Neonatal Herpes

Epidemiology, Diagnosis, Management, and NYC Surveillance findings

Implications for Infection Control Practitioners

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Today's talk

- Biology and pathogenesis of herpes viruses
- Epidemiology of genital herpes
- Epidemiology of neonatal herpes (nHSV)
- nHSV
  - clinical manifestations, morbidity & mortality
  - evaluation and diagnostic testing
  - treatment
  - prevention
- NYC law/regulations related to nHSV
- nHSV in NYC, 2006-2013

Herpes viruses
Biology

- Herpes simplex virus type 1 (HSV-1)
- Herpes simplex virus type 2 (HSV-2)
- Double-stranded DNA viruses
- Latency
- Neurovirulence
- Reactivation precipitated by: stress, UV light, intercurrent illness, tissue damage

Pathogenesis of primary HSV infection

- Herpes viruses spread in secretions from infected skin, mucous membranes (saliva, genital secretions)
- Infection at point of contact with mucous membranes or abraded skin
- Virus travels up peripheral sensory nerve to nerve ganglion; multiplies in ganglion
- Travels back down nerve to skin in area supplied by infected nerve
- Incubation period: genital (2-12 days), neonatal (varies with syndrome, but most cases occur w/in 21 days of delivery
- Antibody develops early in the course of infection (50% by 40 days) and persists indefinitely

Pathogenesis of herpes simplex virus

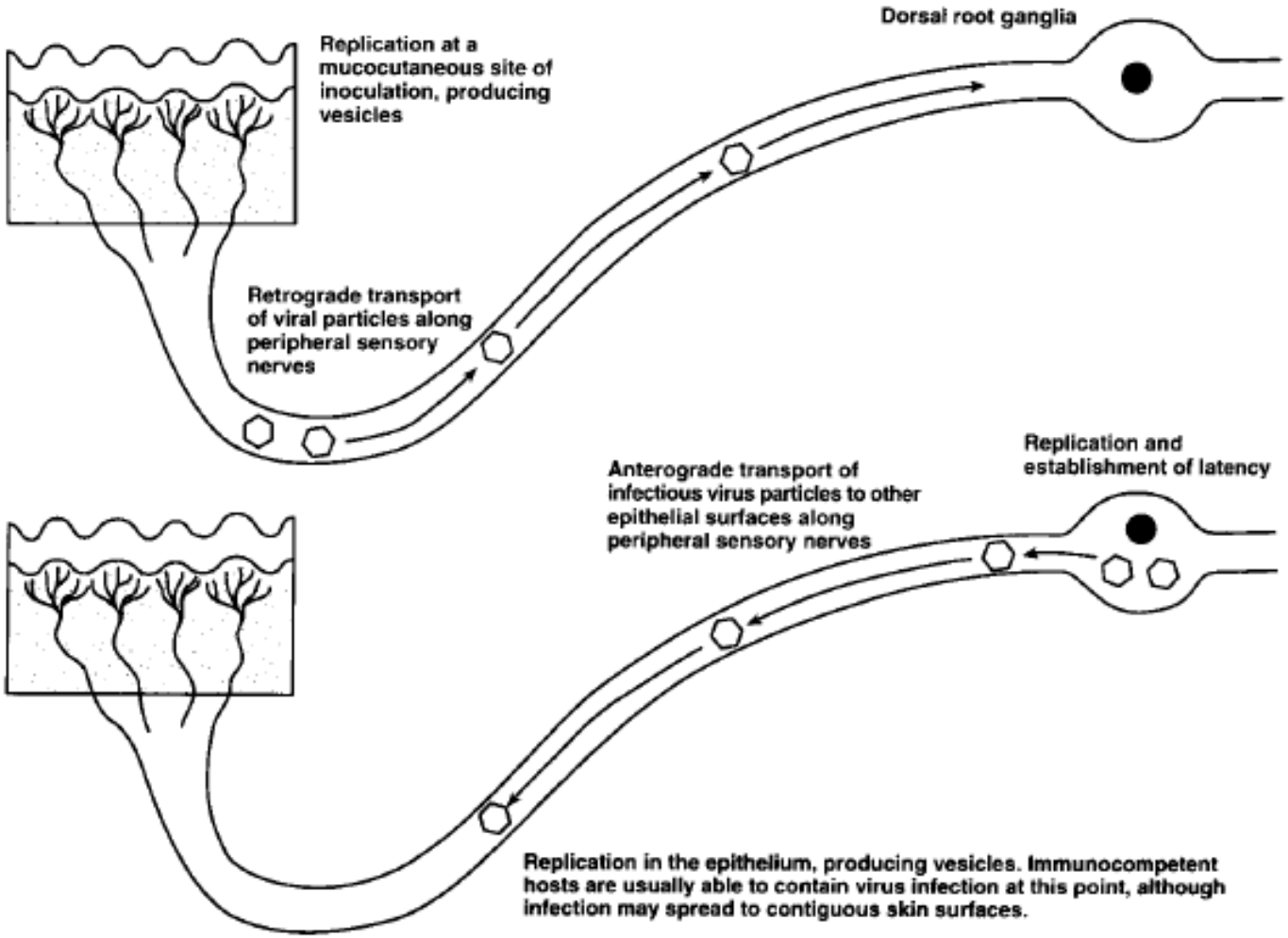


Figure 3. Schematic diagram
primary herpes simplex virus infe
tion.

