INNOVAZIONE E RICERCA
PER LA PRATICA CLINICA

XIII Workshop Nazionale

TERAPIE INNOVATIVE
DELLE EPATITI
CRONICHE VIRALI
E DELLE
INFEZIONI VIRALI

FIRENZE
10-11
GENNAIO
2022

Il paziente pediatrico

Firenze, 10 gennaio 2021

Giuseppe Indolfi

UNIVERSITÀ
DEGLI STUDI
FIRENZE

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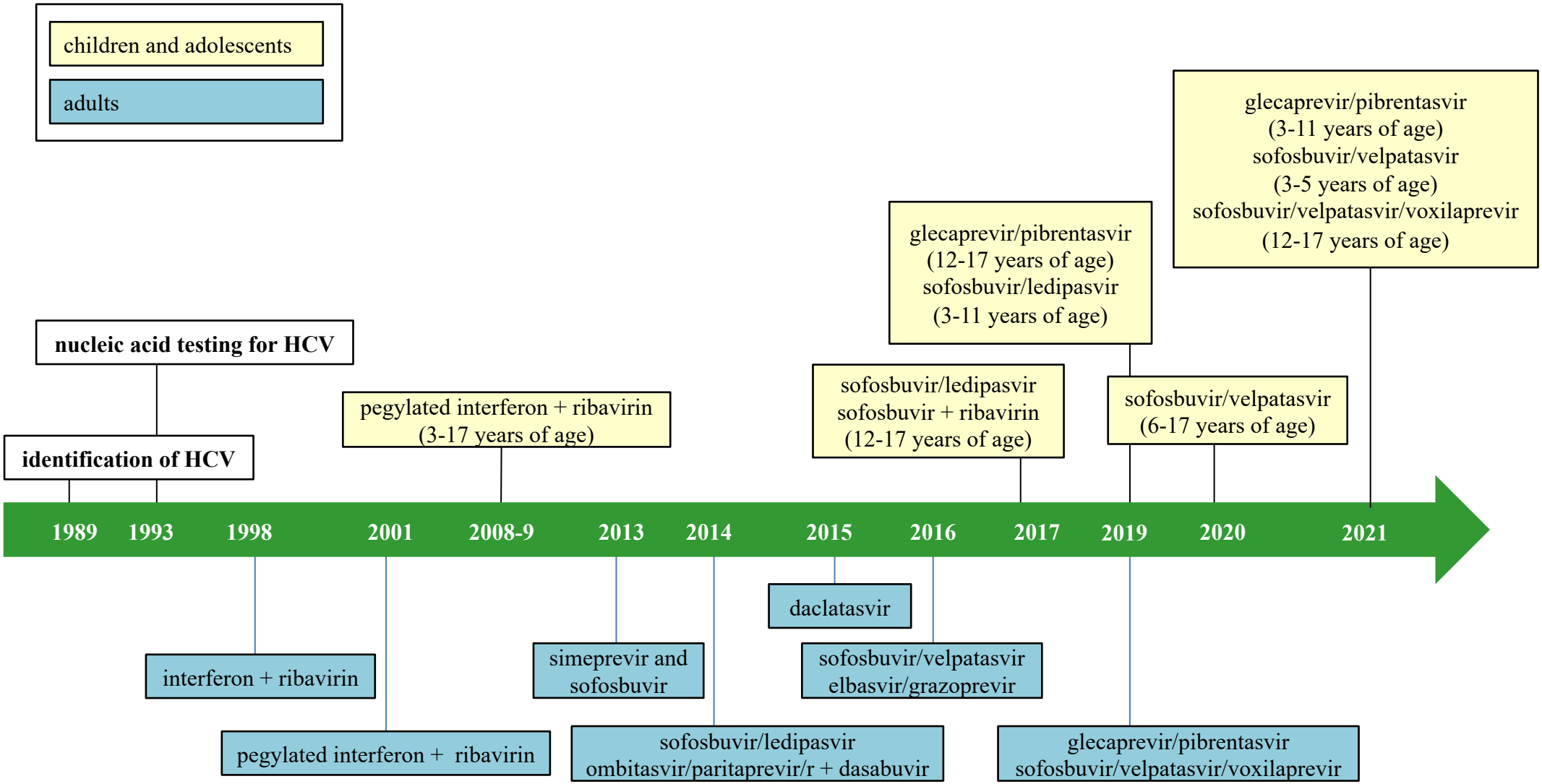

Direct-Active Antivirals Approvals (Jan 2022)

- **Sofosbuvir + ribavirin – 3-17 years**
- **Sofosbuvir/ledipasvir(FDC) – 3-17 years**
- **Glecaprevir/pibrentasvir(FDC) – 3-17 years**
- **Sofosbuvir/velpatasvir(FDC) – 3-17 years (EMA 6-17)**
- **Sofosbuvir/velpatasvir/voxilaprevir(FDC) – 12-17 years (EMA)**

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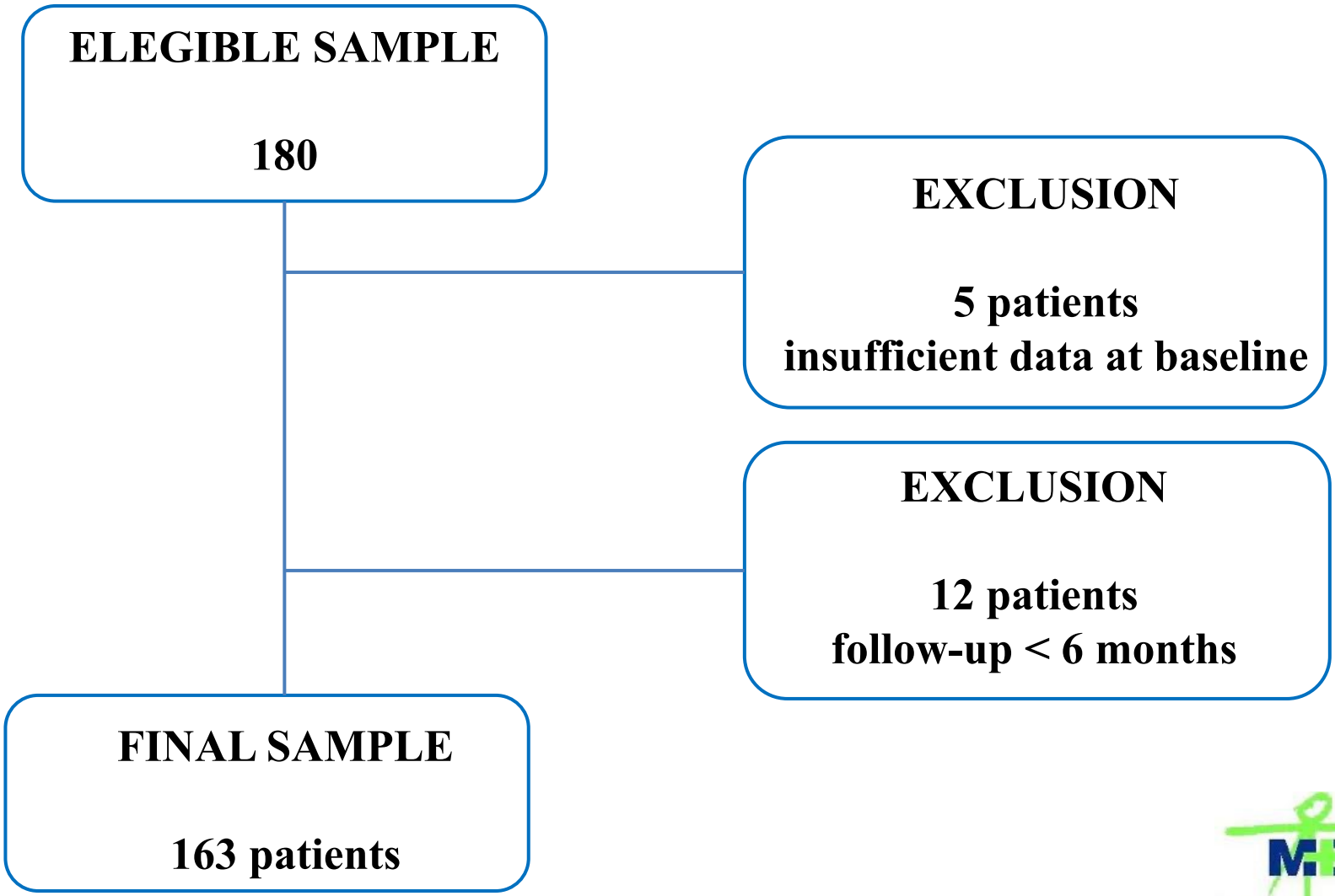
Treatment of HCV in Children

