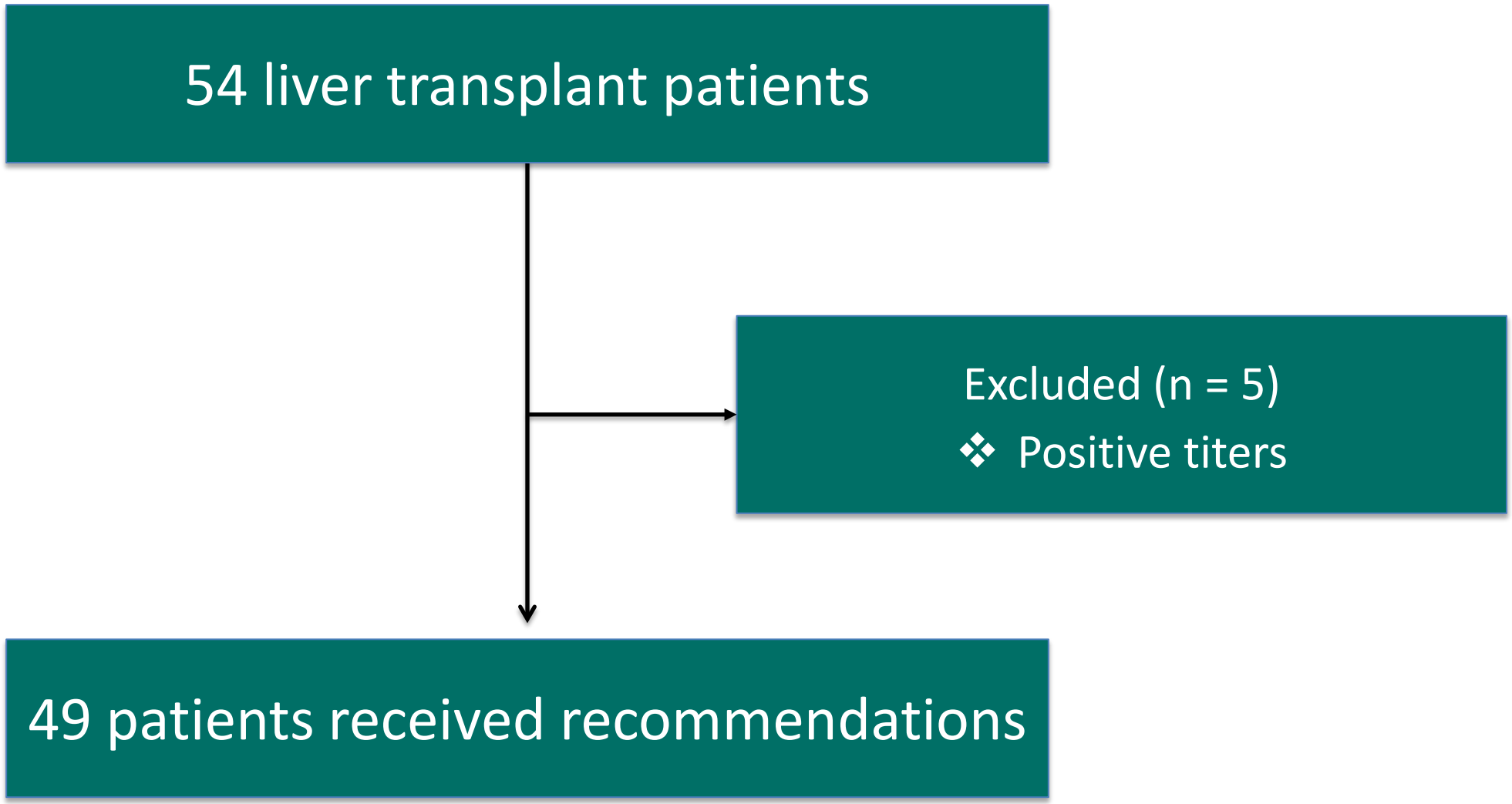
100% (n = 20/20) Measles immune

96% (n = 19/20) Mumps immune

