

***Clostridium sordellii* toxic shock syndrome following medical abortion**

Marc Fischer, M.D., M.P.H.

National Center for Zoonotic, Vector-Borne and Enteric Diseases
Centers for Disease Control and Prevention



Clostridium sordellii

- Gram positive anaerobic bacillus that resides in soil
- Colonizes gastrointestinal or genital tract of healthy humans
 - Uncommonly found in surveys of stool and vaginal flora
 - Isolated from musculoskeletal tissue of 3% (26/795) cadaver donors
- Virulence and clinical manifestations determined by two cytotoxins (i.e., Lethal toxin and Hemorrhagic Toxin)
 - Variably expressed by different *C. sordellii* strains
 - Cytopathic effects altered by environmental conditions (e.g., pH)

***C. sordellii* case reports and series**

- Pneumonia
- Endocarditis
- Arthritis
- Peritonitis
- Corneal ulcer
- Bacteremia

***C. sordellii* wound infections**

- Necrotizing fasciitis
- Myonecrosis
- Tissue allograft infections
- Neonatal omphalitis
- Postpartum endometritis
- Episiotomy infection

***C. sordellii* Toxic Shock Syndrome**

- Acute onset and rapid progression
- Afebrile or low grade fever
- Refractory tachycardia and hypotension
- Local and spreading edema
- Leukemoid reaction
- Hemoconcentration
- High case fatality

McGregor et al. J Obstet Gynecol 1989;161:987.



***C. sordellii* toxic neonatal omphalitis 1976-1993**

- 6 cases reported in the literature
- Infants 2-11 days old
- Clinical findings included abdominal wall swelling, periumbilical erythema/discharge, and elevated WBCs
- 5 (83%) died
- *C. sordellii* isolated from the umbilicus (n=5), peritoneal fluid (n=2), and blood (n=1)

***C. sordellii* TSS among IDUs, 1992-2000**

- Four clusters of wound infections among black tar heroin injecting drug users (IDUs) in California
- Often mixed infections with *C. sordellii*, *C. perfringens*, and other soil contaminants
- *C. sordellii* isolation associated with toxic shock-like syndrome and a high case fatality rate

Kimura et al. Clin Infect Dis 2004;38:e87

Bansberg et al. Arch Intern Med 2002;162:517.

Chen et al. Clin Infect Dis 2001;33:6.

Callahan et al. Arch Surg 1998;133:812.



***C. sordellii* allograft infection, 2001**

- 23 year old male died of *C. sordellii* sepsis and TSS after receiving a contaminated tissue allograft
- Prompted a national investigation of *Clostridium* sp. infections associated with tissue allografts
 - 13 additional cases identified
 - All due to *C. septicum* or *C. bifermentans*
 - None were fatal

CDC. MMWR 2001;50:1035.

Kainer et al. N Engl J Med 2004;350:25.

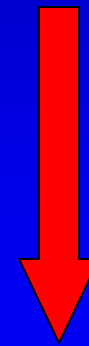
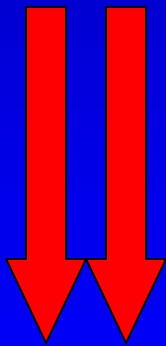
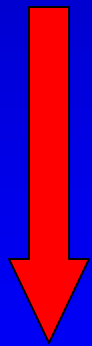


***C. sordellii* genital tract infections and TSS, 1977-2001**

	(n=10)	
Age in years (median, range)	25 yrs	(23-40)
Died (n, %)	10	(100%)
Preceding event (n, %)		
Childbirth	8	(80%)
Medical abortion	1	(10%)
Time course in days (median, range)		
Event to symptoms	3 days	(2-5)
Hospitalization to death	0 days	(0-3)
Laboratory findings (n, %)		
Leukemoid reaction (WBC >50,000)	8	(80%)
Hemoconcentration (Hct ≥50%)	7	(70%)