- **Who to treat?**
- **When to start?**
- **Which regimen to use?**

Natural History of Hepatitis C in Childhood

Single centre experience: Jan 1988 – Sep 2021



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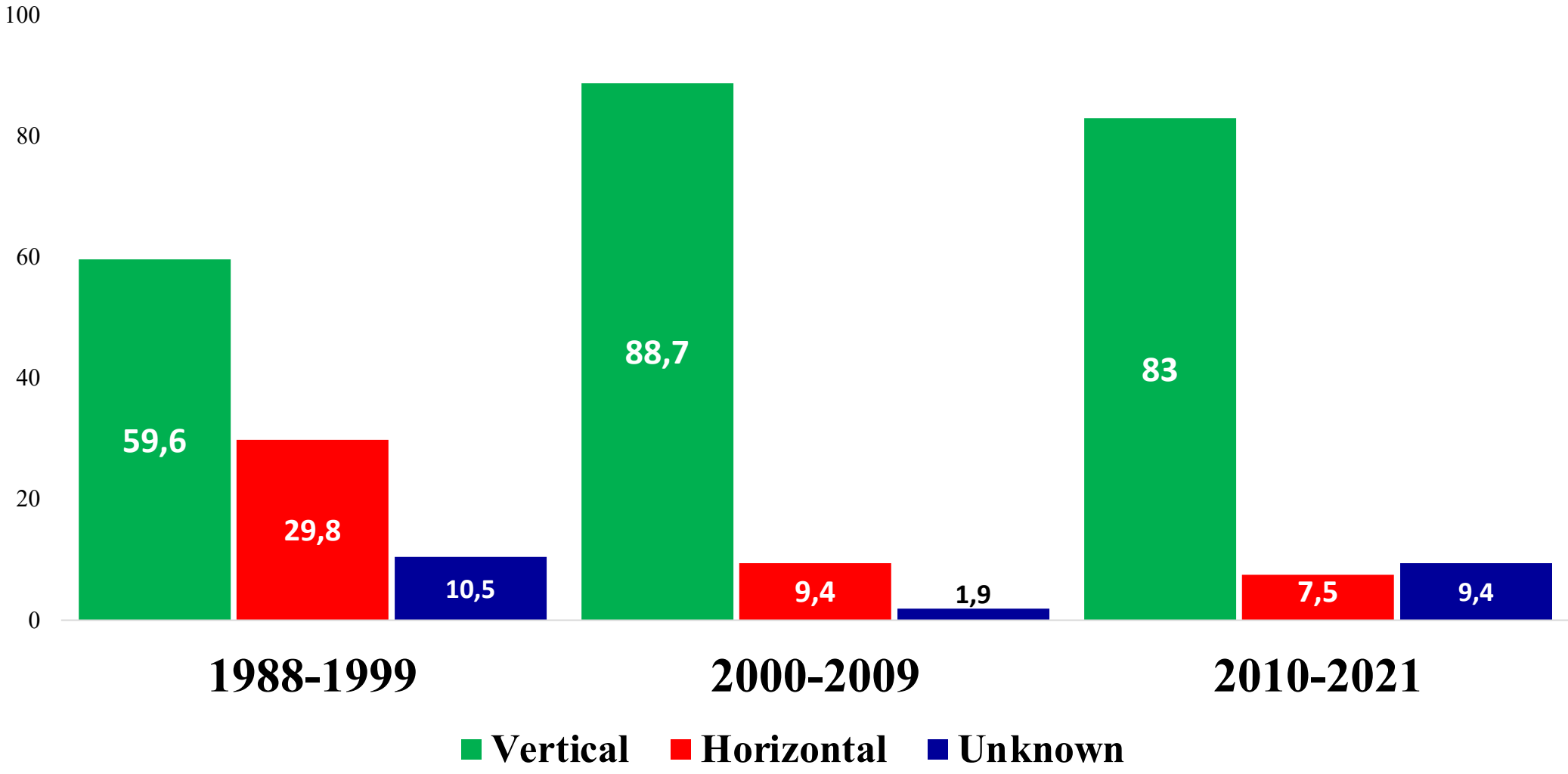
Natural History of Hepatitis C in Childhood

Baseline data

	Enrolled patients n= 163
Age, median (IQR) - years	4 (10)
Gender, n (%)	
Male	89 (54.6%)
ALT, median (IQR) - UI/L	59 (51)
Platelet count, median (IQR) - cells/mm^3	320,000 (129,000)
Genotype, n (%)	
1	99 (60.7%)
2	13 (8%)
3	21 (12.9%)
4	14 (8.6%)
Co-infection	2 (1.2%)
Unknown/not identifiable	6 (3.7%)/8 (4.9%)
Route of transmission, n (%)	
Vertical	125 (76.7%)
Horizontal	26 (15.9%)
Unknown	12 (7.4%)

