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Shigella Azithromyin Working Group

Working Group/Contributors

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Rationale

- Increasing use worldwide of azithromycin for bacterial GI infections, including those caused by *Shigella* species.
- Increasing using of azithromycin in *Shigella* infections is due to the emergence of strains resistant to multiple other classes
- Resistance to azithromycin has also emerged, and resistant strains have been associated with outbreaks

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Proposals

1. Establish ECVs for *S. flexneri* and *S. sonnei* because the data requirement for doing this are fulfilled:
   a. *S. flexneri* ECV = 8 mg/L
   b. *S. sonnei* ECV = 16 mg/L
2. Establish a zone diameter correlate ECV for the *S. flexneri* of [S] ≥16mm. None can be safely established for *S. sonnei* at this time, although isolates <10mm might be screened for MIC or molecular tests
3. Consider publishing (in S100 or as a separate document, e.g. rationale document), ECVs for these two species, and the zone diameter ECV for *S. flexneri*

Breakpoint proposal from Azithromycin/Shigella Breakpoint Ad hoc WG

(See Briefing document 6.3.0)

- **Proposals from the Ad Hoc WG**
- Establish ECVs for *S. flexneri* and *S. sonnei* because the data requirement for doing this are fulfilled:
  - *S. flexneri* ECV = 8 mg/L
  - *S. sonnei* ECV = 16 mg/L
- **BPWG vote:** The motion was passed with a vote of Yes= 12; No = 0; Abstain = 2.

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Breakpoint proposal from Azithromycin/Shigella Breakpoint Ad hoc WG (See Briefing document 6.3.0)

- **Proposal 2**:Establish a zone diameter correlate ECV for the *S. flexneri* of ≥16mm. None can be safely established for *S. sonnei* at this time.
- **BPWG Vote:** Yes= 13; No = 0; Abstain = 1.
- Consider publishing (in S100 or as a separate document, e.g. rationale document), ECVs for these two species, and the zone diameter ECV for *S. flexneri.* (**WG:** No Motion was made on this.)
- Many/most labs just call these *Shigella* spp. No speciation possible. How do labs deal with this?

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BMD MICs

- BMD data are now available on MICs from 3 independent laboratories each examining local strains (USA, Argentina, and Canada). The total numbers for two species, *S. flexneri* and *S. sonnei* are adequate to establish epidemiological cutoff values (ECVs), which are 8 and 16 mg/L respectively.

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Shigella flexneri

MIC	≤0.25	0.5	1	2	4	8	16	32	64	128	256	>256
S. flexneri												
Karlsson	7	6	20	42	30	7	2	7	14	14	4	
Galas	1	11	12	33	4	0	0	0	1			
Melano			4	36	12	0	0	4	5	6	9	11
	8	**17**	**36**	**111**	**46**	**7**	**2**	**11**	**20**	**20**	**13**	**11**
		ECV=	**8**									

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Shigella sonnei

Step 1. Population Data | *S. sonnei* | Azithromycin

MIC	Log_2MIC	Raw Count	Cum. Count	Fitted
0.001	-10		0	0.0
0.002	-9		0	0.0
0.004	-8		0	0.0
0.008	-7		0	0.0
0.016	-6		0	0.0
0.03	-5		0	0.0
0.06	-4		0	0.0
0.125	-3		0	0.0
0.25	-2		0	0.0
0.5	-1		0	0.0
1	0	3	3	0.6
2	1	26	29	28.9
4	2	155	184	154.2
8	3	98	282	99.2
16	4	9	291	7.4
32	5	1	292	0.1
64	6	3	295	0.0
128	7	0	295	0.0
256	8	13	308	0.0
512	9	7	315	0.0
1024	10		315	#N/A

