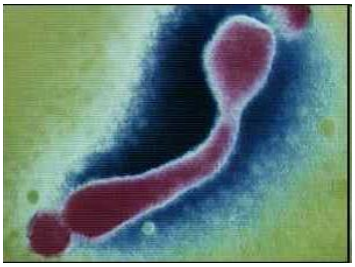
Mycoplasma genitalium: the new chlamydia



Catriona Bradshaw

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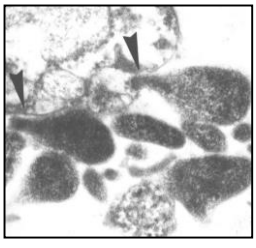
Mycoplasma genitalium

- First isolated in 1980
- Fastidious with slow growth (>50 days)
- Difficult to culture
- Few isolates available for antimicrobial susceptibility testing



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Mg prevalence of 1-3% in community studies

		Mg Prevalence	Ct Prevalence
Manhart 2007	18-27 yo North America NHANES N=2932	Men 1.1% (0.5-2.4%) Women 0.8% (0.4-1.6%)	 4.5% (1.4-13.5%)
Andersen 2006	21-23 yo Denmark Pop Ct screening N=1652	Men 1.1% (0.3-1.9%) Women 2.3% (1.3-3.2%)	8.4% (6.6-10.2%) 5.6% (3.9-7.3%)
Walker 2009	16-25 yo Australia Ct screening in GP/SHC n=1116	 Women 1.6% (0.7-2.6%)	 4.9% (2.9-7.0%)
Oakshott 2009	15-27 yo United Kingdom Female uni students n=2246	 Women 3.3% (2.6-4.1%)	 5.8% (4.9-6.8%)
Sonnenberg 2015	16-44 yo United Kingdom Ntsal-3 Population n=4507	Men 1.2% (0.7-1.8%) Women 1.3% (0.9-1.9%)	1.1% (0.7-1.6%) 1.5% (1.1-2.0%)

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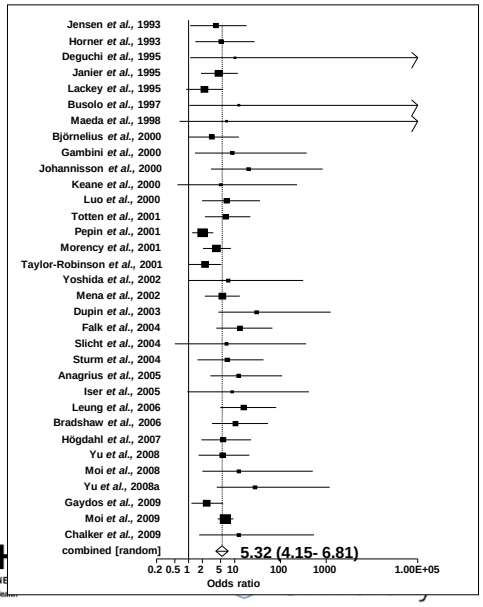
M. genitalium and Non-gonococcal Urethritis

- Established cause of NGU
- Higher prevalence in acute NGU than controls[1-6]
- Responsible for 10-30% of cases of NGU[4,7,8]
- Combined OR= 5 (4-7)
- Co-infection with chlamydia uncommon[3,4]
- Similar clinical features to chlamydia [2-4]



[1] Jensen 2004 [2]Anagrius 2005 [3]Falk 2004
[4]Bradshaw 2006, [5]Horner 2001,
[6]Taylor Robinson 2002 [7]Iser 2005, [8] Bradshaw 2008

