

Salmonella clearance by PCR: CD control considerations



<p>(Includes tartrate-positive <i>S. Paratyphi B</i>)</p> <p>NOTE: CIDT available and included in Probable case definition. CIDT does not differentiate between <i>Salmonella</i>, paratyphi, or typhi. Reflex culture is required per Title 17, Section 2505.</p>	SOS	CMR and Case Report. Restrict/exclude until 2 consecutive stool specimens taken at least 24 hours apart, and collected at least 48 hours after cessation of antibiotics, are negative. ^β	CMR (Probable) + Case Report. Restrict/exclude until 2 consecutive stool specimens taken at least 24 hours apart, and collected at least 48 hours after cessation of antibiotics, are negative. ^β	No restriction. Consider one stool specimen.
	Child \leq 5 years in group setting ^μ	CMR and Case Report. Restrict/exclude until 2 consecutive stool specimens taken at least 24 hours apart, and collected at least 48 hours after cessation of antibiotics, are negative. ^β	CMR (Probable) + Case Report Restrict/exclude until 2 consecutive stool specimens taken at least 24 hours apart, and collected at least 48 hours after cessation of antibiotics, are negative. ^{β, μ}	No restriction. Consider one stool specimen if outbreak suspected.
<p>Applicable Code - CCR 17, §2612. For foodhandlers, also Health & Safety Code §113949-113950.5. (For child care centers, refer to CCR 22 §101626.1 (e)-(i)).</p> <p>^αNOTE: Matrix is for acute salmonellosis cases (<3 months). Restriction of convalescent (3 months) and chronic (12 months) carriers of <i>Salmonella</i> is at the discretion of the local health officer.</p> <p>^β CCR does not specify what testing must be used for clearance. Current standard for clearance is with culture; however, some public health laboratories are in the process of validating polymerase chain reaction [PCR] testing.</p> <p>^μNOTE: Alternative approach: May return to group setting when asymptomatic for at least 24 hours (no stool testing) and LHD monitors for transmission in the setting.</p>				

+ Local health departments may choose to follow more restrictive exclusion and clearance practices than those presented in these guidelines, except where specified in code or regulation. See overarching comments on page 1 of matrix.

§ See California Code of Regulations (CCR), Title 17 for more details; applicable sections listed in Attachment I

* SOS (Sensitive Occupations or Situations) is not defined in either the Code of Regulations or Health & Safety Code. See Attachment II for definition of food worker, as compiled by CACDC, 2008.

CMR = reportable to state by CMR only (paper or electronic); case history form not required by CDPH. CMR (Probable) = report as Probable Case to CDPH; probable case definition exists.

Case report = investigation/case history form required to be sent to CDPH (CMR also required)

Clearance testing: Maximize sensitivity or specificity?

High **sensitivity**

- Fewer false negatives
- More complete detection of persons who are shedding salmonella
- Improved prevention of transmission
 - Exclude/restrict all shedders from SOS

High **specificity**

- Fewer false positives
- More accurately detect persons who are truly shedding salmonella
- Avoid undue financial hardship of excluding persons from SOS who aren't truly shedding salmonella

PCR: High sensitivity, moderate specificity

Parallel testing of clearance specimens: 24-hr culture & PCR

Table 1: PCR versus Culture Results

	Culture (+)	Culture (-)
PCR (+)	38	10
PCR (-)	0	68

- Using 24-hr culture result as the gold standard:
 - Sensitivity 100%
 - Specificity 87%
 - High negative predictive value 100%
 - Moderate positive predictive value 79%



Is 24-hr culture a true gold standard?

- In salmonella-spiked stool study, some samples that tested (-) by 24-hr culture and (+) by PCR were culture (+) if incubated longer (48, 72 hrs)
- If 48- or 72-hr culture result were the gold standard, PCR specificity would likely be higher



Data gaps



- Would findings be replicated with actual clearance specimens?
- Do low levels of bacteria detected only by longer incubation cultures represent a transmission risk?
- Is there literature documenting transmission at quantified levels of *Salmonella* colony forming units (CFUs)?

Operational considerations for using PCR clearance testing

For turnaround time at least as good as culture, PCR must be run at least 2x/week

- Staff time and reagents

To improve overall PPV of testing, consider reflexing PCR(+) specimens to culture (24 hr)

- May increase lab costs
- Feasibility, costs depend on volume of PCR (+) specimens

Strategies to improve PPV & control costs (I)

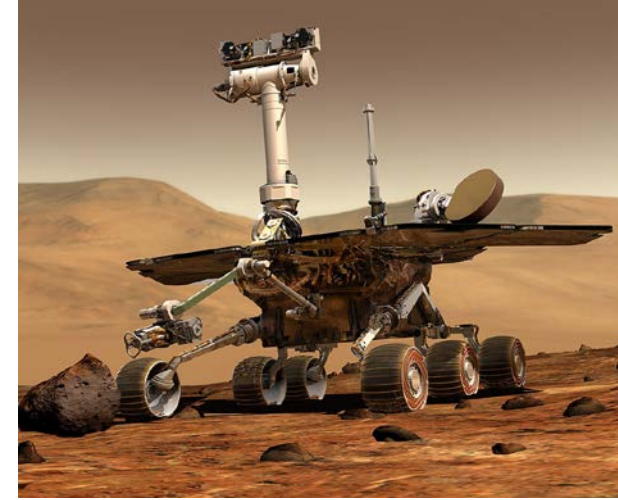
- **To save \$, use PCR & reflex culture (+)s for a subset of samples that are less likely to test (+)**
 - Asymptomatic Salmonella contacts in SOS who are being screened
 - 4.3% of contacts screen positive by 24 hr culture (prelim. analysis)
 - Wait to restrict or exclude from SOS until/unless culture (+)

AND/OR...

Strategies to improve PPV & control costs (II)

- **Define a PCR Cycle threshold (Ct) cutoff value that predicts a true (+) by 24-hr culture**
- Only reflex culture PCR (+) specimens with a Ct > cutoff value
- How to find the Ct cutoff?
 - Concordant samples [culture and PCR (+)]: Ct 17-33.4
 - Discordant samples [culture (-), PCR (+)]: Ct 23.8-34.6
 - Thus far, ranges overlap

Areas for further investigation (I)



- Do specimens that only culture (+) at >24hrs incubation pose a transmission risk?
- Is there a minimum threshold salmonella concentration in stool (measured by CFUs) at which salmonella transmission has been documented?
- Is there a Ct value that predicts a true (+) PCR result?
 - For different candidate Ct values, calculate sensitivity, specificity, PPV, NPV

Areas for further investigation (II)



- Continue parallel testing of cases and contacts
 - If PCR (+), culture (-) at 24hrs → incubate for 48 or 72hrs
- Cost & cost-effectiveness analyses
 - Staff time and reagent costs for different testing algorithms and different proportion of PCR(+) stool specimens

Thank you!

And many thanks to ACPHD epidemiologists Robert Brown, Rita Shiau, and Emily Yette

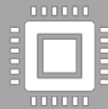
Now, let's talk...

Discussion



Is your LHD currently using PCR for Salmonella clearance?

If so, how has it been operationalized?



Has the ACPHL study presented enough data for you to consider switching from culture-based clearance to PCR?



What other questions do you have about the study?



What other areas of study should we explore?



Are there additional CD control impacts to consider?