Case investigation timeline, 2003-2005

 Four deaths occur among women following medical abortions



Sep
2003

Dec
2003

Mar
2004

Jun
2004

Sep
2004

Dec
2004

Mar
2005

Jun
2005

Sep
2005

Dec
2005

Mifepristone plus misoprostol for medical abortion

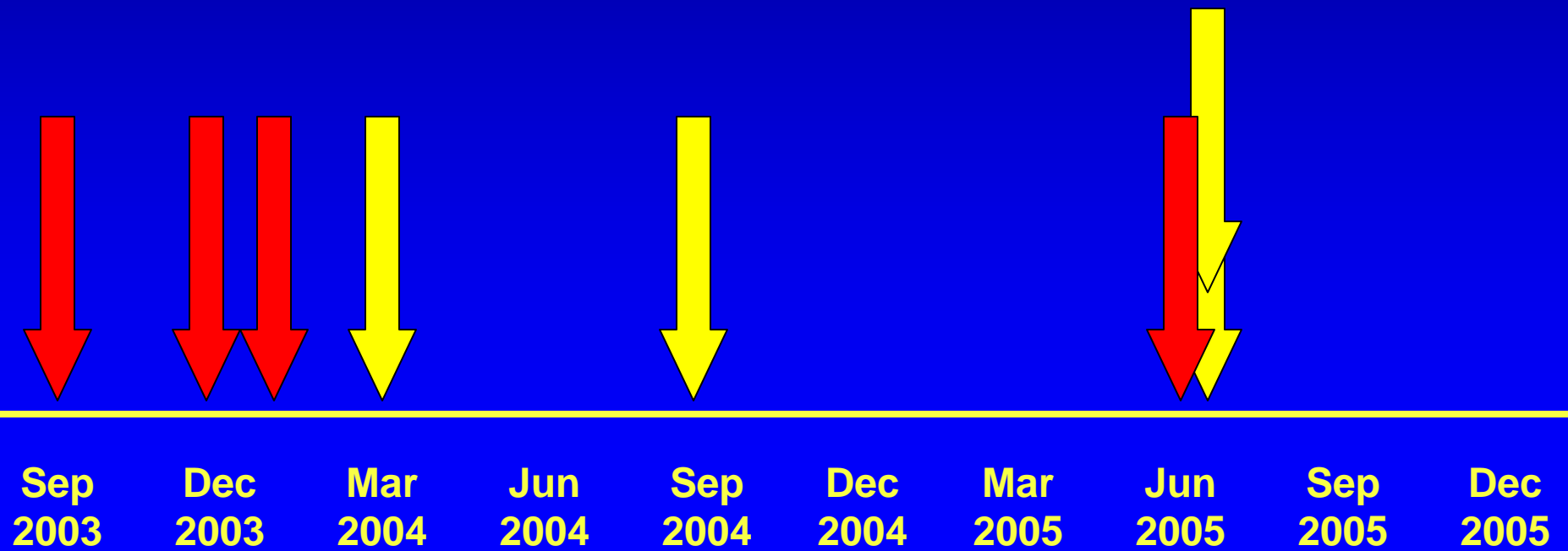
- Mifepristone plus misoprostol approved for medical termination of pregnancy ≤ 7 wks gestation
 - Mifepristone: synthetic steroid with anti-progesterone effects
 - Misoprostol: prostaglandin analog, causes uterine contractions
- FDA-approved regimen
 - 600 mg oral mifepristone followed within 2 days by
 - 400 μg oral misoprostol
- These patients received a common “off-label” regimen
 - 200 mg oral mifepristone followed by
 - 800 μg vaginal misoprostol

Initial investigation

- Fulminant toxic shock-like syndrome
- Similar to a fatal case of *C. sordellii* TSS that occurred following medically-induced abortion in Canada in 2001
- Canadian patient had received the same off-label regimen of mifepristone and misoprostol as these cases