Source: Whitley RJ, Kimberlin DW, Roizman B. Clin Infect Dis. 1998 Mar;26(3):541-53

Herpes transmission to newborns

- Before birth (congenital) – 5%
- During delivery (perinatal) – 85%
- After birth (postnatal) – 10%

Genital herpes in adults

- Genital herpes infections highly prevalent in US
- Historically, most genital infections caused by HSV-2, however,
- HSV-1 increasing cause of new genital herpes infections (20 to > 50% in some populations)
- Most genital herpes infections unrecognized
- Asymptomatic shedding is common

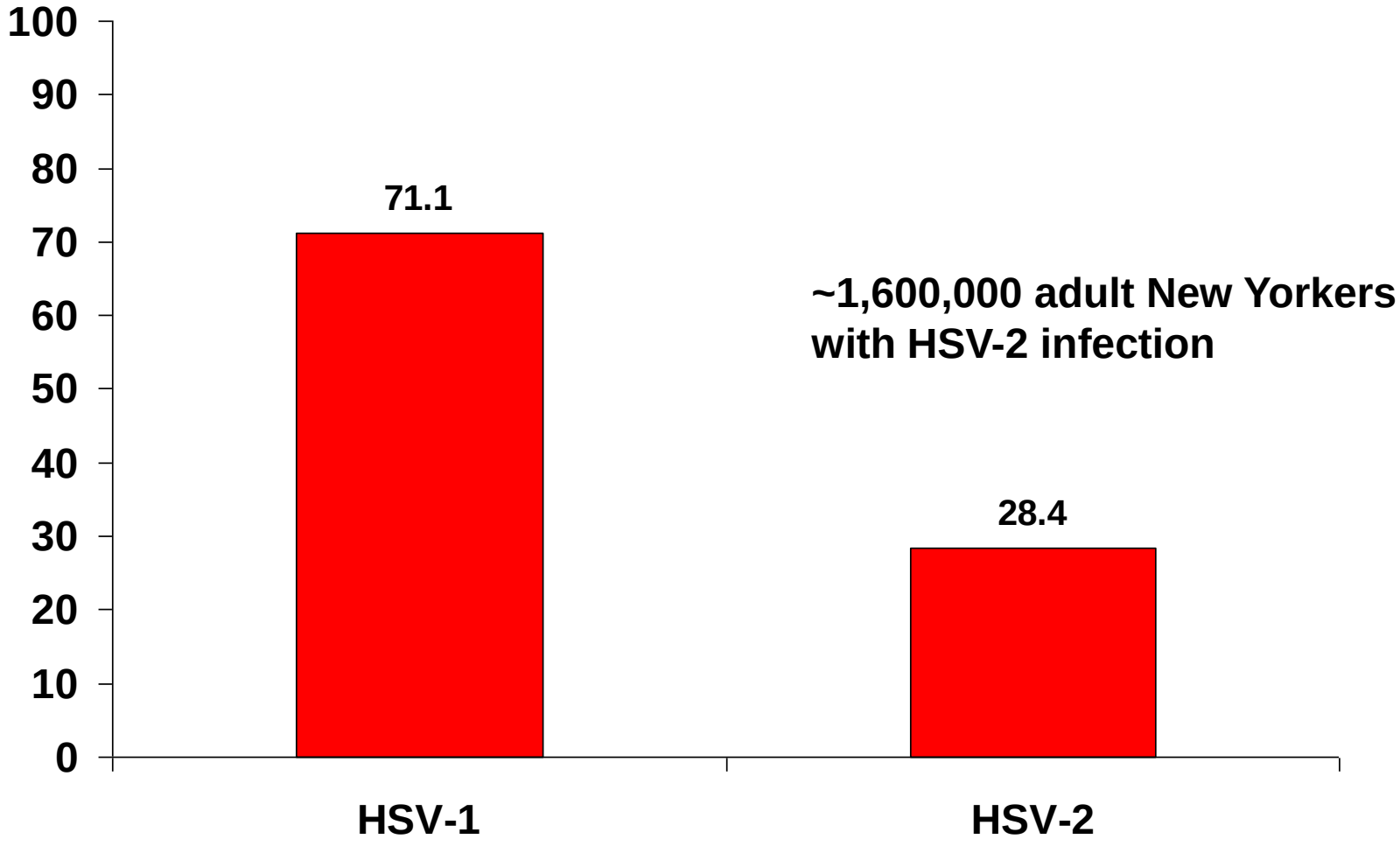
Genital herpes in adults
Types of infection

- *First episode primary infection*:
  - HSV-2 in genital tract; HSV-1 & HSV-2 seroneg.
  - HSV-1 in genital tract, HSV-1 & HSV-2 seroneg.

- *First episode non-primary infection*:
  - HSV-2 in genital tract; HSV-1 seropositive, HSV-2 seroneg.
  - HSV-1 in genital tract; HSV-2 seropositive, HSV-1 seroneg.