Natural History of Hepatitis C in Childhood

Route of acquisition



Natural History of Hepatitis C in Childhood

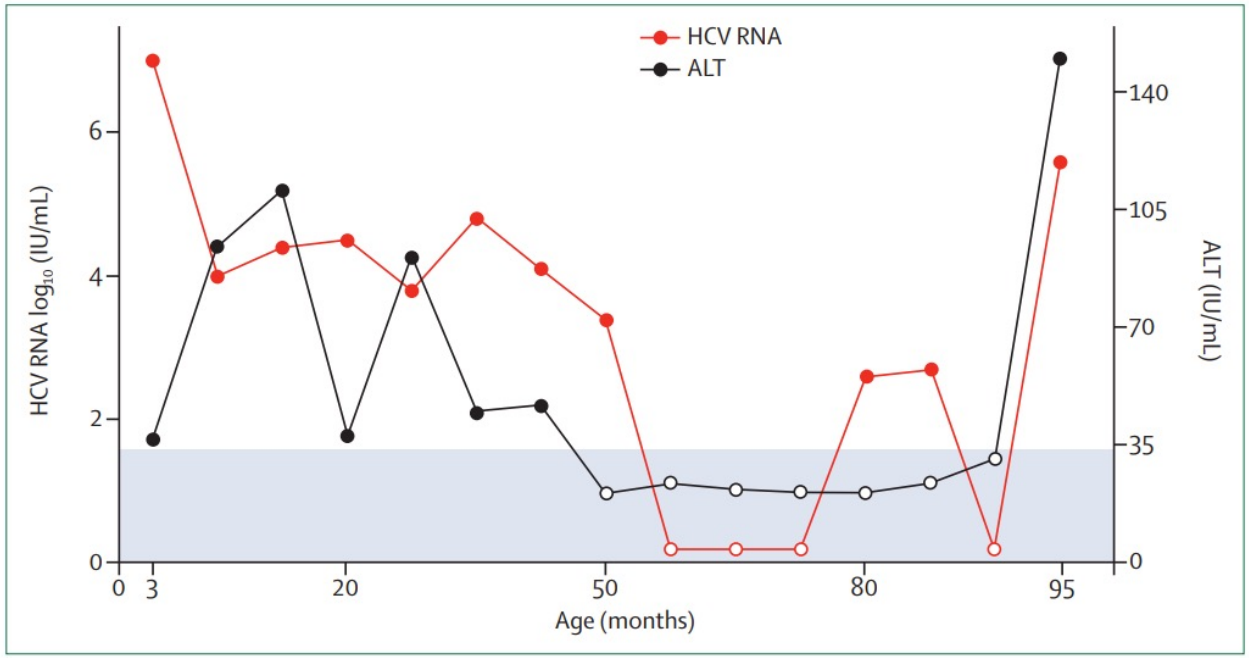
Baseline data

	Chronic infected patients n= 137 (84%)	Patients with spontaneous clearance of infection n= 26 (16%)	p value
Age, median (IQR) - years	5 (9)	1 (7)	0.13
Gender, n (%) Male	 71 (51.8%)	 18 (69.2%)	0.14
ALT, median (IQR) - UI/L	60 (50)	50.5 (57)	0.44
Platelet count, median (IQR) - cells/mm^3	322,000 (125,500)	298,000 (114,500)	0.73
Genotype, n (%) 1 2 3 4 Co-infection Unknown/not identifiable	 90 (65.7%) 12 (8.7%) 19 (13.9%) 14 (10.2%) 1 (0.7%) 1 (0.7%)	 9 (34.6%) 1 (3.8%) 2 (7.7%) 0 1 (3.8%) 5 (19.2%)/8 (30.7%)	0.46
Route of transmission, n (%) Vertical Horizontal Unknown	 105 (76.6%) 22 (16%) 10 (7.3%)	 20 (76.9%) 4 (15.4%) 2 (7.7%)	0.99

Spontaneous Clearance

25/163 (15.3%)

- **10 HCV Ab positive/HCV RNA negative (median age 8.5 years)**
- **15 spontaneous clearance median age 4 years (IQR 2)**



Indolfi G, *Lancet* 2016

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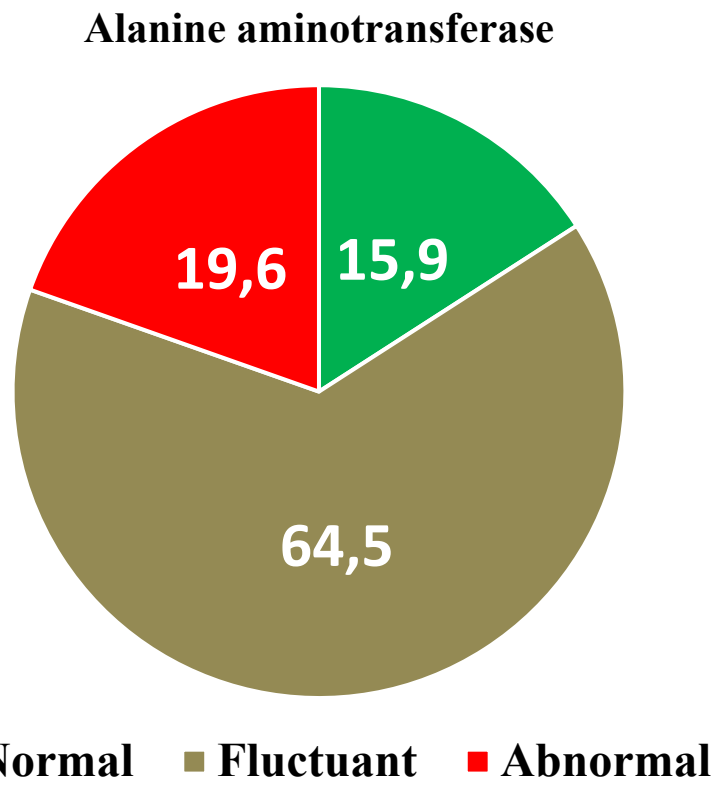
Chronic Infection

138/163 bambini (84.7%)