Case investigation timeline, 2003-2005

- Four deaths occur among women following medical abortions
- Cases reported to CDC Unexplained Deaths project (UNEX)



Patient demographics (n=4)

Age in years (median, range)	22 yrs	(18-34)
Race (n, %)		
White	2	(50%)
Black/ African American	1	(25%)
Asian	1	(25%)
<hr/> California resident (n, %)	4	(100%)

Illness course and outcome (n=4)

Underlying medical conditions (n, %)	0	(0%)
Died (n, %)	4	(100%)
Time course in days (median, range)		
Mifepristone to symptom onset	5 days	(4-5)
Hospitalization to death	0 days	(0-1)

Clinical signs and symptoms (n=4)

	n	(%)
Temperature >38.0 C	1	(25%)
Tachycardia	4	(100%)
Hypotension	4	(100%)
Vomiting or diarrhea	4	(100%)
Abdominal pain	4	(100%)
Rash	0	(0%)

Clinical laboratory findings (n=3)

	n	(%)
Leukemoid reaction (WBC >80,000)	3	(100%)
Hemoconcentration (Hct >50%)	2	(66%)
Thrombocytopenia (Plts <100,000)	2	(66%)
Renal insufficiency (Creatinine >1.1)	1	(33%)
Elevated liver function tests	0	(0%)

Bacterial culture results

	Positive / Performed
Blood culture	0 / 3
Peritoneal fluid	0 / 1
Vaginal swab	1* / 1
Endometrial tissue	1† / 1

