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CONFLICT OF INTEREST

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HCV and Children

A focus on hepatitis C in children and youth of NM

What do we know?

What can we do?

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Date prepared:

Project ECHO HCV Collaborative

Conflict of Interest Disclosure Statement

No disclosures

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Objectives

CME Objectives

- Discuss prevalence of HCV in children
- Discuss screening children and youth for HCV

Additional Objectives

- Identify risk factors for vertical transmission
- Natural history of HCV in children & youth
- Criteria for diagnosis
- Recommended evaluation
- Who, where and how to treat
- Project HepCCY

Prevalence

Worldwide 170,000,000 million infected: 5 million children

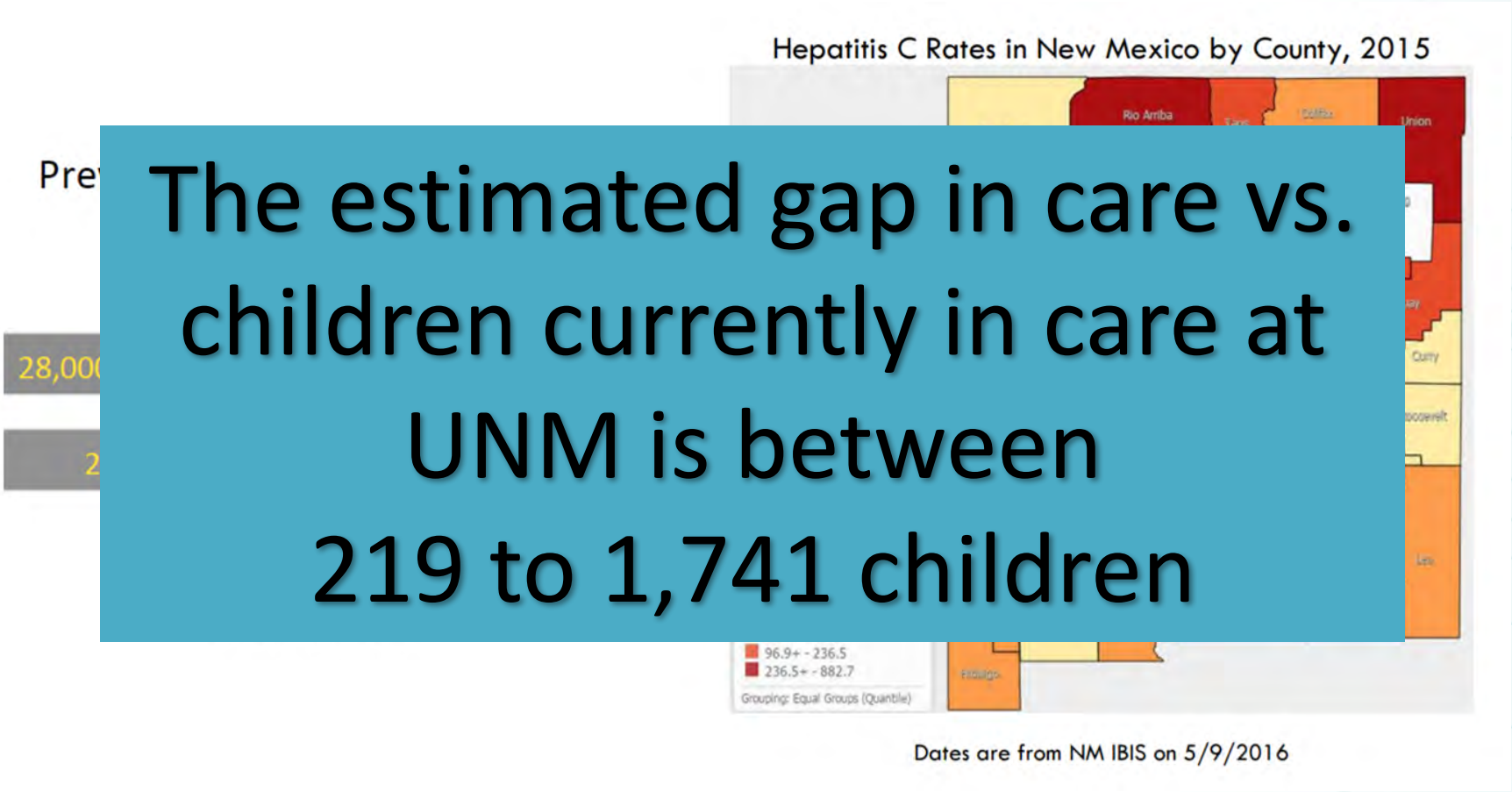
- Highest prevalence in Egypt; 3% prevalence in children