- **aminotransferases**



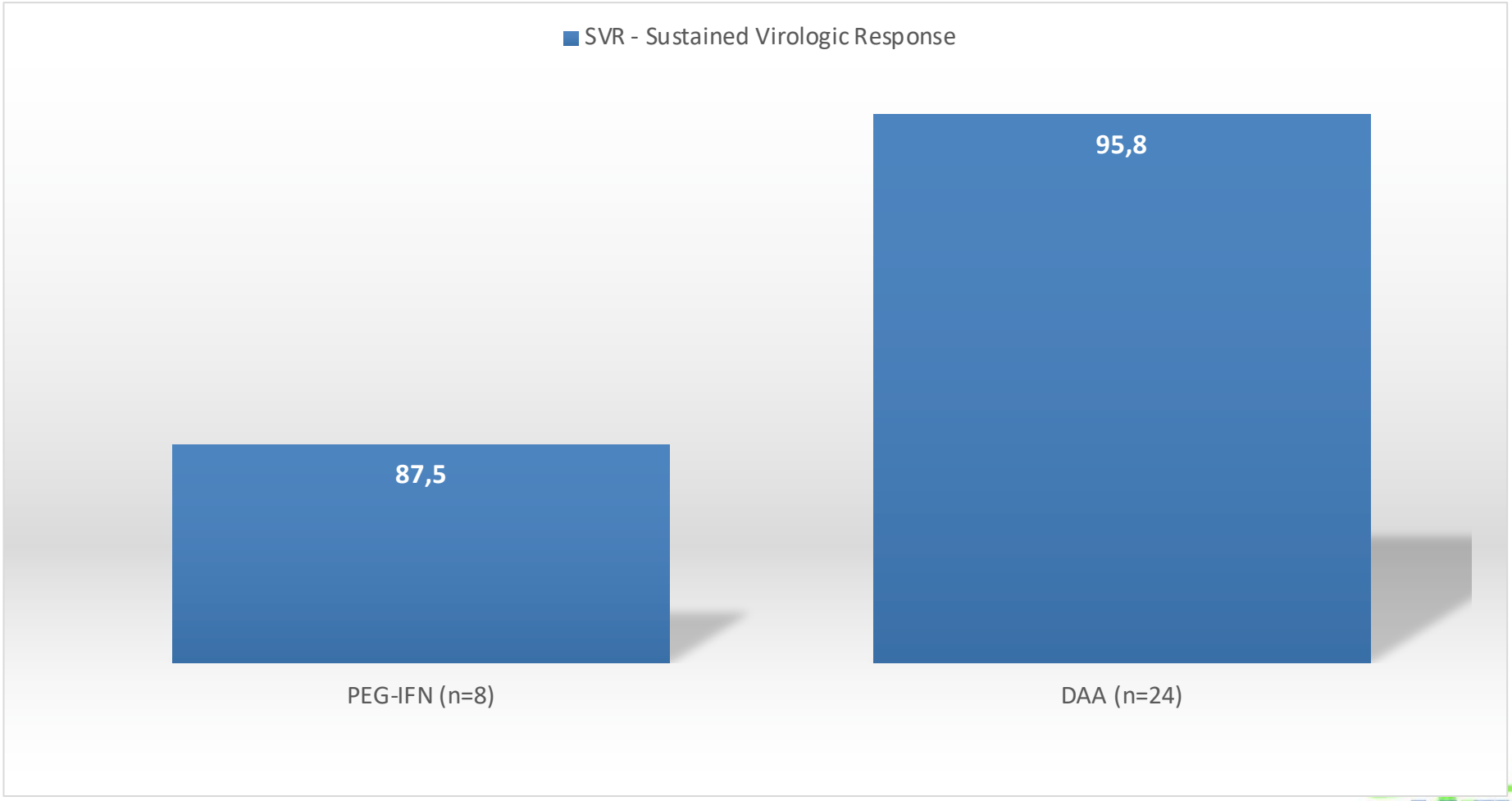
- **160 without symptoms**
- **2 chronic urticaria**
- **1 patient with compensated cirrhosis**

Natural History of Hepatitis C in Childhood

Treatment

	Untreated patients n=105 (76.6%)	Treated patients* n=32 (23.4%)	p value
Age, median (IQR) - years	15 (7)	15 (4)	0.74
Gender, n (%)			0.13
Male	58 (55.2%)	13 (40.6%)	
ALT, median (IQR) - UI/L	56 (36)	40 (26.5)	0.06
Platelet count, median (IQR) - cells/mm^3	264,000 (70,000)	262,500 (111,000)	0.84
Genotype, n (%)			0.63
1	73 (69.5%)	17 (53.1%)	
2	8 (7.6%)	4 (12.5%)	
3	12 (11.4%)	7 (21.9%)	
4	10 (9.5%)	4 (12.5%)	
Co-infection	1 (1%)	0	
Unknown/not identifiable	1 (1%)	0	
Route of transmission, n (%)			0.47
Vertical	78 (74.3%)	27 (84.4%)	
Horizontal	19 (18.1%)	3 (9.4%)	
Unknown	8 (7.6%)	2 (6.2%)	

Antiviral treatment



Hepatitis C Genotype 4 Virus Nonstructural 3 and Nonstructural 5A Resistance-associated Substitutions in a 16-year-old Adolescent Failing Ombitasvir/Paritaprevir/Ritonavir Plus Ribavirin

Daniele Serranti, MD, Giuseppe Indolfi, MD,* Cinzia Caudai, MD,† Elisa Bartolini, MD,* Sandra Trapani, MD,* Maurizio Zazzi,‡ and Massimo Resti, MD**

TABLE 1. Resistance-Associated Substitutions and Prediction of Resistance to Direct-Acting Antivirals

Region Analyzed	Basal	On Treatment	Prediction of Resistance
NS3 region	No mutation	D168H	GT4 resistant to paritaprevir
NS5A region	M28V	M28V	Reduced GT4 susceptibility to ombitasvir
	Y93C	Y93C	Reduced GT1a susceptibility to ombitasvir
NS5B region	None	None	

GT indicates genotype.

Pediatr Infect Dis J 2019;38:e72–e74

Natural History of Hepatitis C in Childhood

Treatment

Treatment regimens	Children, n (%)
PEG-IFN	
PEG-interferon alfa-2b + ribavirin	8 (25%)
DAA	
Sofosbuvir/ledipasvir	16 (50%)
Omvitasvir/paritaprevir-ritonavir + ribavirin	1 (3.1%)
Sofosbuvir + ribavirin	3 (9.4%)
Sofosbuvir/velpatasvir	2 (6.3%)
Sofosbuvir/velpatasvir + voxilaprevir	1 (3.1%)
Glecaprevir/pibrentasvir	1 (3.1%)

Direct-Active Antivirals Available in Italy

- Sofosbuvir + ribavirin – 3-17 years
- **Sofosbuvir/ledipasvir(FDC) – 12-17 years**
- **Glecaprevir/pibrentasvir(FDC) – 12-17 years**
- Sofosbuvir/velpatasvir(FDC) – 3-17 years (EMA 6-17)
- Sofosbuvir/velpatasvir/voxilaprevir(FDC) – 12-17 years (EMA)

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Treatment of HCV in Children

- **Who to treat?**
  - **mainly adolescents**
- **When to start?**
  - **when there is access to the drug**
- **Which regimen to use?**
  - **the one(s) available (not IFN-based)**