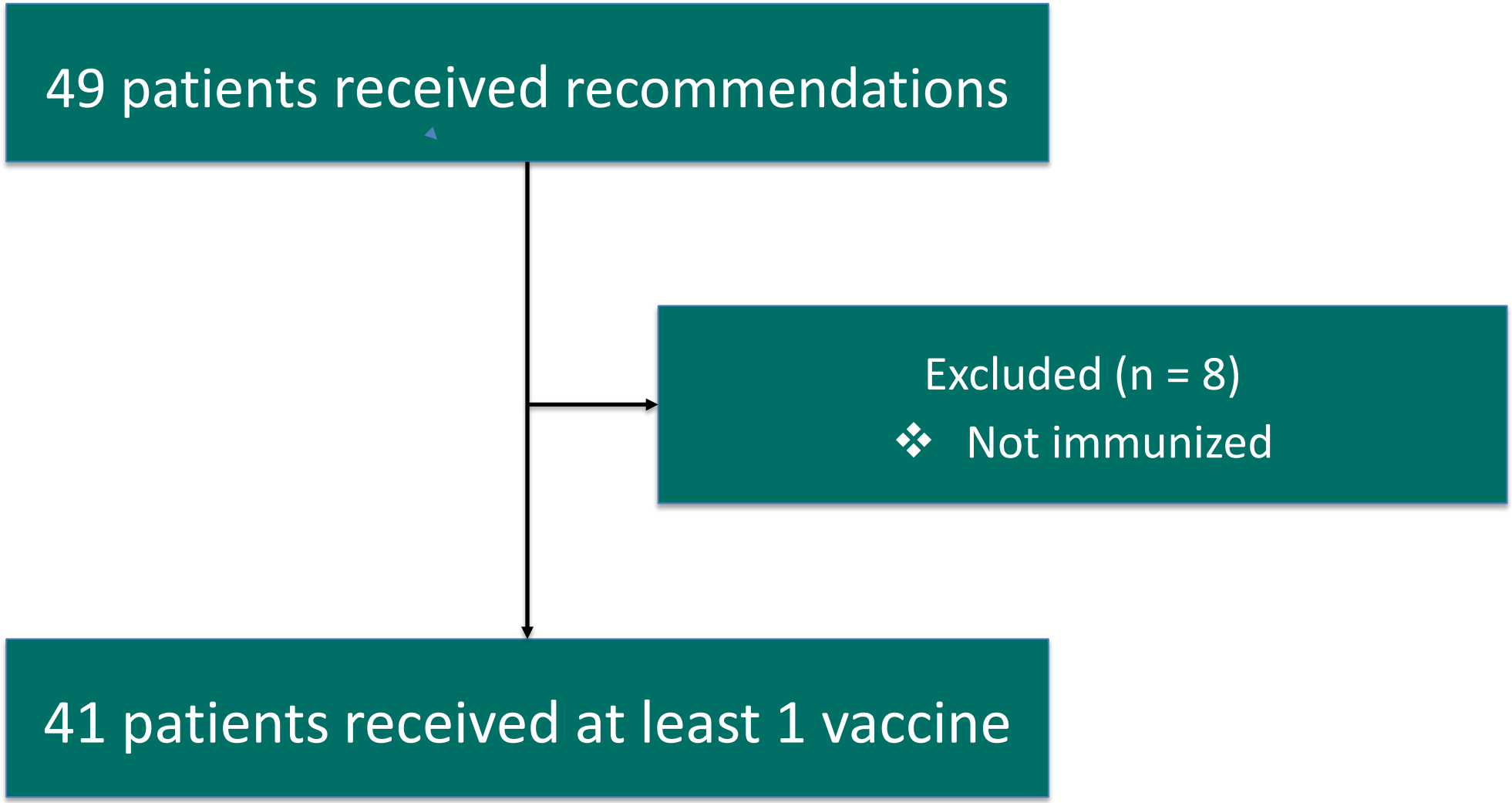
96% (n = 19/20) Rubella immune

95% (n = 17/18) Varicella immune