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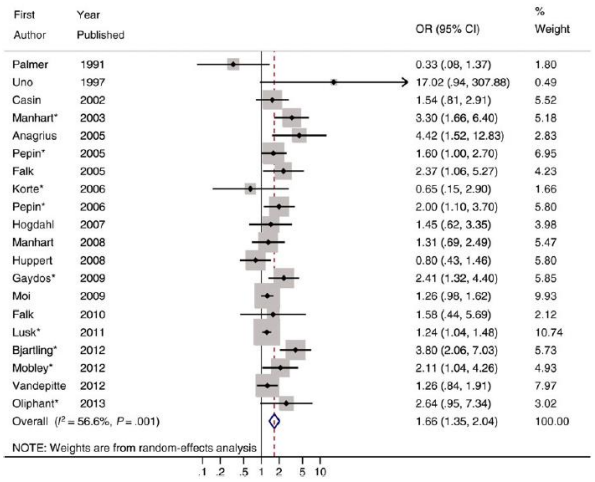
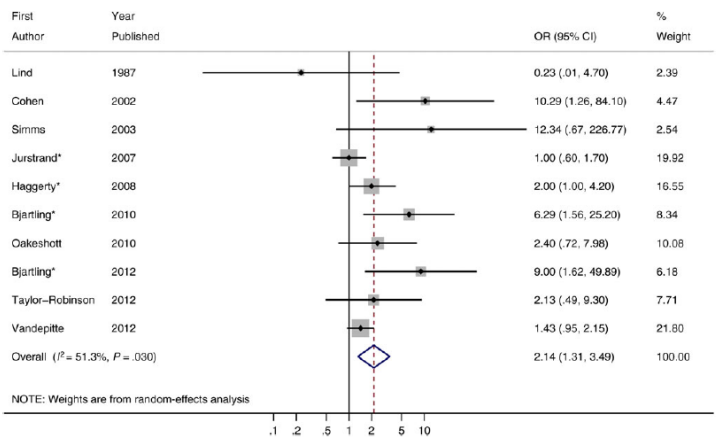
M. genitalium and Cervicitis



Pooled effect estimate of 1.66 (1.35-2.04)

Lis et al CID 2015

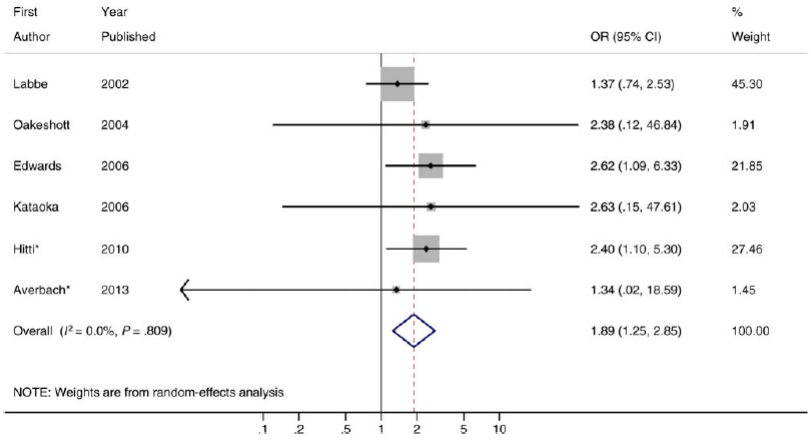
M.genitalium and PID



Pooled effect estimate 2.14 (1.31-3.49)

Lis et al CID 2015

M.genitalium and Pre-term Birth



Pooled effect estimate of 1.89 (1.25-2.85)

Lis et al CID 2015

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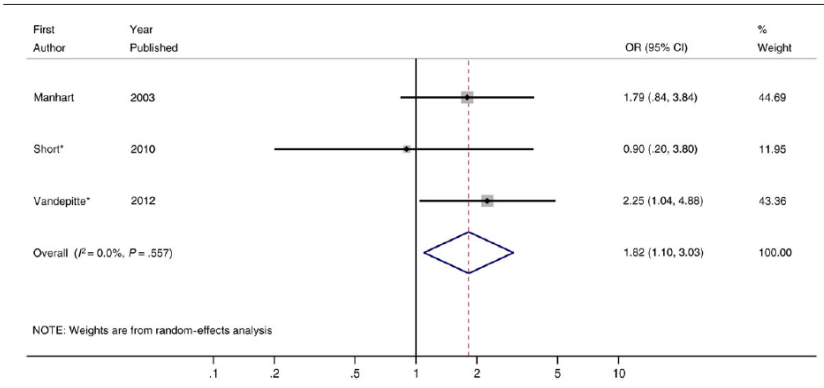
M.genitalium and Spontaneous Abortion