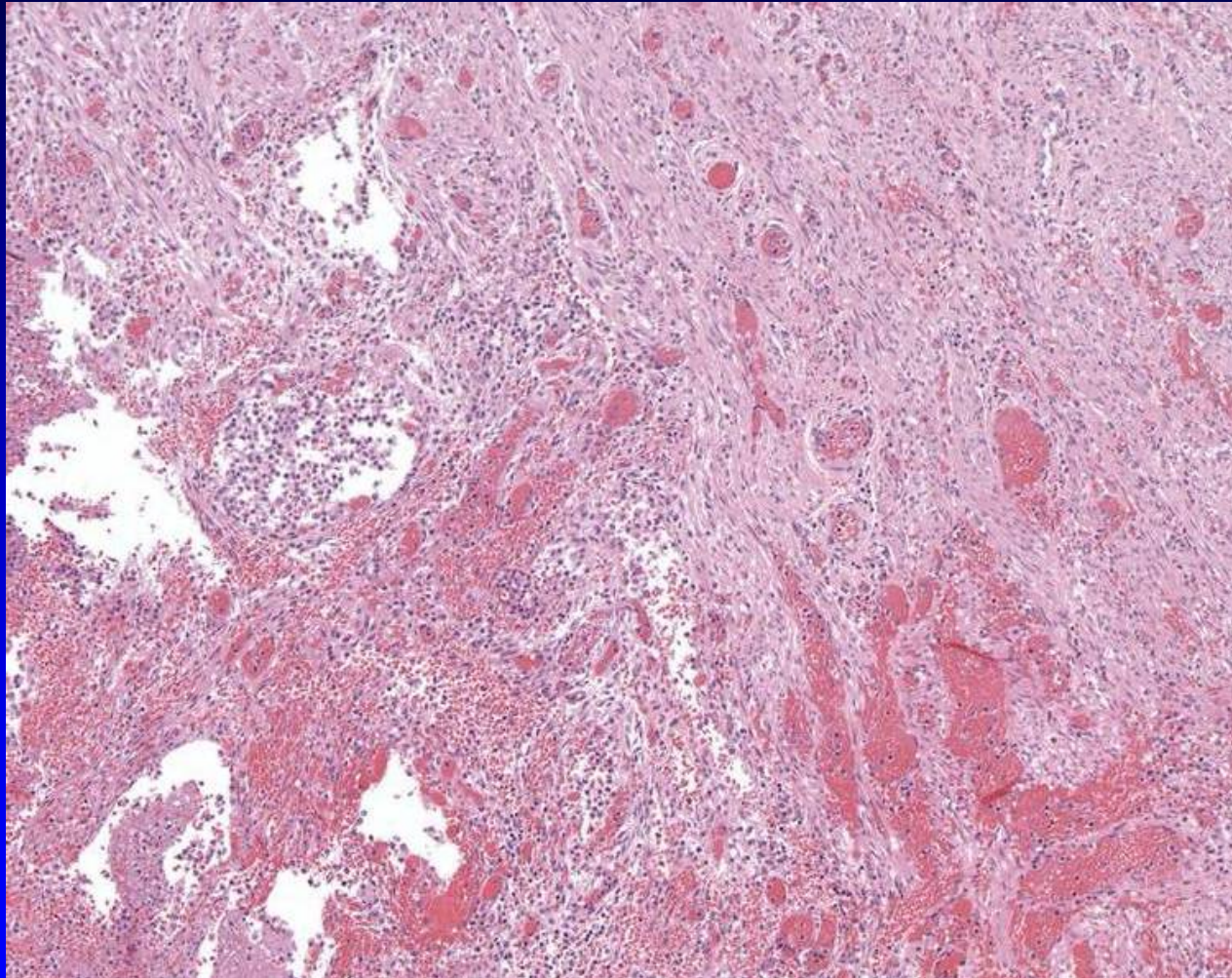
**Gardnerella* species

†*Escherichia coli* and an anaerobic gram-positive bacillus

Radiographic and gross autopsy findings (n=4)

	n	(%)