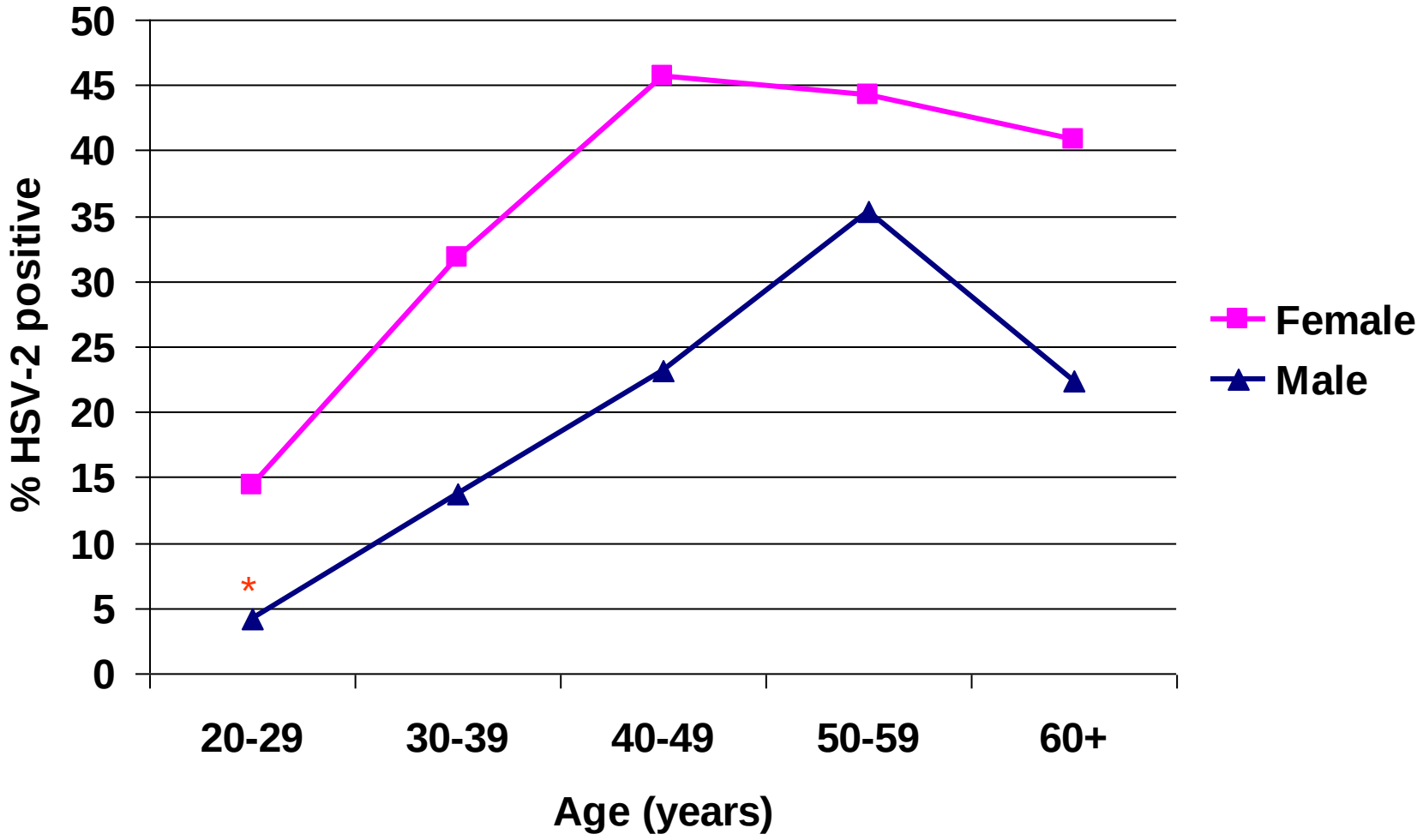
- *Recurrent infection*:
  - HSV-2 in genital tract, HSV-2 seropositive
  - HSV-1 in genital tract, HSV-1 seropositive