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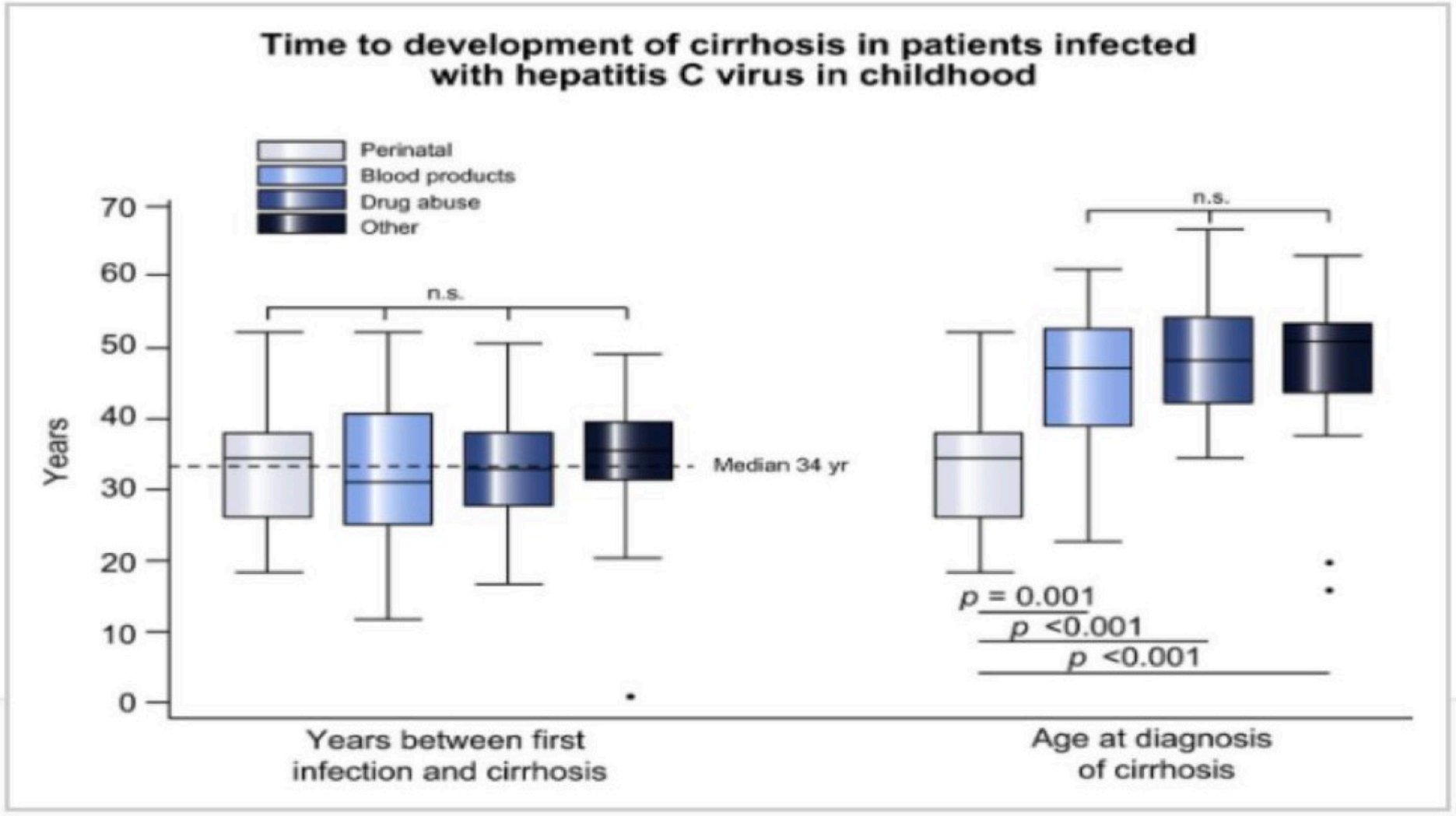
Hepatitis C in Children

Natural history of the infection



Modin J, J Hepatol 2018

Sofosbuvir(nNS5B) / ledipasvir(NS5A) (FDC)

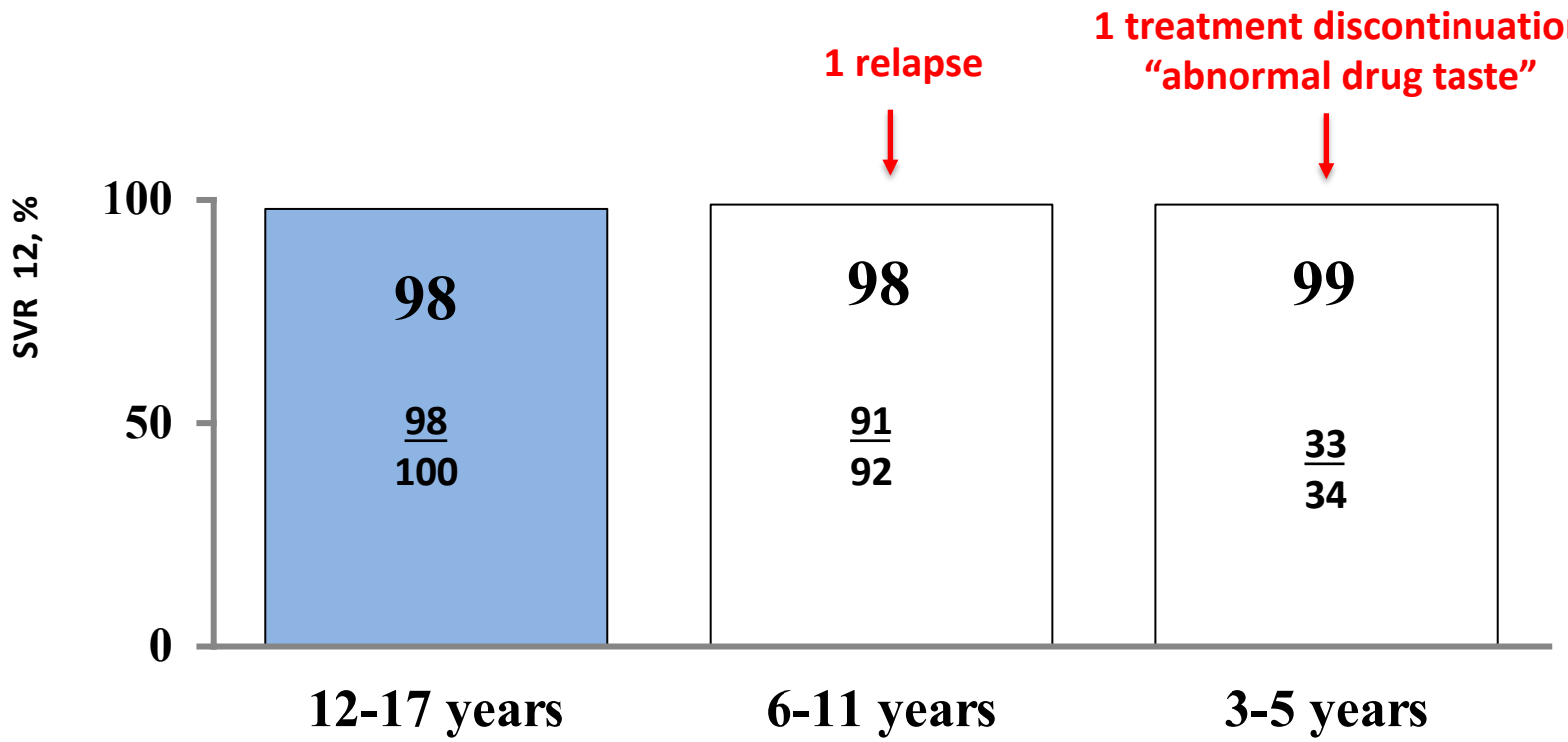
NCT 02249182, industry-driven trial

EMA FDA

3-17 years

3-17 years, HCV GT 1,4,5,6, cirrhotic (n 3) and non-cirrhotic

12 weeks of treatment; treat.-experienced or cirrhosis: 24 weeks



S/L tablets 400/90 and 200/45 mg; granules 200/45 mg and 150/33.75 mg

>35 Kg:	400/90 mg QD;
17-35 Kg:	200/45 mg QD;
< 17 Kg:	150/33.75 mg QD

Balistreri WF, Hepatology 2017
Murray K, Hepatology 2018
Schwarz KB, Hepatology 2020