Pleural or peritoneal effusions	3	(75%)
Pulmonary infiltrates/ edema	3	(75%)
Retained fetal or placental tissue	0	(0%)

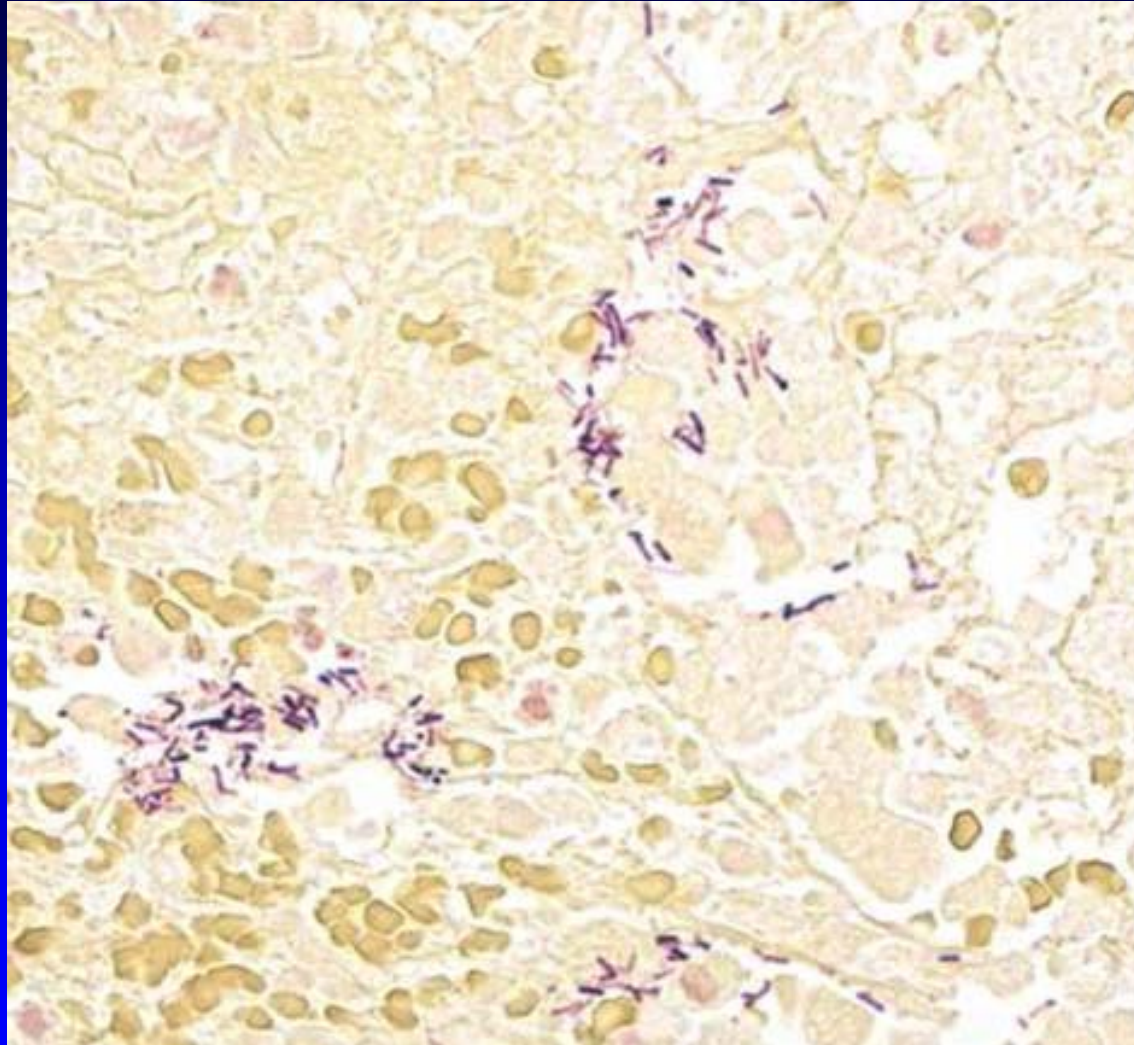
Hematoxylin & eosin staining of uterine tissue