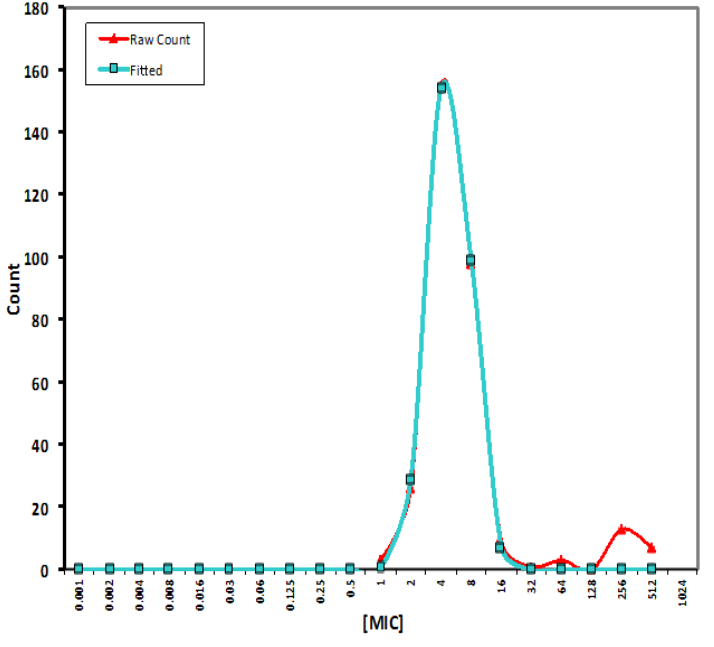
Enter/paste data in this column

Clear All

Modal MIC	4	
Log_2MIC Mode	2	
Max Log_2MIC	9	
Selected Log2 Mean	1.79	=3.46
Selected Log2 SD	0.62	

Selected CO_{WT} Values		%>
CO_{WT} 95.0%	8	10.5%
CO_{WT} 97.5%	16	7.6%
CO_{WT} 99.0%	16	7.6%
CO_{WT} 99.9%	16	7.6%

REVIEW AREA



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Shigella boydii

MIC	≤0.25	0.5	1	2	4	8	16	32	64	128	256	>256
S. boydii												
Karlsson			6	40	33	2	0	1	3			
	0	**0**	**6**	**40**	**33**	**2**	**0**	**1**	**3**	**0**	**0**	**0**
		ECV=	–	single source								

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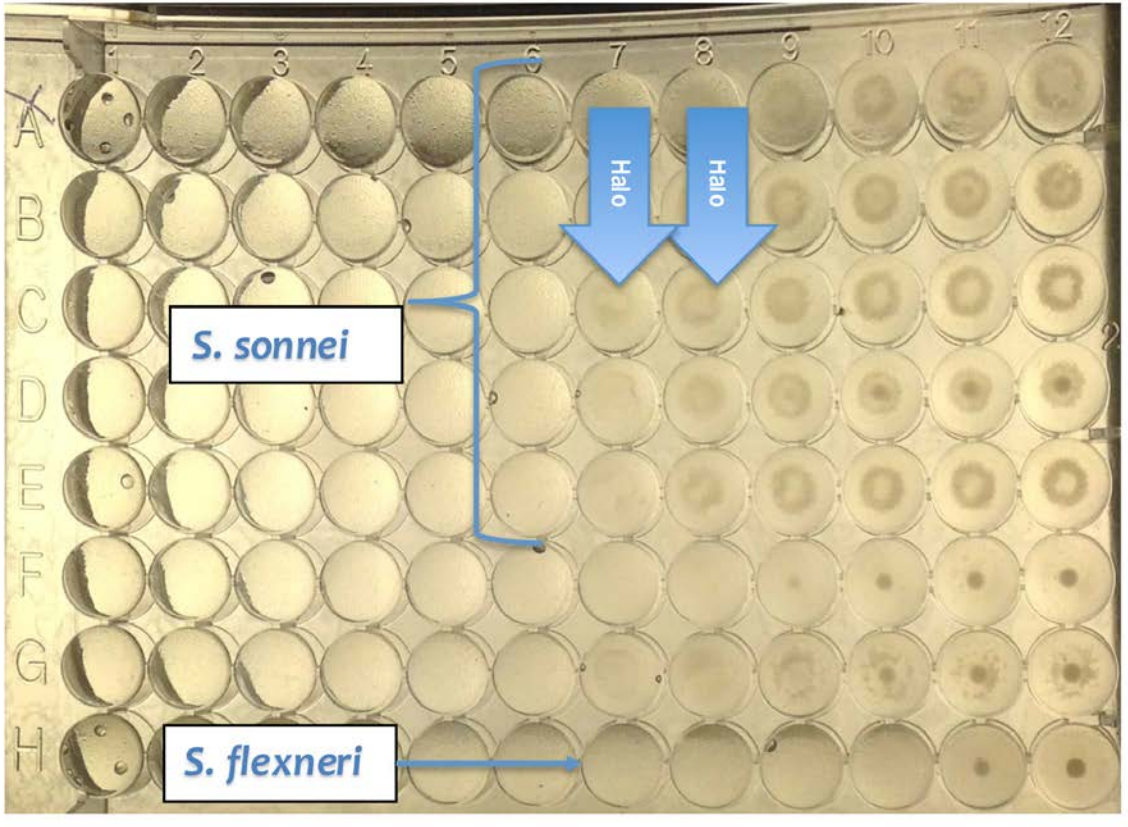
BMD Endpoint Reading Issues