US:

- 4 million adults living with HCV infection; 1-2% adults infected
  - M>F; rising incidence in baby boomers 50-69 y/o
  - Non-Hispanic black 2 x more likely & Native Americans 3 x more likely to be diagnosed as non-Hispanic whites.
- 0.1-0.2% children infected:
  - 0.15% of 6-11 year olds
  - 0.4% of 12-19 year olds
  - 23,000 to 46,000 children in US with HCV

Lee 2015 WMJ; Rayne-Greenow 2015 J Peds & Child Health

What about New Mexico?



The estimated gap in care vs. children currently in care at UNM is between 219 to 1,741 children

Drawing population data from NM 2016 Census:

- Estimate 982 to 1,965 children < age 18 have been exposed to HCV
- Estimate 246to 1,768 children are chronically infected

Vertical transmission

Prevalence of HCV infection in pregnant women (HCV Ab or pcr +ve) 0.75% (range 0.5-1.7%)

Overall risk of transmission 5%:

- 1.7% per pregnancy if mom HCV Ab positive
- 4.3% per pregnancy if mom HCV PCR positive
- 7.1% per pregnancy if mom HCV PCR positive at least twice during pregnancy or around the time of delivery
- 2-3 fold higher if mom co-infected with HIV
- 36% if maternal viral load ≥ 1,000,000 iu/ml

Unknown at what stage of pregnancy transmission occurs

Thought that method of transmission differs from that of HIV

All genotypes can cause MTCT (mother to child transmission), but limited quaisispecies are noted

As HCV is present in monocytes too, suggestion HLA similarity between mother and child may facilitate persistence of maternal cells in newborn blood

Accounts for 7,500 new cases HCV in US per year

HCV transmission from an infected father via sperm has been demonstrated

- (*Ma et al. 2016 Clin Lab*)

HCV can infect placental cells

Vertical transmission risk factors

Maternal risk factors:	Infant risk factors:
Coinfection with HIV	Fetal scalp vein monitoring?
IV drug use?	Fetal anoxia at the time of delivery (cord blood pH)
Prolonged rupture of membranes > 6 hours	Protective HLA types (mismatch favorable?)
High maternal HCV load, >600,0000 IU/ml, but genotype not a factor	Higher risk HLA types: HLA-DRB1*10
Risk of amniocentesis not known (HCV detected in amniotic fluid)	Higher risk for females vs males?
No reduction of risk with elective LSCS (Cochrane)	
Avoid large vaginal tears with vaginal delivery (episiotomy not a risk factor?)	
Maternal HLA: HLA-DRB104 protective	
Not related: maternal age; parity; cigarette smoking; alcohol use	
No benefit to withholding breast feeding unless nipples are bleeding, active mastitis (CDC) or mom has post partum HCV flare with jaundice	

TORCH infections

Infection	US prevalence of congenitally acquired disease
Toxoplasmosis	10-33/100,000 live births
Treponema pallidum	7.8/100,000 live births
CMV	800/1,000,000 live births
Hepatitis B	<0.1/1,000,000 live births
Hepatitis C	<0.1/100,000 live births
HIV	162 infants/yr, 2010

Neu et al, 2015, Clin Perinatol

HCV Screening of Pregnant women

Studies show not cost effective to screen all pregnant women for HCV

Screen high risk pregnant women

Screening transaminases is not helpful as they often improve in 2nd & 3rd trimester

ACOG recommendations

- Screen pregnant women with risk factors such as:
  - IVDU (but self-reporting is unreliable)
  - HIV

Also:

- HBV
- Blood transfusions
- Clotting factors

The case for screening all pregnant women in the new era of DAAs

Proposal to screen all pregnant women and offer treatment with DAAs before next pregnancy? (*2016 Aebi-Popp et al. J Virus Eradication*)

Pregnant women with HCV infection have worse maternal and fetal outcomes:

- Gestational diabetes
- Preeclampsia
- Growth restriction
- Antepartum hemorrhage
- Preterm birth
- Gestational cholestasis
- Physiologic state of later pregnancy may favor viral replication

Infants of HCV positive mother have worse outcomes independent of IVDU:

- Low birth weight
- Ventilator assistance
- NICU admission
- Congenital anomalies?