Hemorrhage, inflammation and necrosis of endometrium

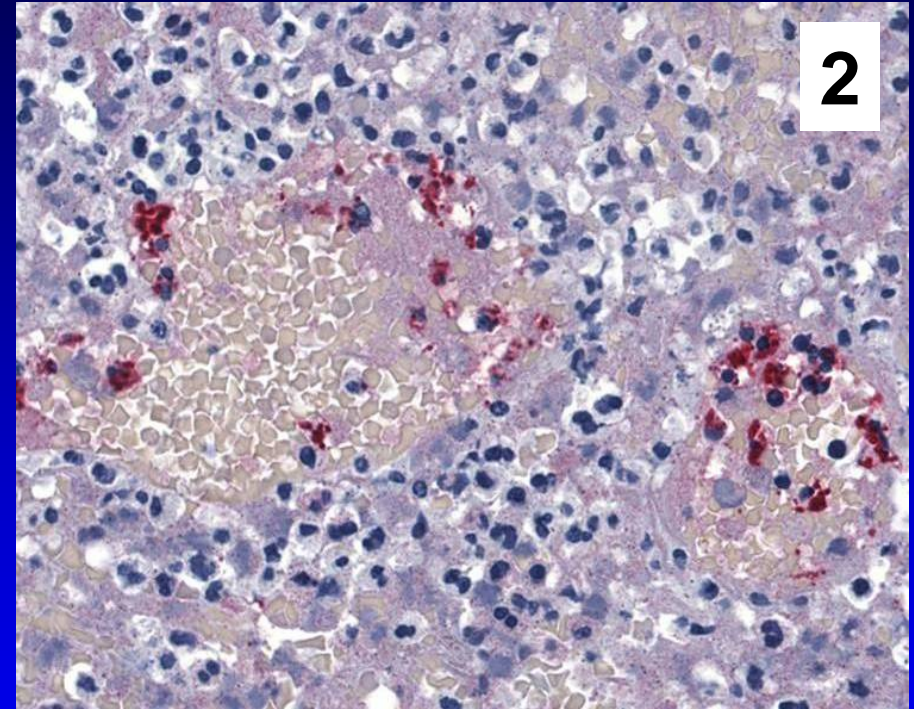
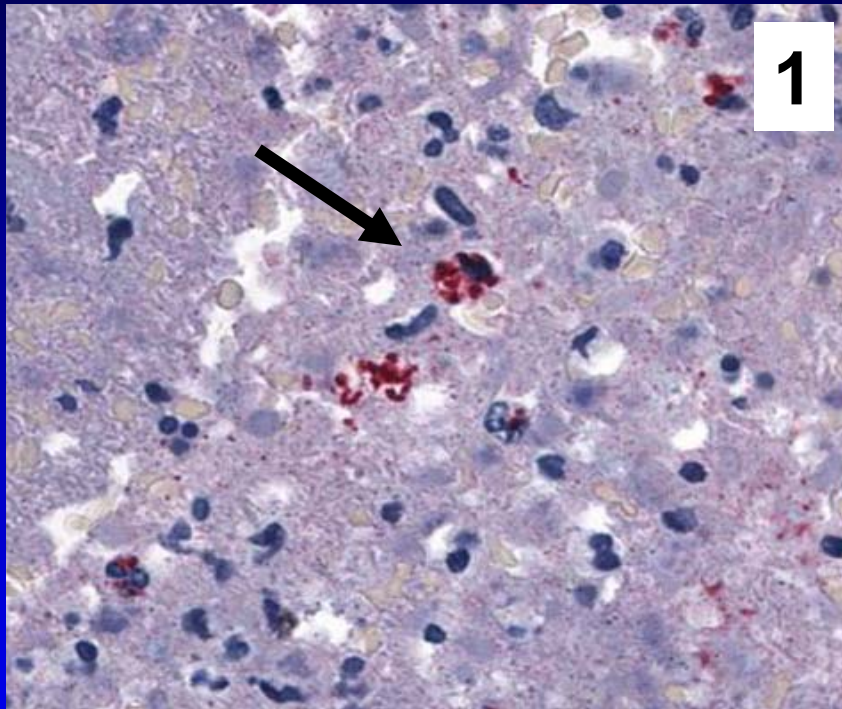
Gram's stain of uterine tissue

Figure



Abundant gram positive bacilli in necrotic endometrial tissue

***Clostridium* sp. IHC of uterine tissue**



Immunohistochemical staining (IHC) of *Clostridium* sp. antigens inside inflammatory cells in necrotic endometrial tissue (image 1) and myometrial blood vessels (image 2).

Positive IHC results on uterine tissue (n=4)

<i>Clostridium</i> species IHC	4	(100%)
<i>Staphylococcus aureus</i> IHC	1*	(25%)
Group A streptococcus IHC	0	(0%)
<i>Neisseria</i> species IHC	0	(0%)

*Antibody staining present on endometrial surface only

Positive PCR results on uterine tissue (n=4)

Broad-range 16S rRNA gene PCR*	4	1 (100%)
<i>C. sordellii</i> 16S rRNA gene PCR	4	(100%)
<i>C. sordellii</i> cytotoxin L gene	4	(100%)
<i>C. sordellii</i> phospholipase C gene	4	(100%)
<i>C. perfringens</i> alpha toxin gene	0	(0%)

*Amplified product sequences showed $\geq 97\%$ identity with *C. sordellii*

Conclusions

- Four deaths attributed to *C. sordellii* endometritis and TSS
- Clinical and pathologic findings similar to 10 other cases of *C. sordellii* genital tract infections previously reported
- Serious infection can occur after medically-induced abortion
- Many questions remain regarding the possible association between mifpristone/misoprostol and *C. sordellii* TSS