HSV-1 & HSV-2 seroprevalence persons ≥20 years, NYC, 2004

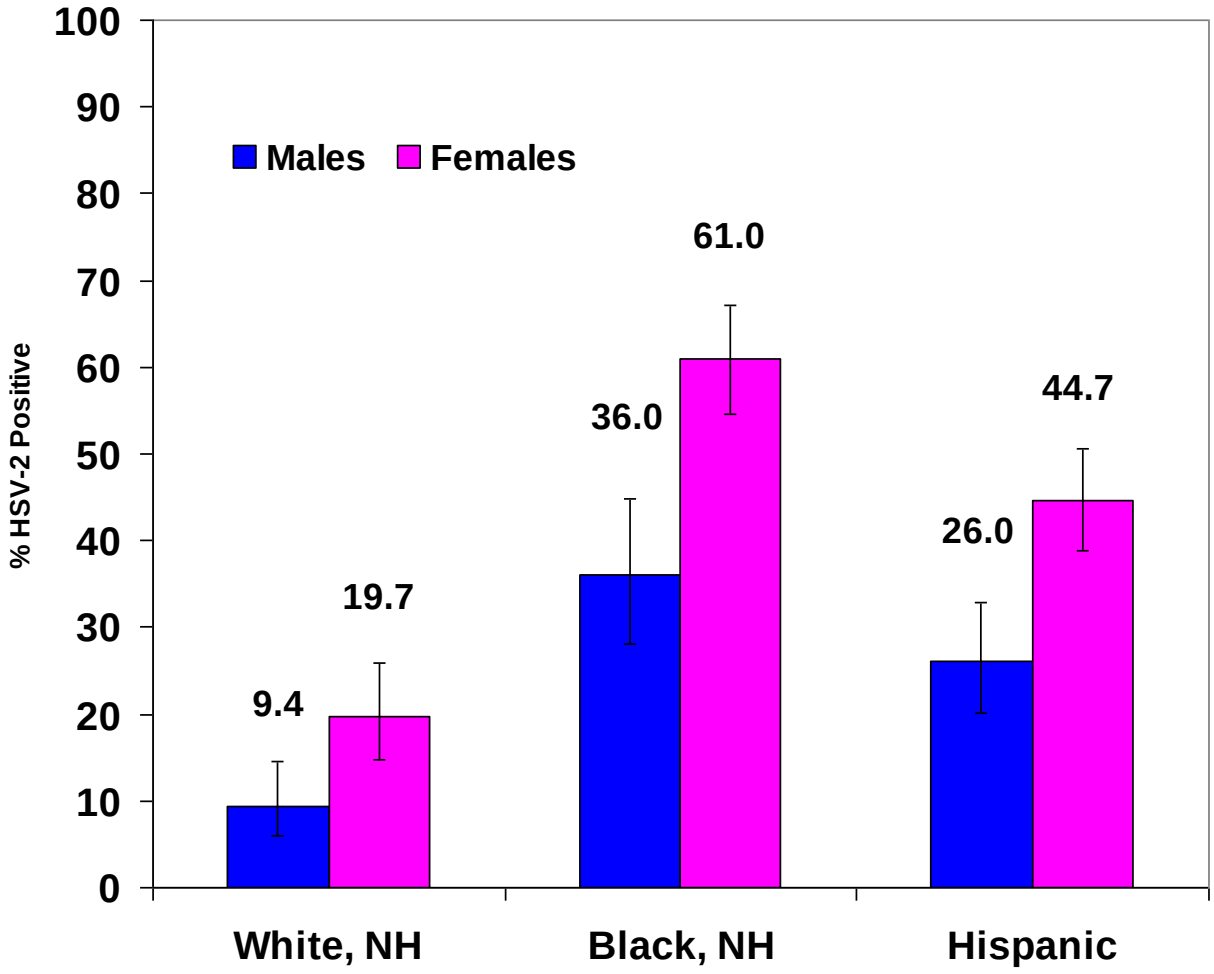


*Age-adjusted to the Year 2000 U.S. Standard Population.

HSV-2 seroprevalence, by sex and age, NYC, 2004



HSV-2 seroprevalence* in persons ≥20 years, by race/ethnicity, sex, NYC, 2004



*Age-adjusted to the Year 2000 U.S. Standard Population.

Herpes transmission from mother to infant during delivery

- Maternal antibody protective to infants exposed to homologous virus during delivery

- Greatest risk for neonatal herpes – infants born to women who acquire genital herpes near term (first episode primary, or first episode non-primary infection)
    - ~2% of women seroconvert during pregnancy
    - 25-60% infants born to women with new HSV infection near delivery will become infected, versus
    - Only 2% of infants born to women w/ HSV acquired early in pregnancy or before, will become infected

- >75% neonatal herpes cases -born to women w/ no hx or clinical findings s/o genital herpes before, during preg.

HSV seroprevalence among women of childbearing age (20-44), NYC HANES*

Characteristic	N	% HSV-1 only positive (95% CI)	% HSV-2 positive, w/ or w/o HSV-1 (95% CI)	% HSV seronegative (95% CI)
All women aged 20-44	636	51.7 (47.3-56.2)	28.1 (23.7-33)	20.1 (16.3-56.2)
Race/ethnicity				
NH-White	132	47.3 (39.2-55.6)	14.3 (8.2-23.7)	38.4 (29.5-48.2)
NH-Black	152	42.7 (34.8-51.1)	43.3 (35.2-51.8)	13.9 (9.3-20.3)
Hispanic	253	55.9 (49.7-61.9)	34.7 (29.1-40.8)	9.5 (6.4-13.7)
Asian	84	66.3 (54.5-76.3)	11.3 (6.5-18.8)	22.5 (13.5-35.1)

*Preliminary data, not for release

Incidence of neonatal herpes

National or State surveillance system	Dates	Rate (per 100,00 live births)	Reference
Canada	2000-2003	5.9	Kroop
Washington State	2000-2004	11.5	Hofmann
Ohio	1999-2003	5.8	Ohio DOH
New York City	2006-2010	13.3	Handel
Hospital Discharge Data			
Washington State	1987-2002	8.4	Mark
New York City	1997-2008	11.8	Handel
California	1995-2003	12.2	Morris
California	1985-1995	11.5	Gutierrez
Managed care database	1997-2002	60.0	Whitley
Prospective cohort study in WA State	1982-1999	31.2	Brown

Median case rate =11.7 per 100,000 or 1 in 8600 live births

Risk factors for neonatal herpes

- Primary, non-primary maternal infection (absence of maternal HSV antibody)
- Vaginal delivery (caesarean protective)
- Prolonged rupture of membranes
- Break in integrity of mucocutaneous barrier (invasive monitoring, scalp electrode, *metzitzah b'peh*)

Disease classification

- Intrauterine infection (congenital)
- Disseminated infection
- Central nervous system infection
- Skin/eye/mucous membrane (‘SEM’) disease

Intrauterine infection

- Rare (1/300,000 deliveries)
- Infection evident at birth
  - Cutaneous, ophthalmic, CNS manifestations
- Often fatal

Disseminated disease

- ~25% of neonatal herpes cases
- Multi-organ involvement, including CNS, liver, lungs, adrenals, SEM
- Present at 10-12 days of life
- Case fatality rate = 30% even with appropriate therapy
- ~10% survivors with neurologic sequelae

CNS disease

- ~30% of neonatal herpes cases
- Encephalitis (with or without SEM disease)
- Present at 16-19 days of life
- Case fatality rate = 5% even with appropriate therapy
- ~50% survivors with neurologic sequelae

SEM disease

- ~45% of neonatal herpes cases
- Early antiviral treatment increases proportion of infections limited to skin
- Sensitive diagnostic tests changing disease classification
  - ~25% infants previously diagnosed w/ only SEM disease have positive HSV PCR on CSF
- Present at 10-12 days of life

Presenting signs and symptoms of infants with neonatal herpes – non specific

- No single set of signs or symptoms identify infants with neonatal herpes
- Infants often afebrile
- Only 2/3 of cases have skin vesicles
- Time to diagnosis/treatment = 5-6 days and has not decreased in past decades

Fever and skin lesions at time of presentation[1]

	Disease category			
Sign	**All (n=186)**	**Disseminated (n=59)**	**CNS (n=63)**	**SEM (n=64)**
Fever	72 (39%)	33(56%)	28(44%)	11(17%)
Skin vesicles	127(68%)	34(58%)	40(63%)	53(83%)

[1]Kimberlin et al. Pediatrics. 2001. 108:223-229

Evaluation

- Infants suspected of herpes infection should be admitted to hospital

- Lumbar puncture should be performed

- Diagnostic laboratory evaluation should include:
  - Culture and PCR of multiple specimen types*
  - Liver function tests (LFT)
  - NYC Health Code requires vesicular specimens to be submitted for PCR at State Public Health Lab

*

Diagnostic testing (AAP Red Book)

(1) Swab specimens: conjunctivae, nasopharynx, mouth, and anus ("surface cultures") for HSV culture

- surface swab specimens can be obtained w/ single swab [ending with anal swab]

(2) Specimens of skin vesicles and CSF for HSV culture and PCR

- PCR is test of choice for CSF
- NYC Health Code requires skin vesicle swab be sent to Wadsworth Laboratories

(3) Whole blood sample for HSV PCR; and

(4) Whole blood sample for measuring alanine aminotransferase (ALT).