Pooled effect estimate =1.82 (1.10-3.03)

Lis et al CID 2015

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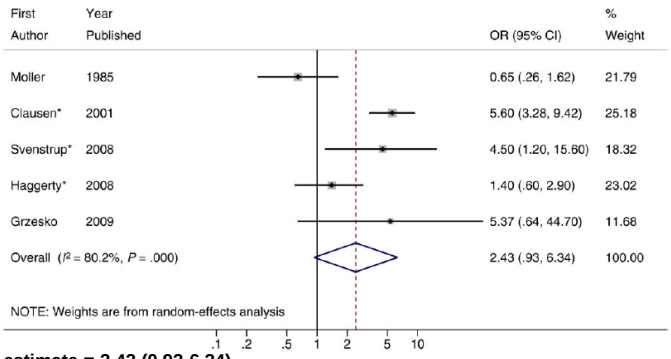
M.genitalium and Tubal Factor Infertility

- Serostudies examined association between *M.genitalium* and TFI
- Antibodies to *M.genitalium* more common in women with TFI compared to fertile women or women with non-TFI
- Consensus in the field that assays are generally poorly performing



Pooled effect estimate = 2.43 (0.93-6.34)

Lis et al CID 2015

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M.genitalium and Rectal Infection

Limited data on *M.genitalium* in rectal infections

Predominantly asymptomatic

Authors	Population	Rectal Mg prevalence (%; 95% CIs)	Association with symptoms/signs and HIV
Francis 2008	500 consecutive rectal samples MSM at STI clinic - USA	27/500 (5.4%; 3.6-7.7%)	Not significantly associated with symptoms/signs or HIV
Bradshaw 2009	521 asymptomatic MSM attending SOPV - AUS	8/497 (1.6%; 0.8-3.0%)	Asymptomatic. No HIV data
Soni 2009	438 MSM attending STI clinic- UK	19/412 (4.6%; 2.6-6.8%)	Not significantly associated with symptoms/signs. Associated with HIV
Zheng 2014	409 consecutive MSM attending VCT Clinic - China	22/405 (5.4%; 3.5-7.7%)	No association with symptoms. Associated with HIV (OR 4.5; 1.2-17.1%)
Philbert 2014	116 asymptomatic MSM attending STI clinic - France	1/115 (1%; 0-2.8%)	Asymptomatic. No HIV association.

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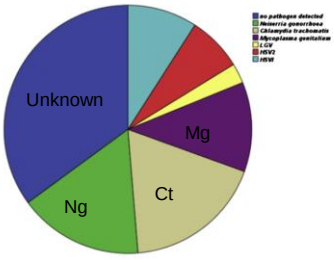
M.genitalium in Proctitis

TABLE 1. Aetiology of proctitis among HIV-positive and HIV-negative men who have sex with men

Pathogens detected	HIV-positive men (n = 48) n (%; 95% CI)	HIV-negative men (n = 106) n (%; 95% CI)	Prevalence ratio (95% CI) p-value
Rectal pain	34 (71; 58–83)	91 (84; 77–90)	0.81 (0.46–1.41) p 0.455
Anal discharge	31 (66; 53–79)	42 (39; 30–48)	1.13 (0.71–1.82) p 0.587
Chlamydia trachomatis	10 (21; 9–36)	20 (19; 12–26)	1.03 (0.57–1.89) p 0.902
Neisseria gonorrhoeae	14 (29; 16–42)	24 (23; 15–31)	0.73 (0.35–1.54) p 0.420
Herpes simplex virus 1	2 (4; 0–10)	14 (13; 7–19)	0.43 (0.12–1.60) p 0.211
Herpes simplex virus 2	7 (15; 5–25)	4 (4; 0.3–8)	2.2 (1.32–3.72) p 0.002
Lymphogranuloma venereum	4 (8; 0.3–16)	1 (1; 0–3)	2.50 (1.34–4.63) p 0.004
Mycoplasma genitalium	10 (21; 9–36)	8 (8; 3–13)	2.73 (1.21–3.28) p 0.006
Two or more pathogens	9[a] (19; 1–17)	8[b] (7; 2–12)	1.86 (1.11–3.13) p 0.020
No pathogen identified	11[c] (23; 11–35)	43 (40; 30–49)	0.55 (0.31–0.949) p 0.049