Hypotheses for potential association

- Product contamination
- Reporting or case detection bias
- Changes in vaginal flora or environment (e.g., pH)
- Incomplete abortion with necrotic decidual tissue
- Immunosuppressive effects of mifepristone
- Increased pathogen virulence (e.g., toxin prevalence)
- Altered host susceptibility
- Interaction of multiple factors

Product contamination ruled out

- No epidemiologic links between the patients
- Medications obtained from different clinics and providers
- Medications received were from different lots.
- FDA tested drug from manufacturing lots of mifepristone and misoprostol and found no contamination with *Clostridium sordellii*

Reporting or case detection bias

- Regional attention and reporting in California
- Enhanced laboratory testing of cases associated with these medications
- No centralized reporting of other pregnancy-associated infections or deaths

Enhanced surveillance activities

■ Objective

- Identify additional cases of severe infection or toxic shock syndrome associated with pregnancy, childbirth or abortion

■ Mechanisms

- Stimulated passive reporting from MMWR or NEJM articles
- Infectious Disease Society of Ob/Gyn (IDSOG)
- National Association of Medical Examiners (NAME)
- Unexplained Deaths Project (UNEX) ongoing surveillance
- Retrospective death certificate review, CA Dept of Health Services

Remaining questions

- Are women who use mifepristone or misoprostol at increased risk of *C. sordellii* infection or TSS compared to other woman following surgical abortion, spontaneous abortion, or childbirth?
- If so, what is the mechanism of that increased risk, and is it limited to *C. sordellii*?
- How can we further reduce the risk and improve the treatment of all *C. sordellii* infections?

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Establishing a research agenda

- Further evaluate the possible association between medical abortion and *C. sordellii* infections
- Define the incidence and full spectrum of illness for pregnancy-associated *C. sordellii* infections
- Reduce the risk and improve the treatment of *C. sordellii* Toxic Shock Syndrome

Primers used in PCR reactions

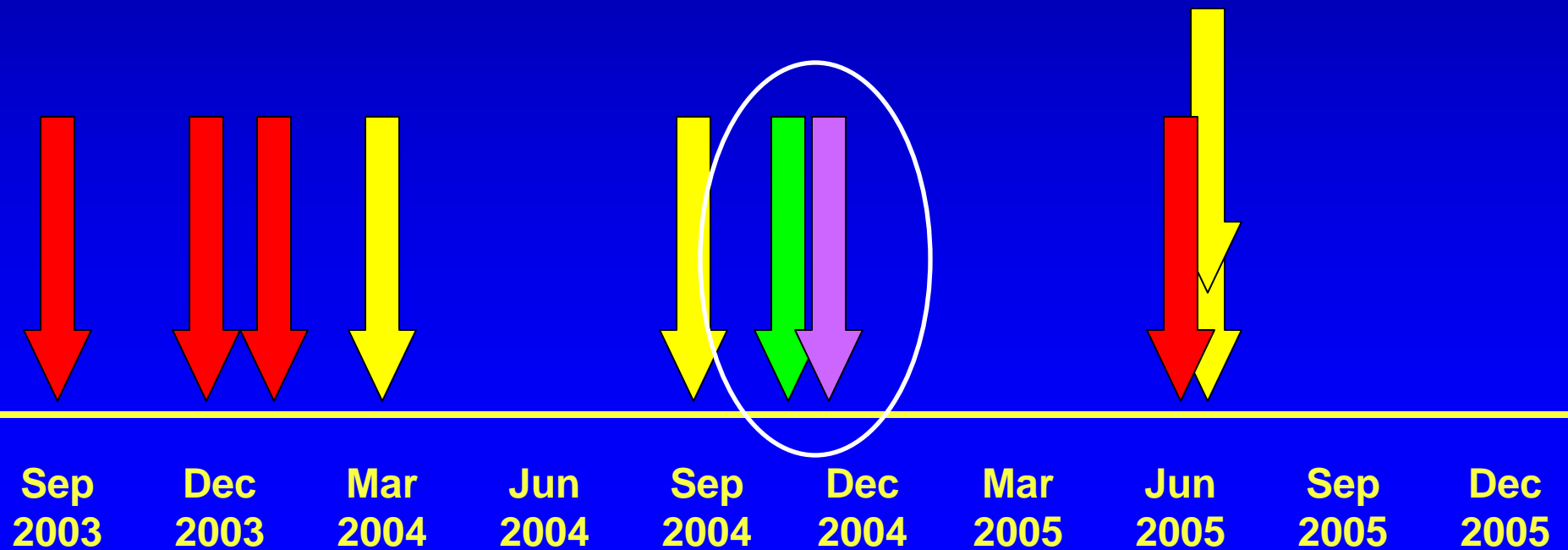
Gene target	Primer	Sequence (5'-3')	Product size (bp)
16S rRNA	F8 357R	AGT TTG ATC CTG GCT CAG CTG CTG CCT CCC GTA	330
16S rRNA	CISOR-F CISOR-R	TCG AGC GAC CTT CGG CAC CAC CTG TCA CCA T	944
CytL	CLS-F1 CLS-R1	ATG AAC TTA GTT AAC AAA GCC CAA AAT ACT TCC ATA GTT AGA TAT TCT TTA	250
Csp	CLS-F2 CLS-R2	TAA AGA TGC AGT AGC TAA TAA GGA TTT TTC CTG AAA TTT GAT CTT CTG AAA CC	223