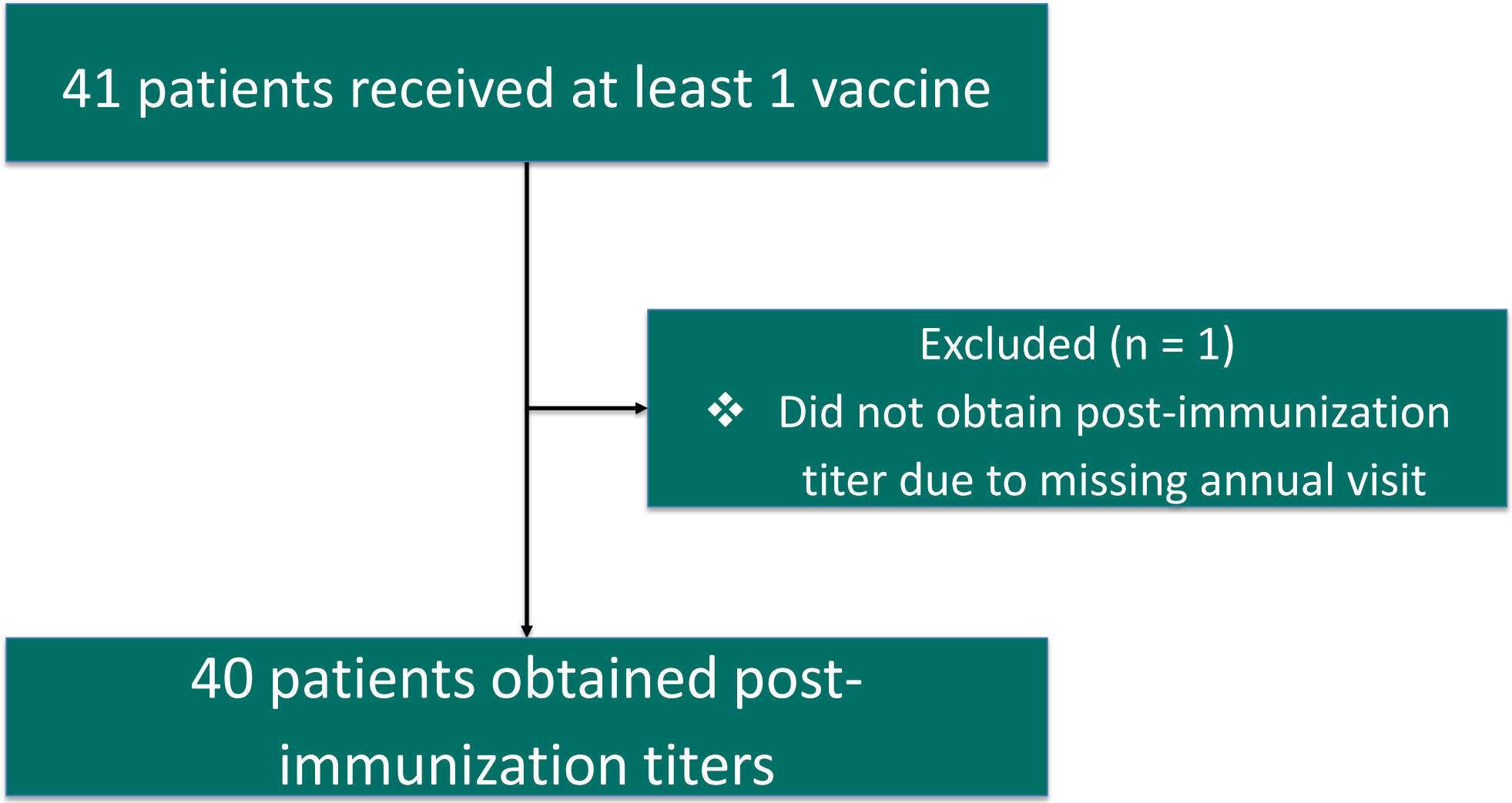
Results: Inactive Vaccine Recommendations