[a]Gonorrhoea plus chlamydia plus *M. genitalium* (n = 1); gonorrhoea plus chlamydia (n = 5); lymphogranuloma venereum (LGV) plus gonorrhoea (n = 1); LGV plus *M. genitalium* (n = 1); *M. genitalium* plus gonorrhoea (n = 1).
[b]Gonorrhoea plus herpes simplex virus 1 (HSV1) (n = 1); *M. genitalium* plus gonorrhoea (n = 2); gonorrhoea plus chlamydia (n = 3); chlamydia plus HSV1 (n = 1); *M. genitalium* plus chlamydia (n = 1).
[c]Two men had anal ulcers that were *Treponema pallidum* PCR-positive.

Case series of 154 MSM with sexually acquired proctitis



Bissessor Clin Micro Infect 2015

How do you test for *M.genitalium?*

- Diagnosis by NAATs
- Testing limited to specialized services using *in house* PCR assays
  - targeting MgPa gene or 16S rRNA gene[1-5]
- Commercial assays undergoing regulatory approval
  - SpeeDx PlexPCR assay –diagnostic-resistance assay – 2017
  - Hologic Aptima TMA (RNA)
- Low loads of *M.genitalium* not uncommon, sensitivity is an issue with assays
- FVU more sensitive than urethral swab in men[6]
- Women - HVS or Cx swab more sensitive than urine[5,7]

[1]Hardick 2006, [2]Yoshida 2002, [3]Jensen 2004, [4]Wroblewski 2006 [5]Edberg 2009 [6]Jensen 2004 [7]Jurstrand 2005

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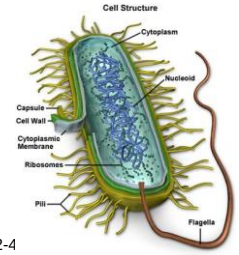
How do you treat *M.genitalium*?

- β-lactams and antibiotics that target the cell wall are not active as *M. genitalium* lacks a peptidoglycan containing cell wall
- Few classes of available antimicrobials[1-4] have activity against *M. genitalium*
  - Macrolides, Fluroquinolones and Tetracyclines
- Although most strains appear to have MICs within susceptible range to doxycycline[1]
- Clinical trials show low overall efficacy with cure rates of 22-45% - not recommended[2-5]
- Reduced susceptibility to 2nd and 3rd generation quinolones
- Greater susceptibility to 4th generation quinolines
  - moxifloxacin, sitafloxacin, sparfloxacin, and gatifloxacin[2-4]



[1] Hamasuna AAC 2005, [2]Hamasuna AAC 2009, [3]Hannan Med Microbiol 1998, [4]Jensen & Bradshaw BMC ID 2015

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1g AZI versus DOXY

- Observational studies & trials of NGU predominantly show
  - 1g AZI is more effective than 7d of DOXY for M.genitalium
  - 67-87% versus 30-45%, p=0.002 [1-3]
- 1g AZI recommended as 1st line therapy for M.genitalium by majority of STI guidelines[4,5]
- Recent meta analysis[6] of 21 studies (1490 participants)
  - pooled microbial cure rate for AZI of 77.2% (71.1-83.4%), p<0.01
- Notable decline over the past decade

[1] Mena CID 2009, [2]Schwebke CID 2011, [3]Manhart CID 2013, [4]STI treatment guidelines, ASHM 2014, [5]2015 CDC STI Treatment Guidelines, [6] Lau CID 2015