If sending to a referral lab - make sure NYS-approved (CLEP) to perform requested testing

Positive cultures obtained from any of the surface sites more than 12 to 24 hours after birth indicate viral replication and, therefore, are suggestive of infant infection rather than merely contamination after intrapartum exposure.

Treatment*

- Acyclovir, 60 mg/kg/day IV, in three divided daily doses
- Duration of treatment
  - CNS and Disseminated infection = 21 days
  - SEM disease = 14 days
- CNS infection - patients with CNS HSV should have lumbar puncture repeated at end of therapy
  - If still PCR positive, continue IV therapy until negative
- Suppressive tx with oral acyclovir (6 mos)

*For asymptomatic infant born to mother w/ lesions at delivery, see 2013 AAP reccs

Treatment
When to initiate *empiric* acyclovir therapy?

- Consensus (expert opinion, Red Book):
  - When clear index of suspicion – infants with vesicles, seizures, elevated LFTs, sepsis-like picture, infant sicker than expected
  - Asymptomatic infants born to mothers w/ first episode 1° or non-1° genital infection at delivery (requires access to PCR and type-specific antibody)

- Not as clear in other cases - expert opinion varies:
  - Preterm infants or prolonged rupture of membranes
  - Age <21 days, rule out sepsis work up
  - CSF pleiocytosis, fever w/ no another clear dx (consider enteroviral season?)
  - Fever in infants ≤14 days

Prevention
Neonatal herpes

- Caesarean section (C/S)
- Antiviral prophylaxis to prevent recurrence at delivery?
- Type-specific herpes serologic testing during pregnancy?
- Vaccine?
- Increase awareness of prevalence of genital herpes and risk for neonatal infection
  - Patients and providers
- Managing asymptomatic infants born to women with lesions at delivery

Guidance on Management of Asymptomatic Neonates Born to Women with Active Genital Herpes Lesions[1]

- HSV transmission to newborn ranges from 2% (recurrent dz) to 60% (first episode primary infection)
- Recommendations: perform HSV PCR or culture of maternal lesions at delivery and type-specific serologic testing
  - Knowing if maternal infection is primary/non-primary (v. recurrent) has substantial impact on management of newborn
  - Newborn w/u at 24 hours of age
- Management of the newborn (w/u, timing and duration of tx) hinge on maternal infection (primary/non-primary v. recurrent
- Pertains to C/S or vaginal delivery
- Communication between OB and Peds is critical

[1]Kimberlin et al. Pediatrics. 2013. 131(2). E635-e646.

Laws/regulations related to neonatal herpes, NYC

(1) Neonatal herpes is a reportable disease[1]

- Added to list of reportable diseases in April 2006
- Laboratory-confirmed & clinically suspect dz must be reported
- Required information is found on the universal report form

(2) Providers must send vesicular swabs specimen to NYS[2]

- Must collect vesicular swab(s) from infants ≤60 days and send to Wadsworth Laboratories for testing

(3) Laboratories must send any positive specimen to New York State Wadsworth Laboratory[3]

- Required to send all herpes-positive specimens from infants ≤ 60 days to Wadsworth laboratories

[1]NYC Health Code, Sections 11.03 and 11.05
[2]NYC Health Code, Section 11.10
[3] NYC Health Code, Section 13.09

Paper URF

Herpes, neonatal - Herpes simplex virus infection in infants aged 60 days or less.

__Clinical diagnosis
__Lab confirmed diagnosis
__Culture __PCR
__Antigen detection __Serologic
__Tzanck

Herpes type: __Type 1 __Type 2 __Not typed

Clinical Syndrome (Check all that apply)
__Skin, eye, mucous membrane infection
__CNS involvement
__Disseminated disease

Herpes lesions present?
__Yes, anatomic site: _____
__No
__UnknownSpecimen collection date: ___ /___ /_____
Treatment for infant: _____
Treatment date: ___ /___ /_____ Unknown
Mother's Name: _____
Mother's DOB: ___ /___ /_____
Mother's Labor and Delivery Medical Record:_____

Additional regulations applying to neonatal herpes, New York City, 2012

(4) Mohelim performing direct orogenital suction must first have written permission from parent(s)[1]

[1]NYC Health Code Section 181.21

Epidemiology of neonatal herpes in NYC

NYC nHSV Surveillance, Since April 2006 - Objectives

Measure disease incidence, by viral type

Identify missed opportunities for prevention by describing:

- fatality rate
- clinical syndrome
- delays in diagnosis
- appropriateness of diagnostic work up and treatment

Use findings to educate NYC providers on diagnosing and treating neonatal herpes

NYC nHSV Surveillance – Reporting and case definitions

Reporting requirements:

- Labs: positive results for HSV from infants aged ≤ 60 d
- Providers: diagnosis of HSV (± lab confirmation) in infants aged ≤ 60 d

Case Definitions:

- Lab confirmed: positive culture, PCR, DFA, Tzanck
- Clinical diagnosis: provider report (w/o lab confirmation if criteria are met)
  - Acyclovir given for ≥ 7 days
  - Illness clinically compatible with nHSV
  - No alternative diagnosis given
  - nHSV considered in differential during course of illness