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Gradient Diffusions MICs

MIC	≤0.25	0.5	1	2	4	8	16	32	64	128	256	>256
S. flexneri												
Parry		1	18	129	26	1	2	1	1	1	1	
Galas			20	27	10							
	0	**1**	**38**	**156**	**36**	**1**	**2**	**1**	**1**	**1**	**1**	**0**

MIC	≤0.25	0.5	1	2	4	8	16	32	64	128	256	>256
S. sonnei												
Parry			1	5	173	99	0	2	0	1		
Galas			1	2	17	13						
	0	**0**	**2**	**7**	**190**	**112**	**0**	**2**	**0**	**1**	**0**	**0**

The MIC distributions are similar to those observed with BMD.

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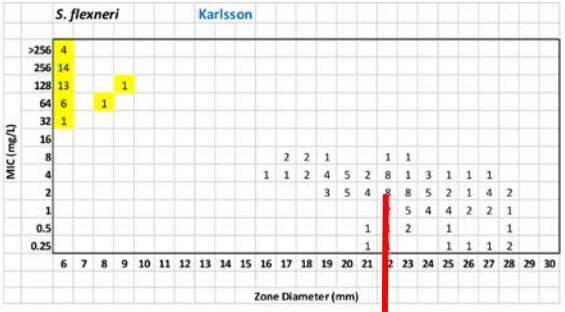
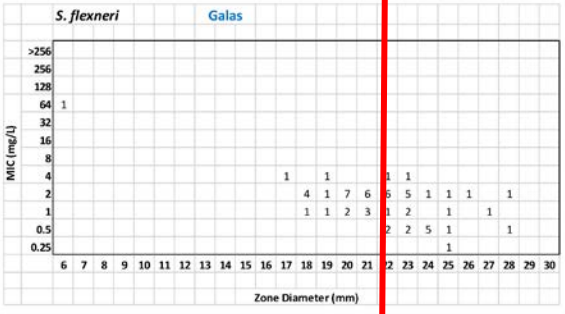
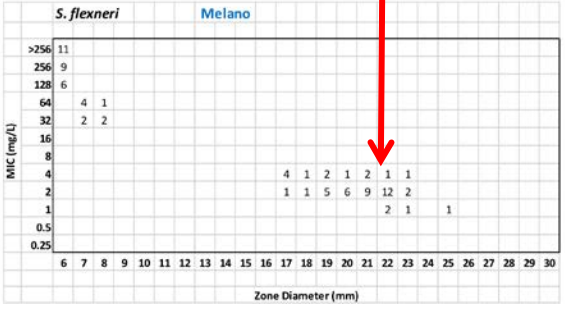
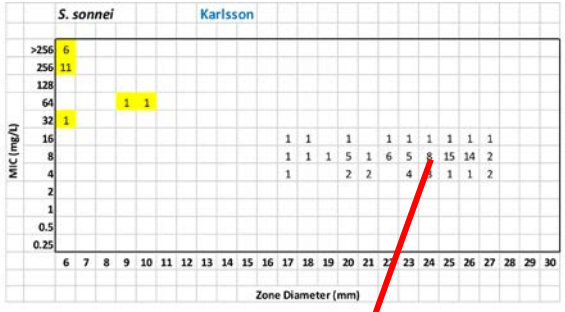
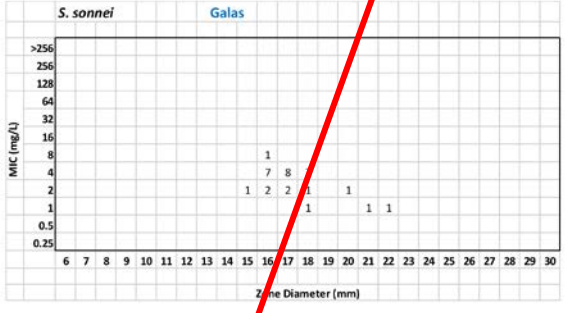
Disk Diffusion