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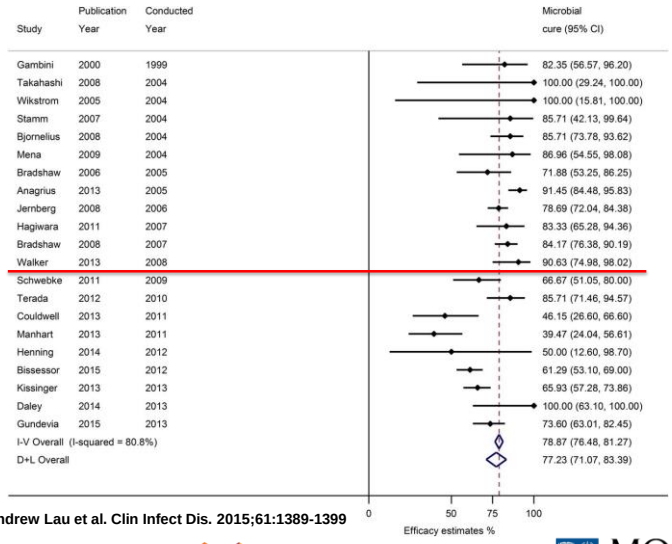
Cure following 1 g of AZI for urogenital *M.genitalium*



85.3%
(82.3-88.3%)

67.0%
(57.0-76.9%)
p<0.01

Andrew Lau et al. Clin Infect Dis. 2015;61:1389-1399

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Loss of Azithromycin

- At MSHC experienced a similar decline in cure rates
  - 85% (77-90%) in 2005-7[1] to 61% (53-69%) in 2012-13[2] p<0.001
- Accompanied by increase in macrolide resistance mutations (MRM) in 23S rRNA gene
- In 2016 at MSHC
  - MRM detected in >50% of infected patients [3]
  - preliminary data indicates 80-90% in MSM
  - shown that extended regimens of azithromycin are not more effective than 1g and still select for MRM[3]
- MRM prevalence now exceeds 30% in Asia-Pacific[4,5], North America and Northern Europe/UK[6,7]

[1]Bradshaw EID 2006, [2]Bissessor CID 2015, [3] Read CID 2016[4]Tagg JCM 2013, [5]Kikuchi JAAC 2014, [6] Pond CID 2014, [7]Gesink Int J Circum Health 2012

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Moxifloxacin for *M.genitalium*

- Moxifloxacin most commonly used 2nd line antimicrobial since 2006
  - 400mg daily for 7-10 days
- Bactericidal, and generally well tolerated, and in early studies had a cure rate approaching 100%[1-4]
- Recent warnings -hepatotoxicity, tendonitis, arrhythmias by FDA and restricted to second line indications in Europe[5].
- Last decade reports of MOXI failure emerged particularly in the Asia-Pacific region accompanied by mutations (Par C)[6-9]
  - treatment failures now reported in 12% of patients at MSHC[6]
  - 9% of strains had dual macrolide/quinolone resistance leaving very limited treatment options (G. Murray, unpublished data)

[1]Bradshaw EID 2006, [2]Bradshaw PLosOne 2008, [3] Anagrius PLoS One 2013, [4] Jernberg Int J STD AIDs 2008
[5] Kaye Pharmaco 2014, [6]Bissessor CID 2015, 7 Gundevia Int J STD AIDS 2015,
[8]Couldwell Int J STD & AIDs 2013, [9] Terada J Infect Chem 2012

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Need for New Antimicrobials

- Urgent need for new antimicrobials
- Pristinamycin - streptogramin comprising two structurally unrelated synergistic components
- Binds to bacterial ribosome arrests protein synthesis
- Wide range of *in vitro* activity –GPC, Clostridium, Haemophilus, Neisseria, Ureaplasma and Mycoplasma spp[2-3]
- Not routinely available in Australia
- Imported via SAS from France (tertiary services)
- Favourable MICs for *M.genitalium*
- Evaluated in 114 patients with macrolide or dual class resistance
  - 1g qid or 1g tds with doxycline 100mg bd for 10d
  - Cure rates of 75% (66-82%)[4]
  - Well tolerated

[1] Guschin BMC ID 2015, [2]Reid AA Chemo 2010, [3]Cooper J Achemo 2014, [4]Read TRH unpublished data

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Treatment recommendations for Mg?