Results: Inactive Vaccine Administration



Results: Inactive Vaccine Post-Immunization Titers

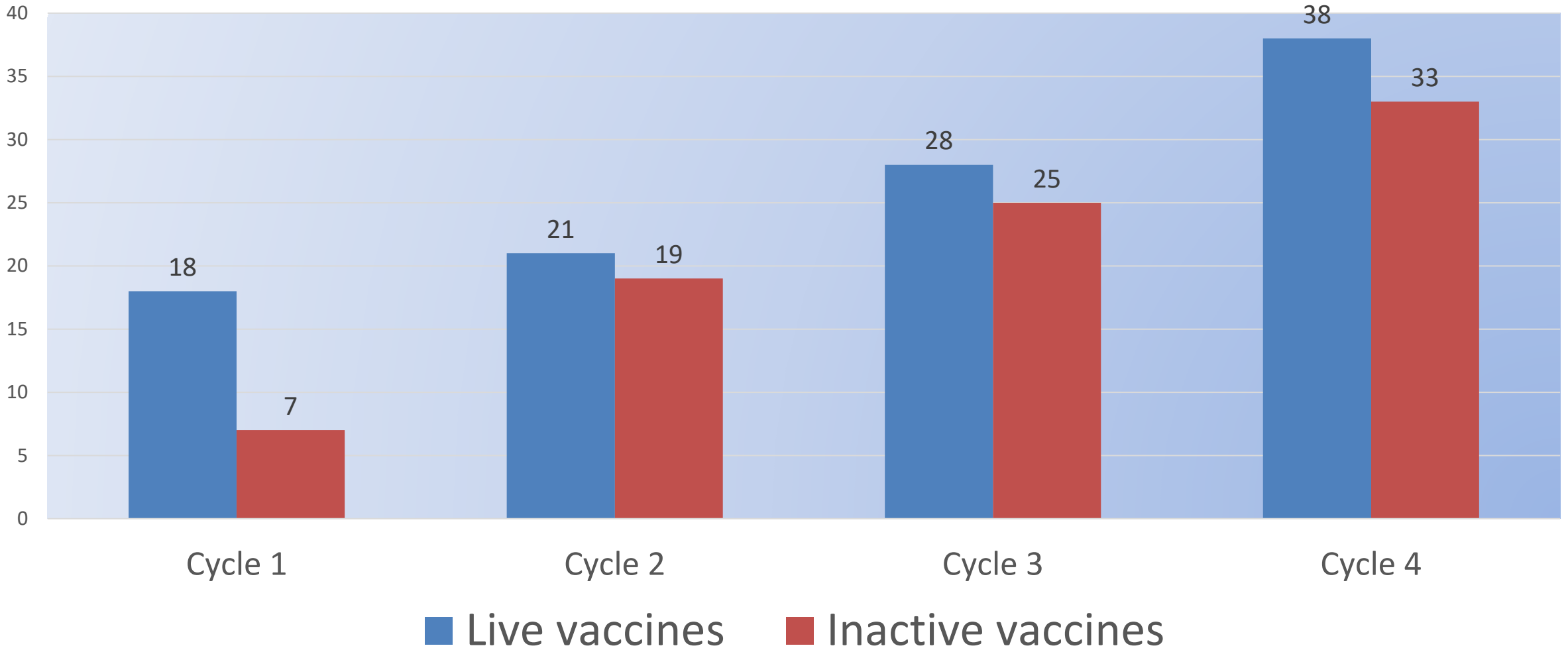


Results: Inactive Vaccines Immunity

40 patients obtained post-immunization titers

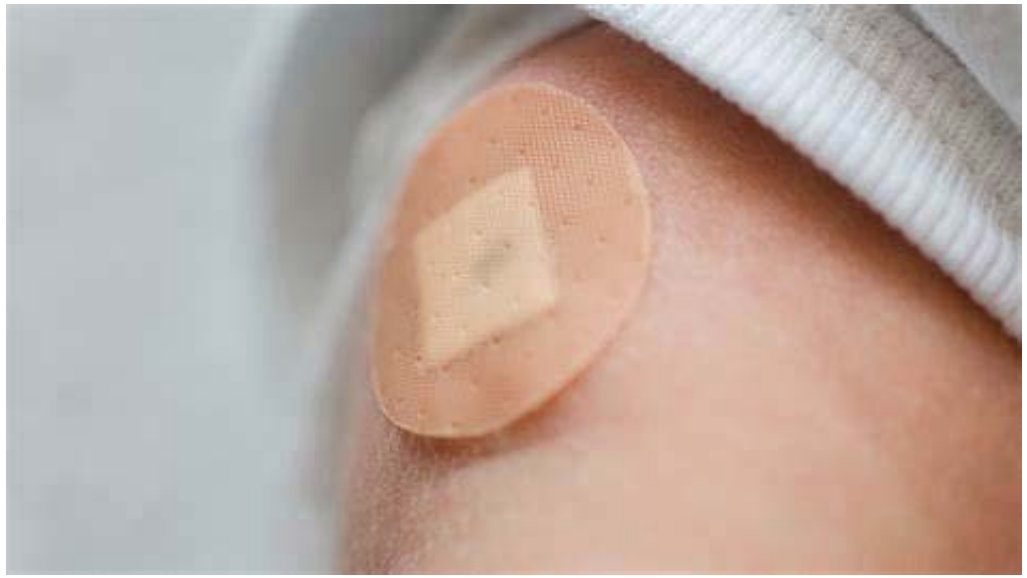
64% (n = 9/14) HAV Immune
65% (n = 21/32) HBV immune
65% (n = 17/26) HiB immune