Sofosbuvir(nNS5B) + ribavirin

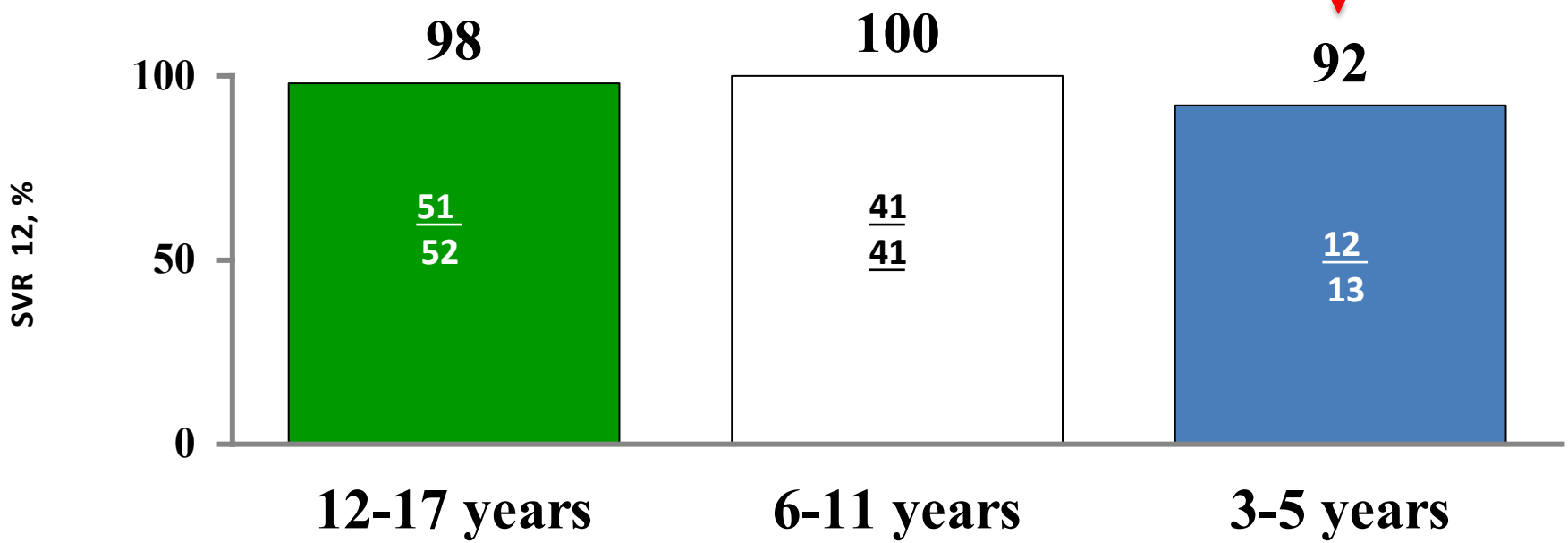
NCT 02175758, industry-drive trial

EMA FDA

3-17 years

GT2:12 weeks; GT3 24 weeks of treatment

1 treatment discontinuation
"abnormal drug taste"



Ribavirin weight based
S tablet 400 mg, 200 mg; granules 200 mg , 150 mg
>35 Kg: 400 mg QD
17-35 Kg: 200 mg QD
< 17 Kg: 150 mg QD

Wirth, Hepatology 2017
Rosenthal P, Hepatology 2020

Glecaprevir(PI) / pibrentasvir(NS5A) (FDC)

NCT 03067129, industry-driven trial (DORA part 1 and 2)

EMA FDA

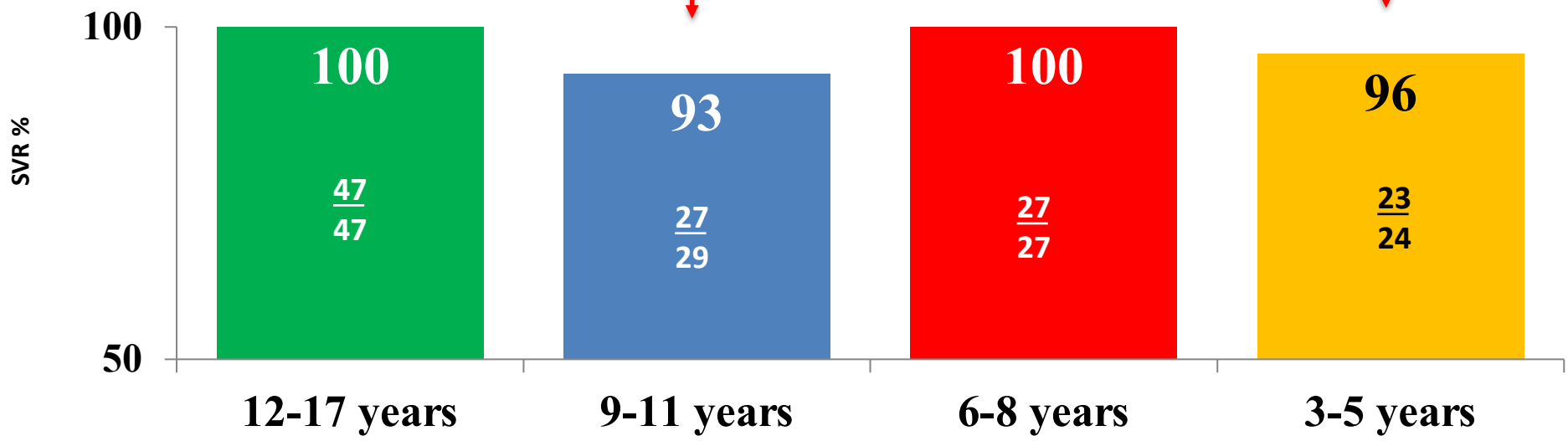
3-17 years

3-17 years, HCV GT1-6, non-cirrhotic, HIV (n 3)

non-cirrhotics 8 weeks; cirrhotic 12 weeks (n 0); GT3 treatment experienced 16 weeks (n 4)

1 treat. discontinuation
1 relapse PTW4

1 treatment discontinuation
"abnormal drug taste"



G/P, with food; tablet 100/40 mg; granules 50/20 mg	
12-17 years:	300/120 mg QD
9-11 years:	30 to < 45 Kg: 250/100 mg QD
6-8 years:	20 to < 30 Kg: 200/80 mg QD
3-5 years:	12 to < 20 Kg: 150/60 mg QD