- Treatment guidelines for *M.genitalium* lag well behind those for chlamydia
- Considerable resistance to *M.genitalium* specific guidelines in many countries
  - Lack of commercial assays, delays in establishing disease in women…….
- Specific treatment guidelines have not been available in the majority of countries until 2014+ - Aus, CDC, Europe.
- Focus exclusively on urogenital *M.genitalium* infections - little or no mention of rectal infection
- Now we finally have *M.genitalium* guidelines their recommendations do not reflect the current status of antimicrobial resistance

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Australian and US MG guidelines

Australian MG Guidelines

Principal Treatment Options

Situation	Recommended	Alternative
Uncomplicated genital infection	Azithromycin 1g PO, stat	Seek specialist advice.

CDC 2015 MG guidelines

Urethritis and cervicitis - 1-g dose of azithromycin.

A longer course of azithromycin (500-mg dose followed by 250 mg daily for 4 days) might be marginally superior to the single dose but not if 1g has failed.

If azithromycin has failed use moxifloxacin (400 mg daily x 7, 10 or 14 days)

Neither guideline has indications for rectal MG

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2016 European *M.genitalium* guidelines

Treatment for uncomplicated M.genitalium:

- Azithromycin 500 mg stat, then 250 mg on days 2-5

2nd line treatment and for uncomplicated macrolide resistant M. genitalium:

- Moxifloxacin 400 mg od for 7 -10 days.

3rd line treatment for persistent M. genitalium infection after azithromycin and moxifloxacin

- Pristinamycin 1 g four times daily for 10 days

Recommended treatment for complicated M. genitalium infection (PID, epididymitis)

- Moxifloxacin 400 mg daily for 14 days

Patients with anal infection should be informed about the risk of transmission from this site and that the infection may be more difficult to eradicate.

Test of cure is important

UK does not have MG guidelines – only mentioned within NGU

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Summary

- *M.genitalium* is very similar to chlamydia in its clinical manifestations and sequelae
- Commercial assays are about to emerge onto the market
- Who should you test?
  - no evidence for screening asymptomatic individuals
  - evidence supports testing in NGU, cervicitis, PID, proctitis, and sexual contacts
- What sample should you collect?
  - Men – FVU
  - Women – HVS or Cx swab
  - If anal sex – anal swab
- What test should you use?
  - if available one that provides macrolide resistance status to direct choice of antimicrobial therapy

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Conclusion

- *Overall M. genitalium* is becoming challenging to treat
- Guidelines lag behind resistance data and still recommend 1g AZI
  - May be associated with ≥50% treatment failure
- Test of cure 3-4 weeks following treatment and partner treatment is essential
- No readily available antimicrobial in the community to treat AZI failures
- Moxifloxacin 400mg daily for 7-10 days is recommended for failure following AZI or for macrolide resistant infections
- PID should be treated at 400mg daily for 14 days

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Conclusion

- Call a specialist sexual health physician if
  - cannot access moxifloxacin or moxifloxacin failure occurs
- Only current option for moxifloxacin failures is pristinamycin
  - 1g qid for 10 days - limited availability
- Emergence of commercial assays will result in an escalation in community diagnosis of *M.genitalium* and infections that are challenging to cure in primary care
- Need funding for evaluation of registered and new antimicrobials, combinations of antimicrobials and treatment trials

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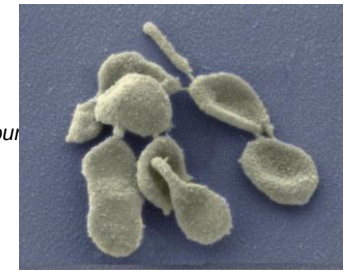

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