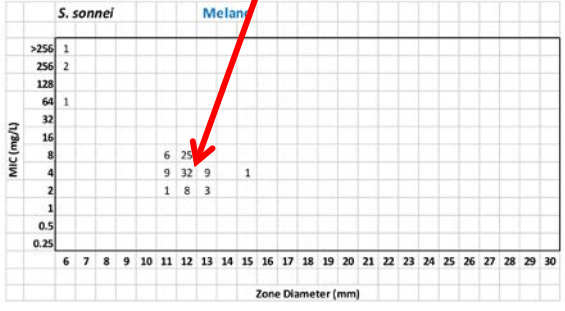






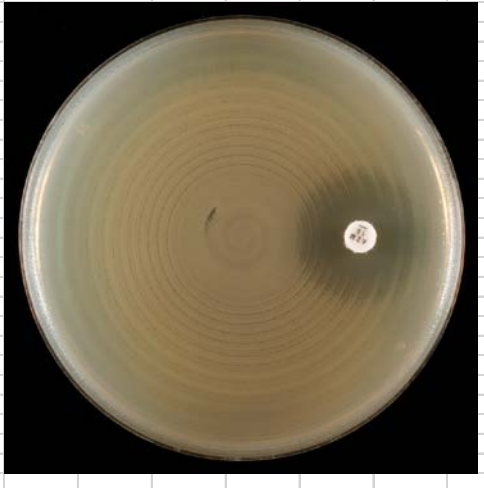






Disk Diffusion Variation due to Medium

S. sonnei is harder to read and is affected by medium brand. Experiments conducted at the EUCAST Development Laboratory show this variation clearly.

Isolate 13-521417	Isolate 13-521417	Isolate 13-521417
		
Oxoid MH	**BBL MH**	**Bio-Rad MH**
Clear inner zone	Very thin inner zone	Clear inner zone