Jonas MM, Hepatology 2020 and 2021

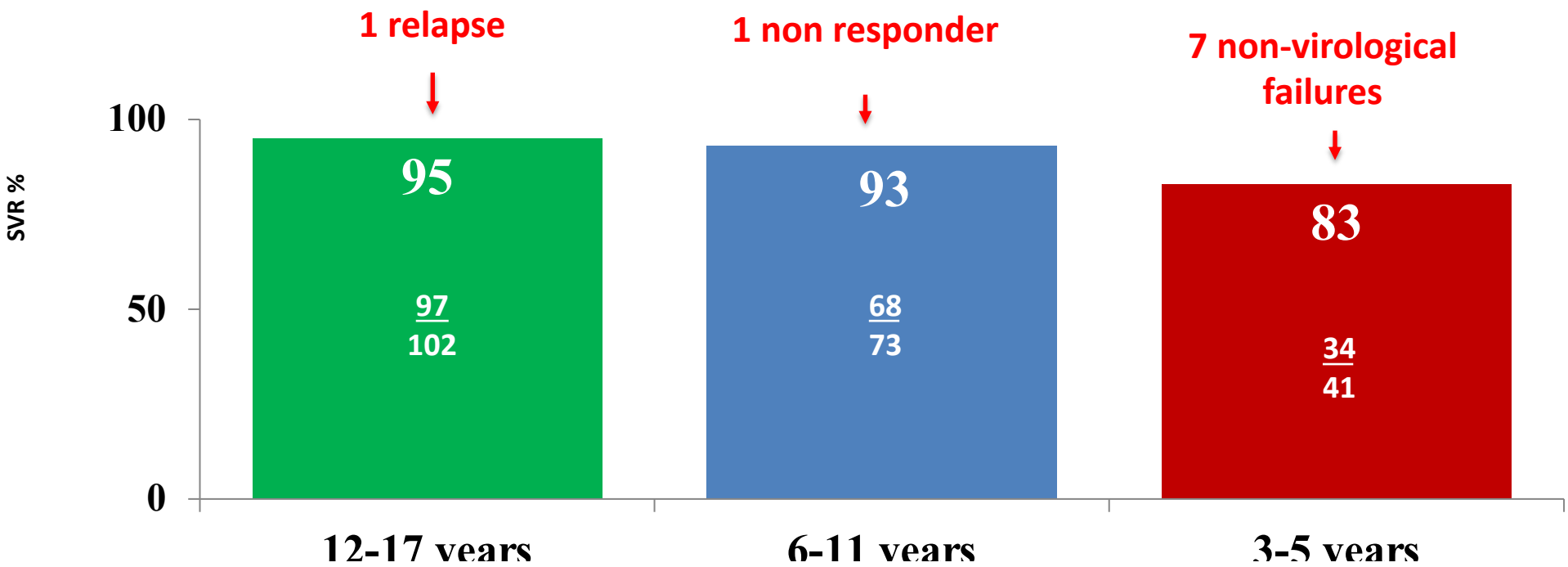
Sofosbuvir(NS5B) / velpatasvir(NS5A) (FDC)

NCT 03022981, industry-driven trial

EMA ● 6-17 years FDA ● 3-17 years

3-17 years, HCV GT1-6, cirrhotic (n 0) and non-cirrhotic

12 weeks



S/F tablet 400/100 and 200/50 mg; granules 50/12.5 mg

>30 Kg:	400/100 mg QD
17-30 Kg:	200/50 mg QD
<17 Kg:	150/37.5 mg QD

Jonas MM, AASLD 2019
Sokal E AASLD 2020

Sofosbuvir(NS5B) / velpatasvir(NS5A) (FDC)

NCT 03022981, industry-driven trial

EMA ● 6-17 years

FDA ● 3-17 years

3-17 years, HCV GT1-6, cirrhotic (n 0) and non-cirrhotic

12 weeks

	12-18 years	6-11 years	3-5 years
n	102	73	41
Virological failure	1	1	0
Treatment discontinuation due to adverse event	0	1	1
Lost to follow up/non compliance with study drug	4	3	6

Jonas MM, AASLD 2019 and 2020
Clinicaltrial.gov

Sofosbuvir(NS5B) / velpatasvir (NS5A) / voxilaprevir (NS5A) (FDC)