Detailed investigation done for every case

nHSV Surveillance: Case investigations

- Infant
  - Inpatient providers
  - Outpatient providers
  - Infection control staff
  - Lab staff
  - Medical record review
  - Birth (and death) certificates obtained
- Mother
  - Prenatal records
  - Labor and delivery records

nHSV Cases Reported to the NYC DOHMH, April 2006 – December 2013 (~7.5 years)

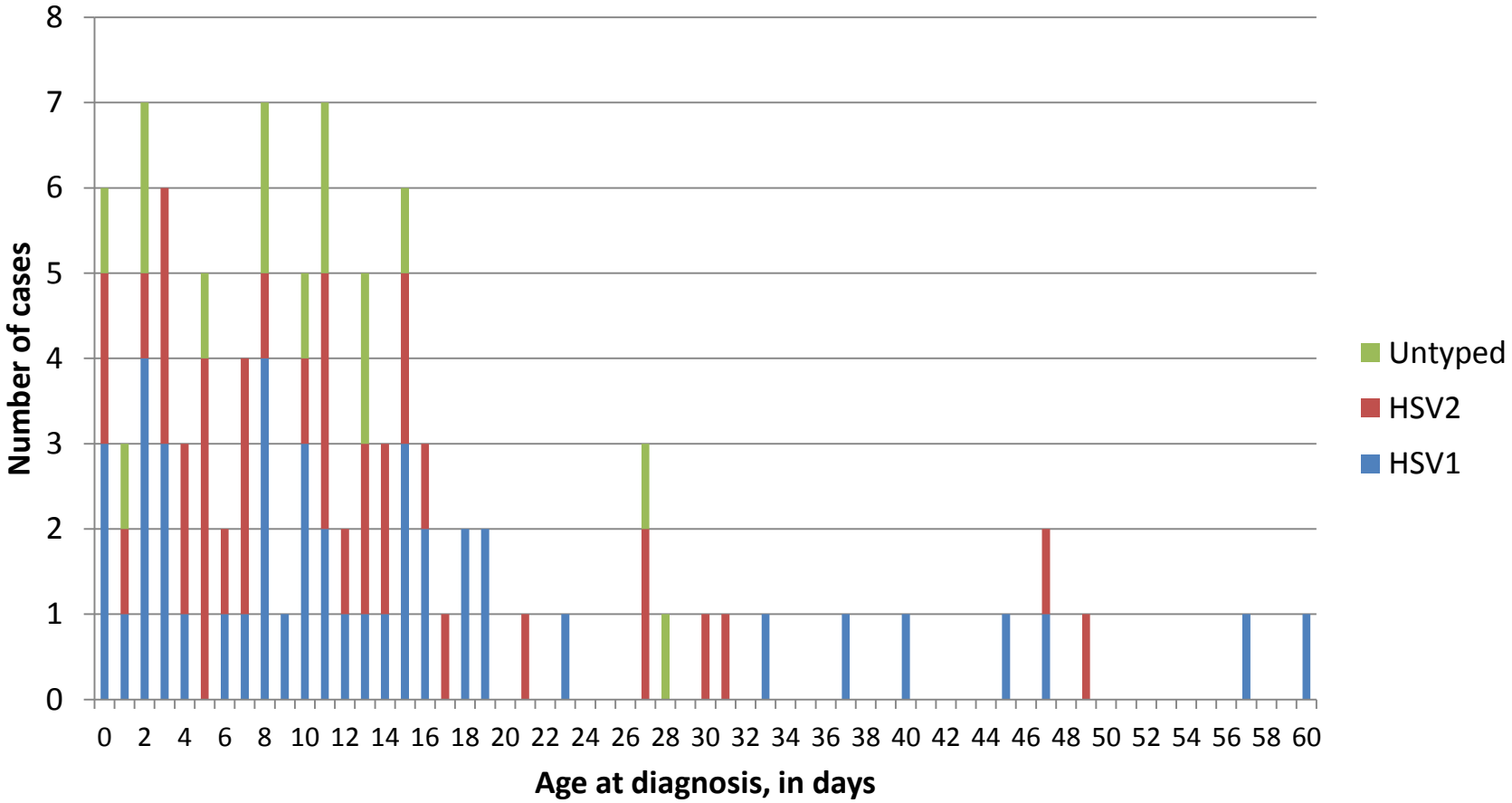
	HSV Type				
	Total No. (%)	**HSV-1 No. (%)**	**HSV-2 No. (%)**	**Untyped (Lab Confirmed) No. (%)**	**Not Lab Confirmed No. (%)**
Viral Type	116 (100)	44 (38)	38 (33)	15 (13)	19 (16)
Sex					
Male	69 (59)	27 (61)	18 (47)	9 (60)	15 (79)
Female	47 (41)	17(39)	20 (53)	6 (40)	4 (21)
Deaths	18	7	9	2	0
Case Fatality Rate	15.5%	15.9%	23.7%	13.3%	0

Incidence Estimate ~13 / 100,000 live births (~1 / 7,800)

Frequency of nHSV reporting by NYC hospitals, 2006-2013

- 36 hospitals reported one or more case
  - One hospital reported 16 cases
  - A second hospital reported 13 cases
  - Eight other hospitals reported $\geq$ 4 cases
  - Remainder of hospitals reported $\leq$ 3 cases
    - 15 hospitals reported only 1 case in 7.5 years

Age at diagnosis, in days, of laboratory-confirmed cases of nHSV reported in NYC, April 2006-December 2013



Median age, in days, at diagnosis: Overall (10 days); HSV-1 (10.5 days); HSV-2 (10.5 days); Untyped (10 days)

nHSV Surveillance in NYC
Additional findings

- Racial disparities in incidence
  - Black non-Hispanic (18/100k) > Hispanic > White > Asian (5/100k)
- Younger women - greater risk for infant w/ neonatal herpes
  - < 20 yo, 47/100k; >34, 10/100k
- C/S does not obviate risk for neonatal herpes
  - 38% neonatal herpes cases delivered by C/S
    - 80% had obstetric risk factor (eg. >4 h ROM, invasive procedure)
    - Only 2 C/S done because of visible genital lesions
- Negative maternal history of herpes not useful
  - Among 13 deaths, only 3 had a maternal history of herpes

*Handel et al. Population-based surveillance for neonatal herpes in New York City, April 2006-September 2010. STD. 2011. 38(12).