Immunity Over Time



Adverse Effects for Live Vaccines

- Adverse Effects Monitored:
  - Fever
  - Local site reaction (5)
  - Rejection
  - Pustules (Varicella)
  - Disseminated infection
  - Hospital Admission



- No hospitalization or rejection episodes

Barriers to Immunizations

Barrier	n (%)
Did not schedule appointment with the Pediatrician	3 (19%)
Families that decline vaccinations	3 (19%)
Miscommunication that their child needed vaccines	2 (12.5%)
Forgot their child needed vaccines	1 (6%)
Pediatrician did not get the letter with our new protocol	1 (6%)
Hesitant about live vaccines	2 (12.5%)
Unknown (parent did not answer phone)	4 (25%)

Conclusion

There was a consistent annual increase in vaccine-induced immunity over the 4 years in the PDSA program

Administration of live and inactive vaccines was safe and effective

Response to live vaccines was comparable to other studies and to that of general population

Response to inactive vaccines was less than that of the general population, although remained significant

For PDSA cycle 5 will offer immunizations in transplant clinic

Future Directions:
What Does This Mean for You?

JAMA Network Open

Original Investigation | Infectious Diseases

Safety and Immunogenicity of Live Viral Vaccines in a Multicenter Cohort of Pediatric Transplant Recipients

Amy G. Feldman, MD, MSCS; Brenda L. Beaty, MSPH; Jose A. Ferrolino, MD, MPH; Gabriela Maron, MD, MS; Hillary K. Weidner, BS; Saira A. Ali, MBBS; Leandra Bitterfeld, MSN, RN; Mary Alice Boulware, MSN, CPNP; Kathleen M. Campbell, MD; Emily Carr, MD, MPH; Shelley Chapman, BSN, DNP; Yeh-Chung Chang, MD; Ryan Cunningham, MSN, CPNP; Ronald H. Dallas, PhD; Keerti L. Dantuluri, MD, MPH; Bryanna N. Domenick, BS; Noelle H. Ebel, MD; Scott Elisofon, MD; Rima Fawaz, MD; Marc Foca, MD; Hayley A. Gans, MD; Vani V. Gopalareddy, MD; Cindy Gu, MS; Nitika A. Gupta, MD; Katherine Harmann, PA-C; Jessica Hollenbeck, RN, BSN; Anna R. Huppler, MD; Catalina Jaramillo, MD, MS; Nagraj Kasi, MD; Nanda Kerkar, MD; Stacee Lerret, PhD, RN; Steven J. Lobritto, MD; Maclovio J. Lopez, MD; Elizabeth Marini, MSN, CPNP; Alisha Mavis, MD; Sonia Mehra, MD; Lynnette Moats, MSN, RN; Sindhu Mohandas, MD; Flor M. Munoz, MD, MSc; Krupa R. Mysore, MD, MS; Ceren Onsan, RN, BSN; Nadia Ovchinsky, MD, MBA; Kerrigan Perkins, MPH; Stacy Postma, BS; Lauren Pratscher, RN, BSN; Elizabeth B. Rand, MD; Regina K. Rowe, MD, PhD; Danielle Schultz, RN, BSN; Katherine Sear, RN, MSN, CPNP; Megan L. Sell, PharmD; Tanvi Sharma, MD, MPH; Janis Stoll, MD; Mychoua Vang, MPH; Dominique Villarin, RN, BSN; Carly Weaver, BA; Phoebe Wood, BA; Olivia Woodford-Berry, BS; George Yanni, MD; Lara A. Danziger-Isakov, MD, MPH

Elisa Benetti[11] | Edith Nachbaur[12] | Ana Rita Sandes[13] | Ana Teixeira[14] | Sandra Ferreira[15] | Maja Klaudel-Dreszler[16] | Oanez Ackermann[17] | Olivia Boyer[18,19] | Laura Espinosa[20] | Luis García-Guereta[21] | Marco Saivarez[22] | Björn Fischler[23,24] |

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Questions and Discussion