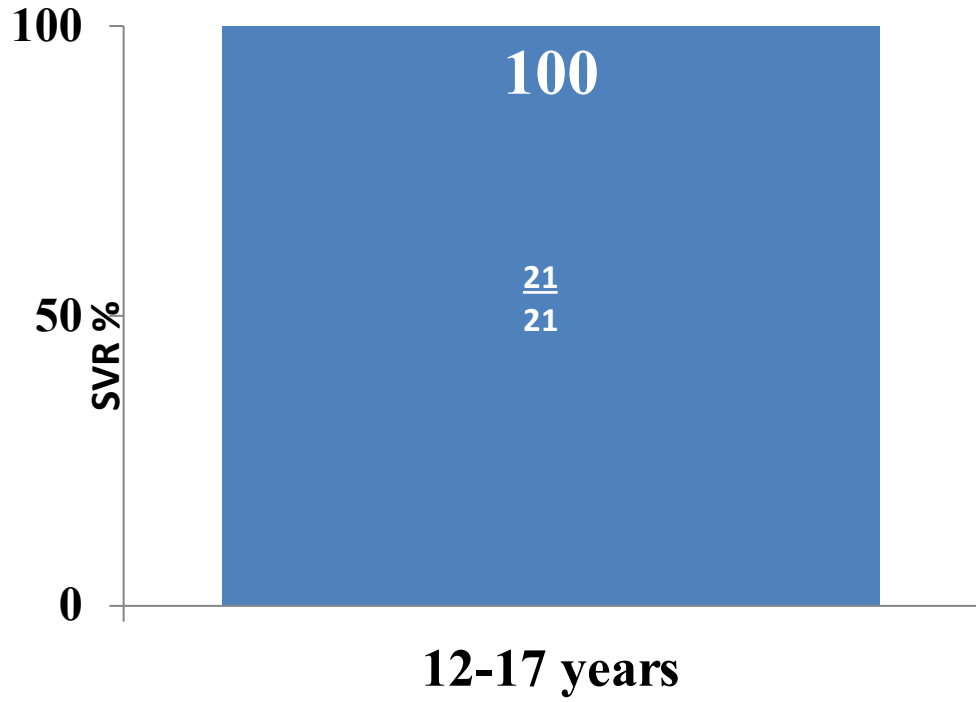
NCT 03022981, industry-driven trial

EMA

12-17 years

12-17 years, HCV GT1-6, cirrhotic and non-cirrhotic

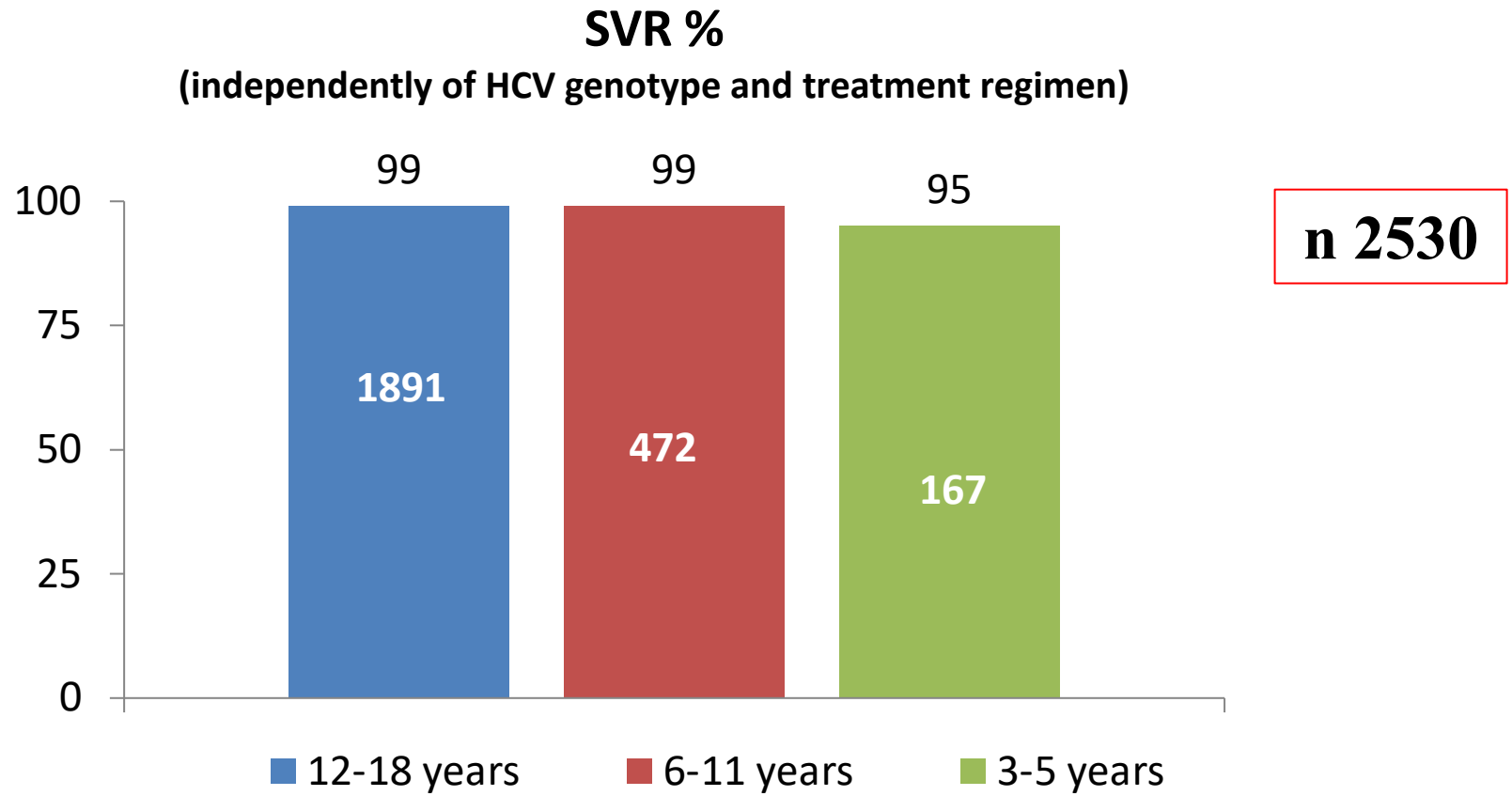
non cirrhotic 8 weeks; cirrhotic (n 0) or treatment exp. (n 5) 12 weeks



S/V/V tablet 400/100/100 mg QD

Indolfi G, Hepatology 2022

Paediatric trials Direct-Acting Antivirals Efficacy: systematic review with meta-analysis



n 2530

Indolfi G, Aliment Pharmacol Ther 2020; update 2021 WHO Guidelines

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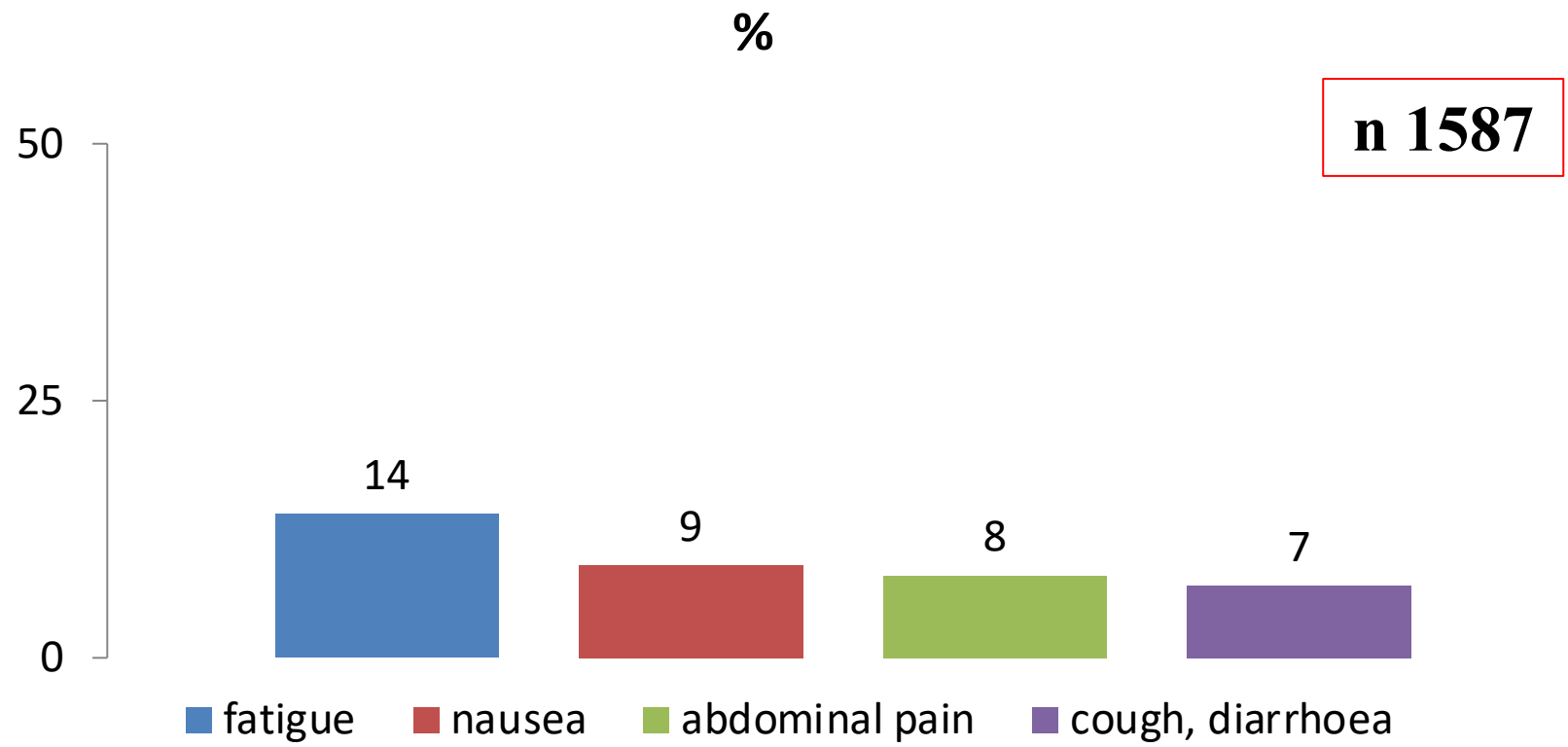
Paediatric trials Direct-Acting Antivirals Safety: systematic review with meta-analysis



Indolfi G, Aliment Pharmacol Ther 2020

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Treatment of HCV in Children

- **Who to treat?**
  - **all children >3 years of age**
- **When to start?**
  - **when the child is able to take the oral medication**
- **Which regimen to use?**
  - **the available regimen and the age-appropriate formulation**

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