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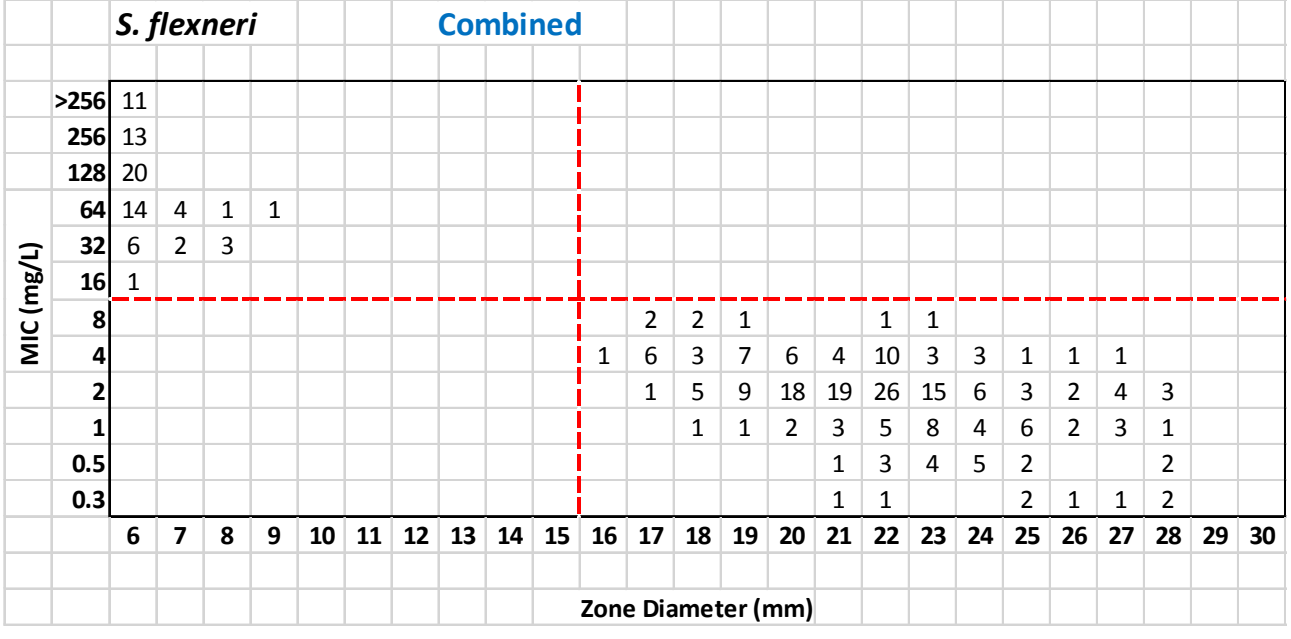
S. flexneri zone diameter correlates



MIC (mg/L)	*S. flexneri*				Combined																				
	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
>256	11																								
256	13																								
128	20																								
64	14	4	1	1																					
32	6	2	3																						
16	1																								
8												2	2	1			1	1							
4											1	6	3	7	6	4	10	3	3	1	1	1			
2												1	5	9	18	19	26	15	6	3	2	4	3		
1													1	1	2	3	5	8	4	6	2	3	1		
0.5																1	3	4	5	2			2		
0.3																1	1			2	1	1	2		

Zone Diameter (mm)

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Clinical Outcome Data (CDC)

ID	species	Year of isolation	State of residence	Age (y)	Sex	Additional antimicrobial resistance*	Azithromycin MIC (µg/mL)	Mechanism(s)	Treatment	Duration of illness (days)	Duration of shedding (days)	Notes
2012C-4448	sonnei	2012	Indiana	8	M	AMP, STR, SXT	256	mphA	AZM, then CFM	9	38+	3 pos convalescent cx up to 38 days after onset. Excluded from school for 38 days.
2014C-3799	sonnei	2014	Missouri	3	M	AMP, AUG, FOX, STR	128	Non- mphA, non-ermB	AZM x 5 d; later AXO x 5 d	Unknown	13+	Initial cx (day 3 of illness) did not have DSA but first 2 repeat cultures did. Had pos cx at days 3, 9, 13 after onset. Neg cx day 28. Hosp 2 days with bloody diarrhea. Older sibling in childcare had preceding shigellosis susceptible to AZM. No other DSA found in larger community outbreak.
2015C-3283	sonnei	2015	Missouri	2	M	AMP, STR sulfisoxazole, AUG, TMP/SMX, *intermediate* to cefoxitin	64	mphA positive and ermB negative	AZM	4	14+	Had positive cultures on day 3 and 14. Next culture on day 28 was negative.
MN___E2014021599	sonnei	2014	Minnesota	27	M	AMP, STR, TMP/SMX, TET	>256	mphA and ermB positive	AZM	17	Unknown	Linked to outbreak of 22 DSA-shigellosis infections among men who have sex with men (MSM) in Chicago and Minneapolis; lost to follow-up
MT_201516154	sonnei	2015	Montana	41	M	AMP, STR, TMP/SMX, CIP, NAL, TET	>256	mphA and ermB positive	CIP x 3 d, then AZM x 3 d	16+	16+	MSM; linked to outbreak of ~300 cases reported in MMWR. Hosp 3 days. Positive culture at day 16. Additional follow-up info not available.