Sequence analysis of PCR products showing percent nucleotide identity for each case

Case	16S rDNA (944 bp)	CytL gene (250 bp)	Csp gene (223 bp)
1	98	99	97
2	98	98	97
3	97	99	98
4	98	98	97

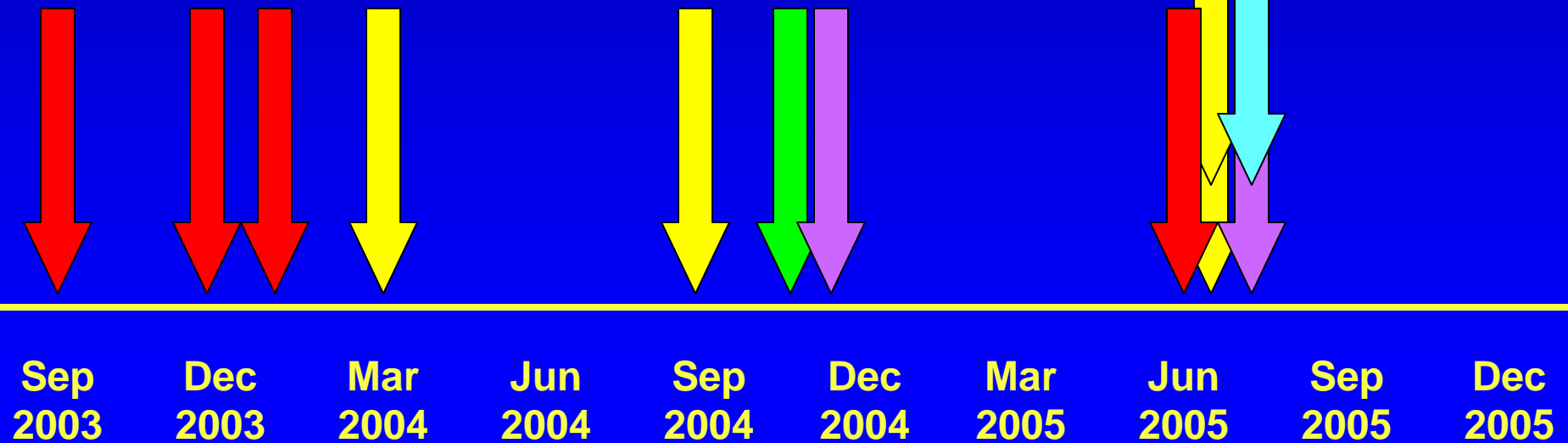
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