Other methods of infection of children

- IV drug use /needle sharing
- High-risk sexual behaviors (negligible risk for sexual intercourse in stable relationship)
- Household exposure <2%
- Tattooing or body piercing

Whom to test?
Identifying at risk & infected children

Group	Screening
Adolescents who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users	Antibody
Children and adolescents with conditions associated with a high prevalence of HCV infection including: • Persons with human immunodeficiency virus (HIV) infection • Persons who have ever been on hemodialysis	Antibody or RNA
Children born to HCV-infected mothers	Antibody >18 months RNA ≤ 18 months
Present sexual partners of HCV-infected persons	Antibody
Children or adolescents with chronically elevated transaminases	Antibody
Children and adolescents with signs or symptoms of hepatitis: • Jaundice, dark urine, pale stool, fatigue, nausea and vomiting, abdominal pain, especially in the RUQ, loss of appetite, low-grade fever, joint pain	Antibody and/or RNA
Children and adolescents with intrafamilial exposure: • Siblings, parents, household contacts	Antibody

Whom to test?

Group	Screening
Children and adolescents emigrating from a region with high prevalence of HCV infection: • North Africa/Middle East: (Egypt, Iraq, Yemen) • Central Sub-Saharan Africa: (Burundi, Democratic Republic of the Congo, Gabon) • Central Asia: (Georgia, Mongolia, Uzbekistan) • Eastern Europe: (Moldova, Russia, Ukraine)[3]	Antibody
Adolescents incarcerated in a correctional institution	Antibody
Adolescents who received tattooing and body piercing in unregulated settings	Antibody
Children or adolescents after a needle stick injury or mucosal exposure to HCV-positive blood.	Antibody
Adolescents diagnosed with a new sexually transmitted disease **	Antibody

Whom to Test? References/notes

Note: All of the positive anti-HCV antibody tests should be followed up with an HCV RNA test to determine active infection.

The serum HCV RNA can be tested before 18 months of age; however, infants should be at least 2 months old.[4] If serum HCV RNA is positive in early infancy, it should be rechecked after 12 months of age to determine presence of chronic hepatitis C (CHC).

1. Squires, J.E. and W.F. Balistreri, *Hepatitis C virus infection in children and adolescents.* Hepatology Communications, 2017. **1**(2): p. 87-98.

2. Mack, C.L., et al., *NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents.* J Pediatr Gastroenterol Nutr, 2012. **54**(6): p. 838-55.

3. Petruzziello, A., et al., *Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes.* World J Gastroenterol, 2016. **22**(34): p. 7824-40.

4. Polywka, S., et al., *Accuracy of HCV-RNA PCR tests for diagnosis or exclusion of vertically acquired HCV infection.* J Med Virol, 2006. **78**(2): p. 305-10.

Natural History in Children (vertical transmission)

1) **Spontaneous clearance:** 25-40% perinatally infected
   - Clearance of transient neonatal viremia vs. true AHCV with increased transaminases?
   - Typically by 2 years of age, can occur as last as 7 y/o.
   - Greatest clearance genotype 3 and IL-28B polymorphisms (response of interferon to viral antigens) and other genotype polymorphisms
   - Positive association between increased ALT in first 2 years and viral clearance

2) Chronically infected: no clearance by 2 y/o

- A) Asymptomatic 50%:
  - normal transaminases
  - intermittent viremia
- B) Chronic active infection 30%:
  - Frequently abnormal transaminases
  - Hepatomegaly
  - Persistent viremia
  - Bridging fibrosis, cirrhosis O.5 to 10% (1-2%)
  - hepatocellular carcinoma can occur
  - Risk factors for fibrosis include positive anti LKM Ab

- 80% have minimal to no liver fibrosis by 18 y/o
- ALT level is a poor predictor of liver fibrosis
- Very rare reason for liver transplantation children

Natural history in children (non-vertical infection)

- Similar to adults
- 6-12% spontaneous clearance, but some studies show higher rates; highest for Genotype 3.
- 80% develop **chronic HCV**
  - 1-2% develop cirrhosis in childhood
  - Chronic liver disease with cirrhosis in 20-30 years
  - Risk factors for more severe disease:
    - Obesity
    - Treatment for childhood cancer
    - Congenital anemia requiring chronic transfusion
    - Coinfection with HBV or HIV
    - Social factors:
      - Homelessness
      - IVDU & alcohol use
      - incarceration
- HCV associated comorbidities (vertical and non-vertical HCV):
  - Glomerulonephritis – membranoproliferative
  - No reports of cryoglobulinemia or lymphoma
  - (cryoglobulins and autoantibodies can be detected but generally not clinically significant)
  - CNS infection? -> learning impairment
  - Decreased QOL

Criteria for diagnosis?