Delays in care-seeking, diagnosis, treatment*

Delays in care seeking

- 20% (12/59) had >1 day betw. 1st symptom and seeking care
  - Median: 2 days (Range: 2-10)

Delay in diagnosis

- 39% (26/66) had >1 day betw. seeking care and date first specimen was collected
  - Median: 4 days (range 2-21)

Delay in initiating acyclovir treatment

- 30% (18/61) had >1 day betw. HSV specimen collection and starting acyclovir
  - Median: 3 days (range 2-18)

*Handel et al. Population-based surveillance for neonatal herpes in New York City, April 2006-September 2010. STD. 2011. 38(12).

Adequacy of diagnostic work up & treatment*

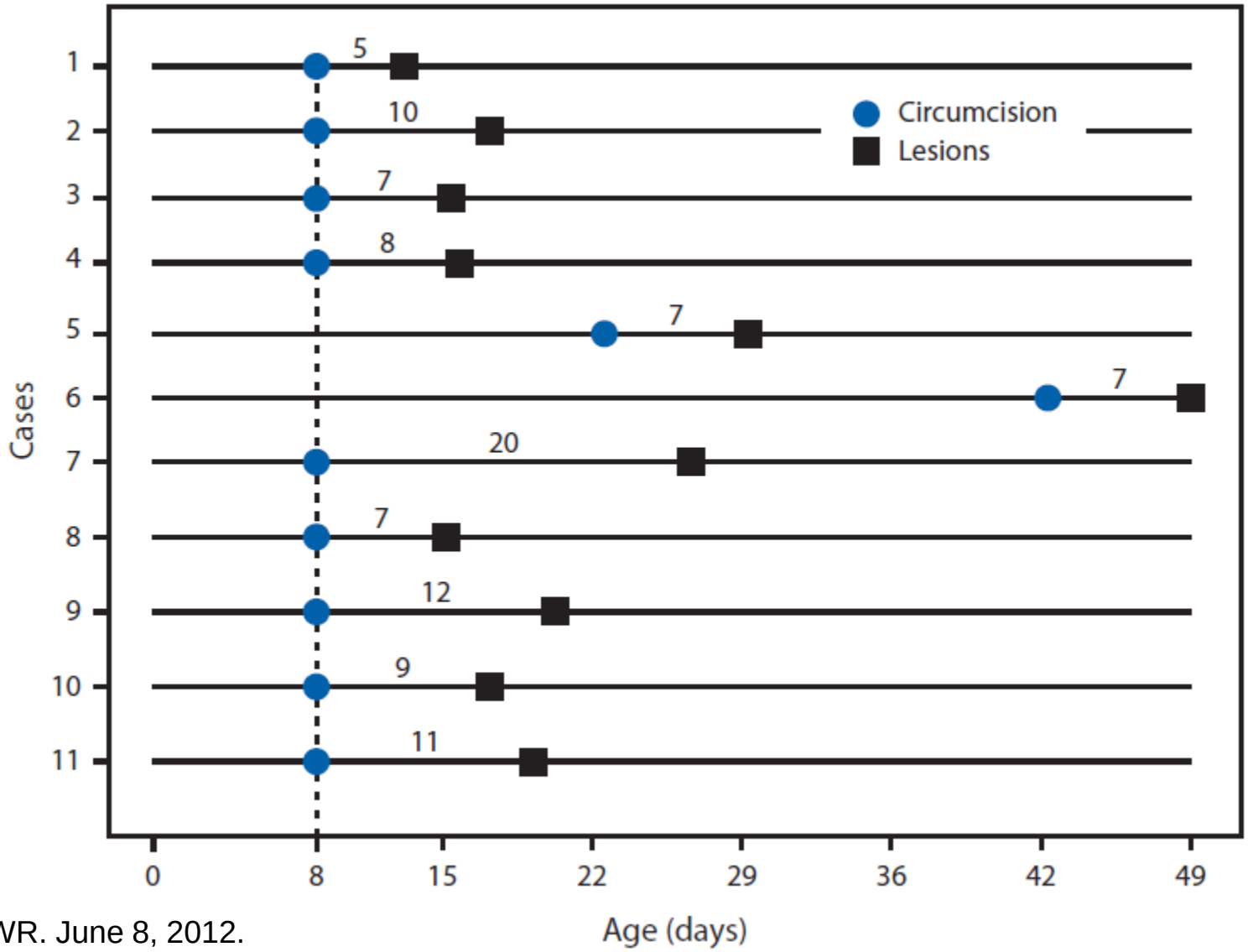
- Appropriate work up
  - LP Done: 86% (57/66)
  - LFT Done: 79% (50/63)

- Appropriate treatment
  - 51% (19/37)

- *Overall, 68% (52/76) lacked either timely or ideal diagnostic evaluation or treatment*