Positive confirmed HCV antibody at least once in child ≥ 18 months

- Confirm with positive HCV RNA PCR

Positive HCV RNA test, PCR at any age > 3 months old (2 months)

- High rate of temporary false positives in children < 3 months
- Peripheral transient viremia typically occurs days 0-5 of life
- Cord blood viremia not indicative of neonatal infection
- Should be rechecked after 12 months of age to confirm CHCV

Positive HCV RNA at 2-6 months and positive RNA and Ab at 18-24 months

Criteria to rule out infection?

Criteria to rule out vertical transmission:

- Two negative HCV-PCR tests at least 2-3 months apart

Criteria for HCV clearance after chronic infection:

- Two negative HCV-PCR tests at least 6 months apart

Evaluation

- HCV PCR viral load quantitative
- HCV genotype
- Transaminases; GGT;
- Liver function: albumin; bilirubin; PT & inr; (+/- glucose; fibrinogen; ammonia)
- BUN & Cr (GFR) +/- urinalysis
- Nutrition:
  - Fat soluble vitamin levels: A, D, E and PT & inr
  - CBC
- Thyroid: TSH, FT4
- Baseline abdominal USS

Evaluate for other liver disease?

- Infection:
  - HIV antibody
  - Hep B sAb; aAg; eAg; cAb
  - TORCH
  - CMV & EBV
  - Adeno
- Infants:
  - Genetic:
    - Alpha-1-antitrypsin deficiency
    - Cystic fibrosis
  - Inborn errors of metabolism
- Teens:
  - NAFLD/steatohepatitis
  - Autoimmune hepatitis
  - Gilbert's syndrome
  - Wilson's Disease

When to treat

- Medical indications:
  - Children with aggressive liver disease (with fibrosis)
  - Persistently elevated transaminases
  - Children with genotype 2 or 3
- Treat all children?
  - 26 fold increased risk of liver related death if HCV acquired in childhood
  - Economic burden of years of decades of infection
  - Prevent transmission
- Family treatment?
- Goals of treatment:
  - Eradicate infection
  - Preventing end stage liver disease and HCC
  - Removing stigma of HCV infection
  - Decrease global burden of disease/ HCV eradication

- Exclusions:
  - No treatment < 3 years of age
  - Severe co-morbid disease
  - Active IVDU or alcohol use? (Patient-Centered Models of HCV Care for People Who Inject Drugs (HERO))
  - Active psychiatric disease
  - Seizures
  - Incarceration?
  - Solid organ transplant?

Treatment:
Currently approved for children under 12 y/o

- Pegylated interferon and ribavirin (2008):
  - PEG-IFN-α sq q week and ribavirin PO BID
  - Genotype 1 or 4 - 45% achieve sustained viral response (SVR = no virus detected in blood by HCV-PCR) at 24 weeks after completing treatment) after **48 weeks** of therapy
  - Genotype 2 or 3 – SVR 80% after **24 weeks** of therapy
  - HIV or HBV coinfection require 48 week treatment irrespective of genotype
- Better SVR:
  - Genotype 2 & 3
  - Genotype 1 with viral load <600,000 IU/ml or $<2 \times 10^6$ copies/ml
  - Two positive genetic polymorphisms of IL-28B receptor
- Worse SVR with obesity
- IFN-α: cytokine which activates the innate antiviral immune system
- Ribavirin: oral nucleoside analogue with antiviral and immunomodulatory effects

April 2017:
DAA approved for children 12-17 y/o

Harvoni (ledipasvir and sofosbuvir) 90mg/400 mg tablet:

- Pediatric patients 12 years of age and older or weighing at least 77 pounds (35 kilograms)
- HCV genotype 1, 4, 5 or 6 infection without cirrhosis or with mild cirrhosis.
  - Genotype 1, Tx-naïve patients: 1 tab PO qd x 12 wk
  - Genotype 4, 5 or 6, Tx-naïve patients: 1 tab PO qd x 12 wk

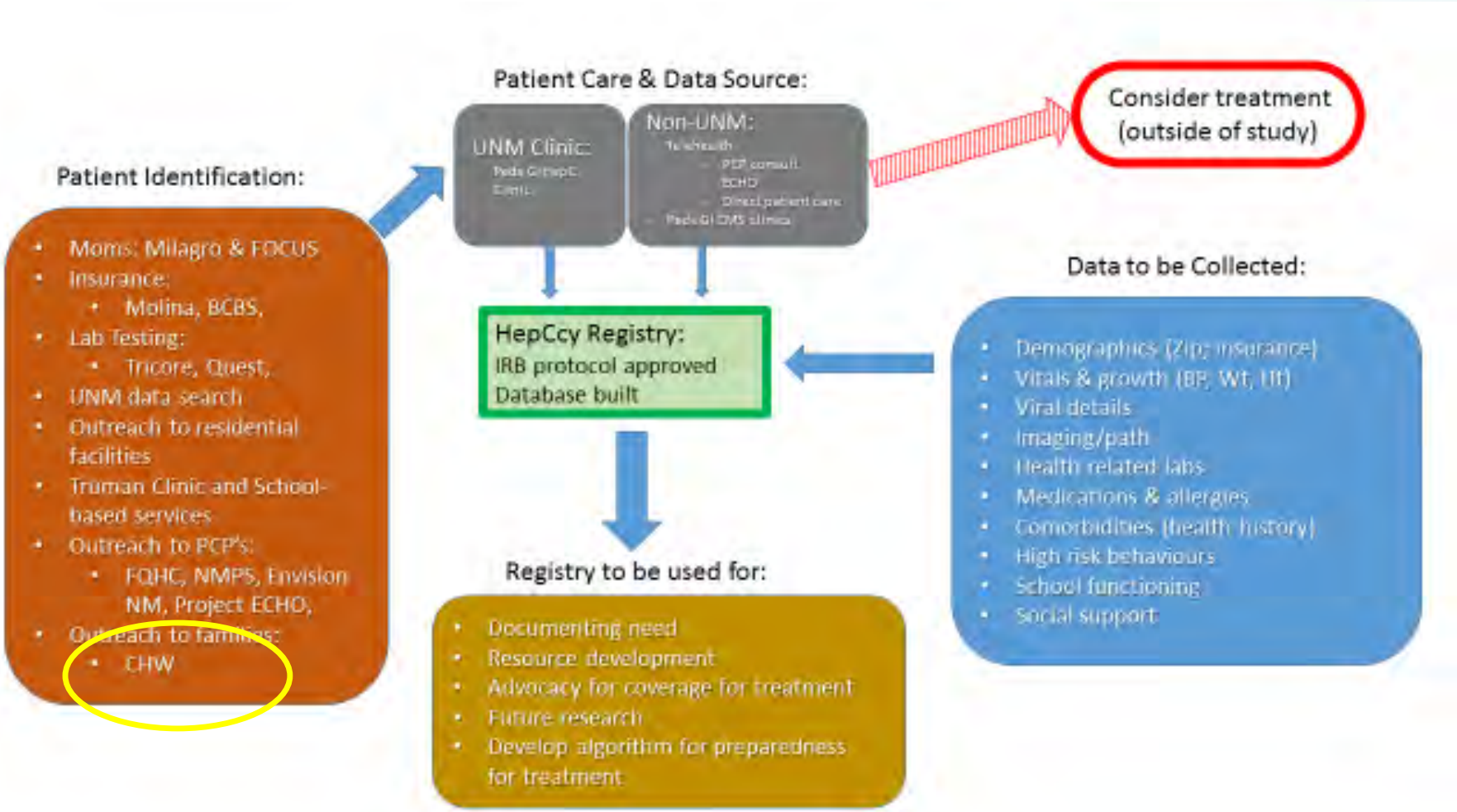
Sovaldi (sofosbuvir) 400 mg tablet:

- Sovaldi in combination with ribavirin
- Pediatric patients 12 years of age and older or weighing at least 77 pounds (35 kilograms)
- HCV genotype 2 or 3 HCV infection without cirrhosis or with mild cirrhosis.
  - Genotype 2: 400 mg PO qd w/ribavirin x 12 wk
  - Genotype 3: 400 mg PO qd w/ribavirin x 24 wk
  - Ribavirin 200 mg capsule or tablet (do not open/crush/chew cap):
    - 35-46kg: 15mg/kg/day PO divided BID
    - 47-49kg: 600 mg/day PO divided BID
    - 50-65kg: 800 mg/day PO divided BID
    - 66-80kg: 1,000 mg/day PO divided BID
    - > 80kg: 1,200 mg/day PO divided BID

- Harvoni and Sovaldi: Black Box warning for Hepatitis B reactivation
- Ribavirin: Black Box warning for hemolytic anemia and teratogenic/embryocidal effects

Project HepCCY – UNM IRB approved registry

Hepatitis C in Children and Youth of NM



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End of Presentation

Questions?

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