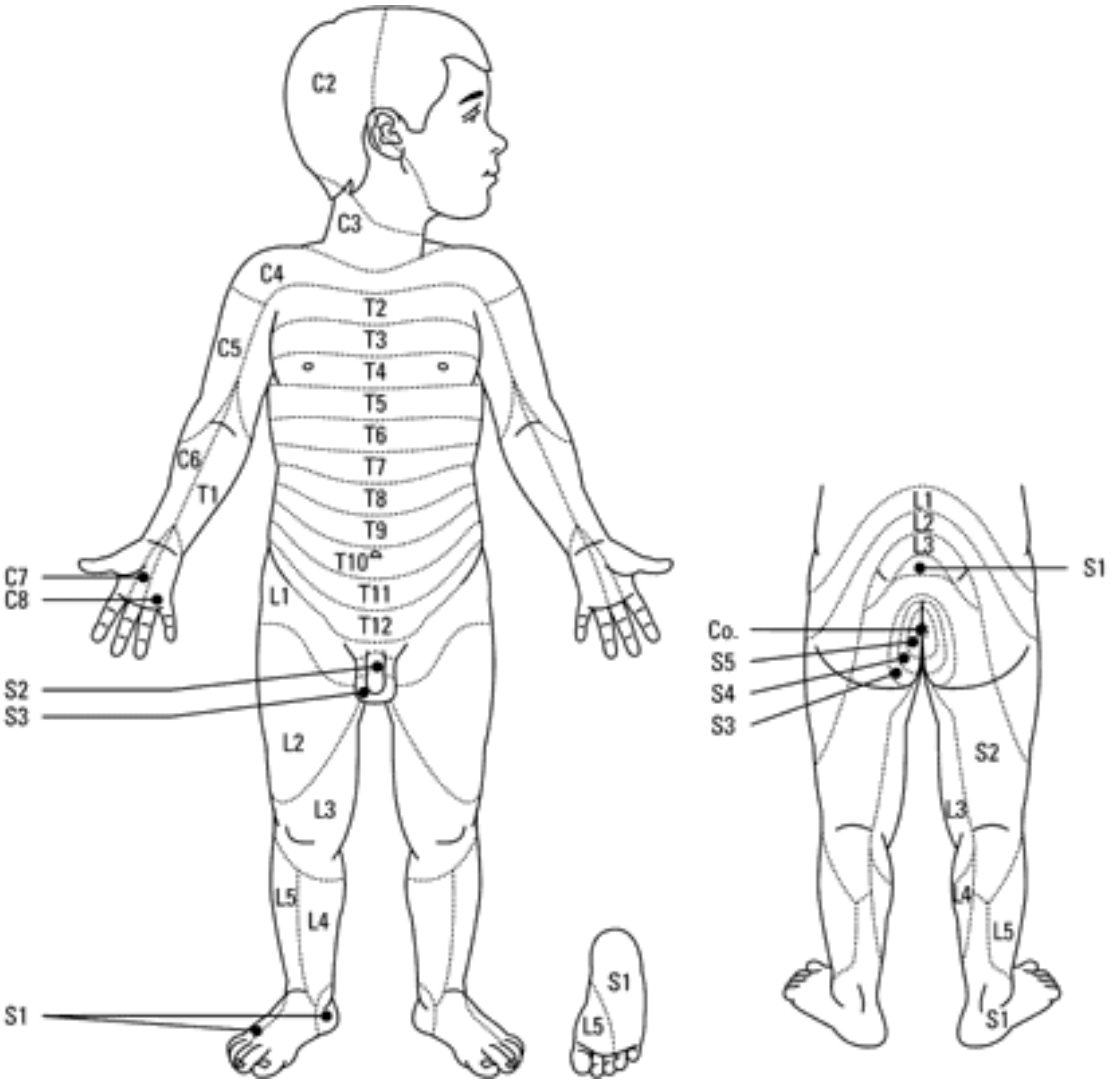
*Handel et al. Population-based surveillance for neonatal herpes in New York City, April 2006-September 2010. STD. 2011. 38(12).

No. days between Jewish ritual circumcision and appearance of herpes lesions; male infants with neonatal herpes with presumed or confirmed direct orogenital suction



CDC MMWR. June 8, 2012.

Dermatomes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Summary – I

Neonatal herpes – epidemiology

- Genital herpes infection is highly prevalent among adults and usually asymptomatic
- The epidemiology of neonatal herpes reflects the epidemiology of genital herpes in child-bearing women
- Greatest risk for neonatal herpes - infants born to mothers acquiring herpes in the last trimester
- Most infants with neonatal herpes are born to mothers with no history of genital herpes

Summary II

Neonatal herpes – provider/pt awareness

- Persons diagnosed with genital herpes should be informed of risk for neonatal herpes
- Providers should seek history of genital herpes
- Serologic screening advocated by some clinicians to identify susceptible women

Summary – III

Neonatal herpes – clinical issues

- Up to 20% of neonatal herpes cases do not have skin lesions
- Physicians must maintain a high index of suspicion for neonatal herpes
  - Consider herpes in differential diagnosis for ill neonates
  - Time to diagnosis has not improved over past decades
  - Disseminated disease has high case fatality rate despite treatment
- Evaluation should include LP and LFTs
  - 25% infants diagnosed w/ SEM have HSV DNA in CSF

Summary – IV
Neonatal herpes - NYC

- Case fatality rate high
- Substantial proportion of nHSV cases born by C/S, however most have ROM >4 h or invasive procedures before delivery
- Treatment delays, and incomplete diagnostic w/u suggest need for provider education
- Cases resulting from direct orogenital suction are preventable, account for 1-2 cases/year

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Implications for Infection Control Practitioners (ICPs)

- ICPs poised to ensure:
  - Providers conduct an appropriate work up, *including* sending a vesicular swab to Wadsworth Labs (hospital lab must ship specimen)
  - Hospital laboratories detecting HSV in infants ≤60 days send specimens and associated materials to Wadsworth Labs
  - Cases of nHSV reported to NYC DOHMH
  - Communication between OB and Peds
- ICPs play a key role in nHSV case investigation
  - Laboratory, clinical info on baby, and mother

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