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Discussion and debate: Use of topical antibiotics with intravitreal injections

Professor Jean-François Korobelnik

Professor Anat Loewenstein

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Session aims

- To debate and discuss evidence ‘for’ and ‘against’ the use of topical antibiotics with intravitreal injections
- To provide a summary of the Vision Academy’s Viewpoint on the use of topical antibiotics with intravitreal injections
  - The Viewpoint can be found in your symposium pack

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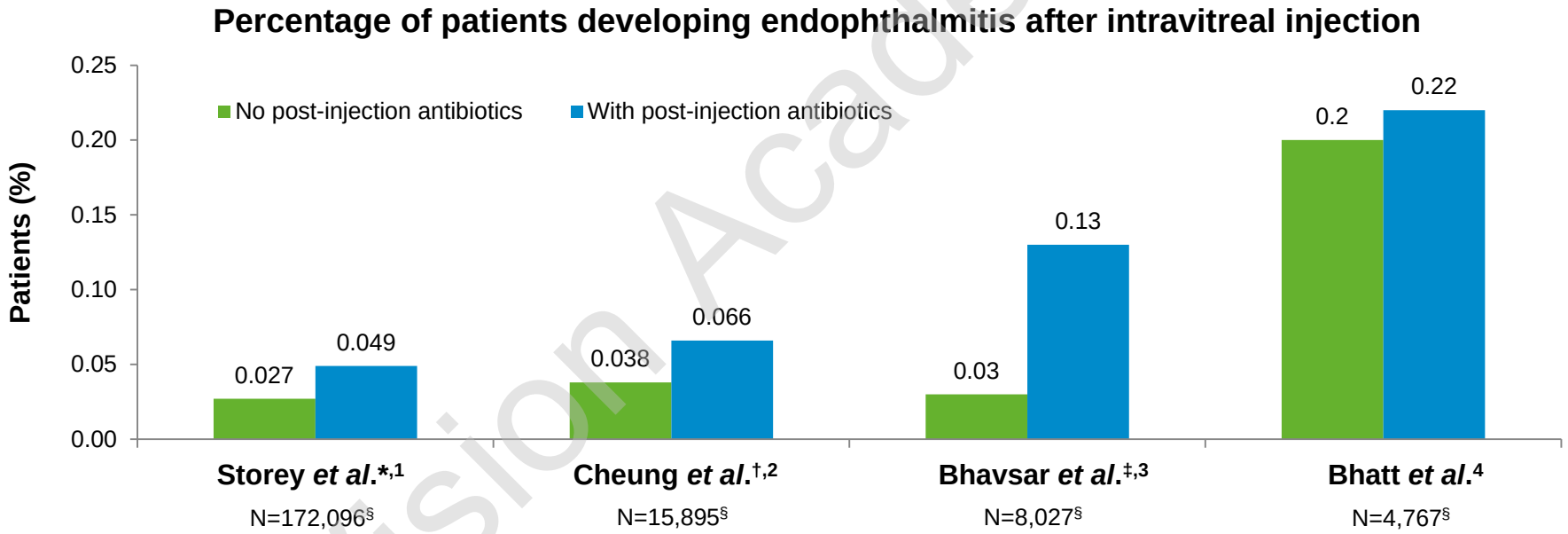
Debate:

Topical antibiotics should not be used alongside intravitreal injections

Professor Jean-François Korobelnik
University Hospital of Bordeaux,
France

Post-injection antibiotics have no effect on the rate of endophthalmitis

- Large studies have shown that the use of post-injection antibiotics does not reduce the incidence of endophthalmitis[1–4]



- A similar outcome was also reported in one of the largest (316,576 injections), retrospective, nationwide, studies conducted in France[5]

*For the Post-Injection Endophthalmitis Study Team. †8,259 patients were given antibiotics for 5 days after injection; 2,370 patients received antibiotics immediately after injection.
‡For the Diabetic Retinopathy Clinical Research Network. §Injections.

1. Storey P *et al. Graefes Arch Clin Exp Ophthalmol* 2016; 254 (2): 235–242. 2. Cheung CS *et al. Ophthalmology* 2012; 119 (8): 1609–1614. 3. Bhavsar AR *et al. Arch Ophthalmol* 2012; 130 (6): 809–810. 4. Bhatt SS *et al. Retina* 2011; 31 (10): 2032–2036. 5. Dossarps D *et al. Am J Ophthalmol* 2015; 160 (1): 17–25.e1.

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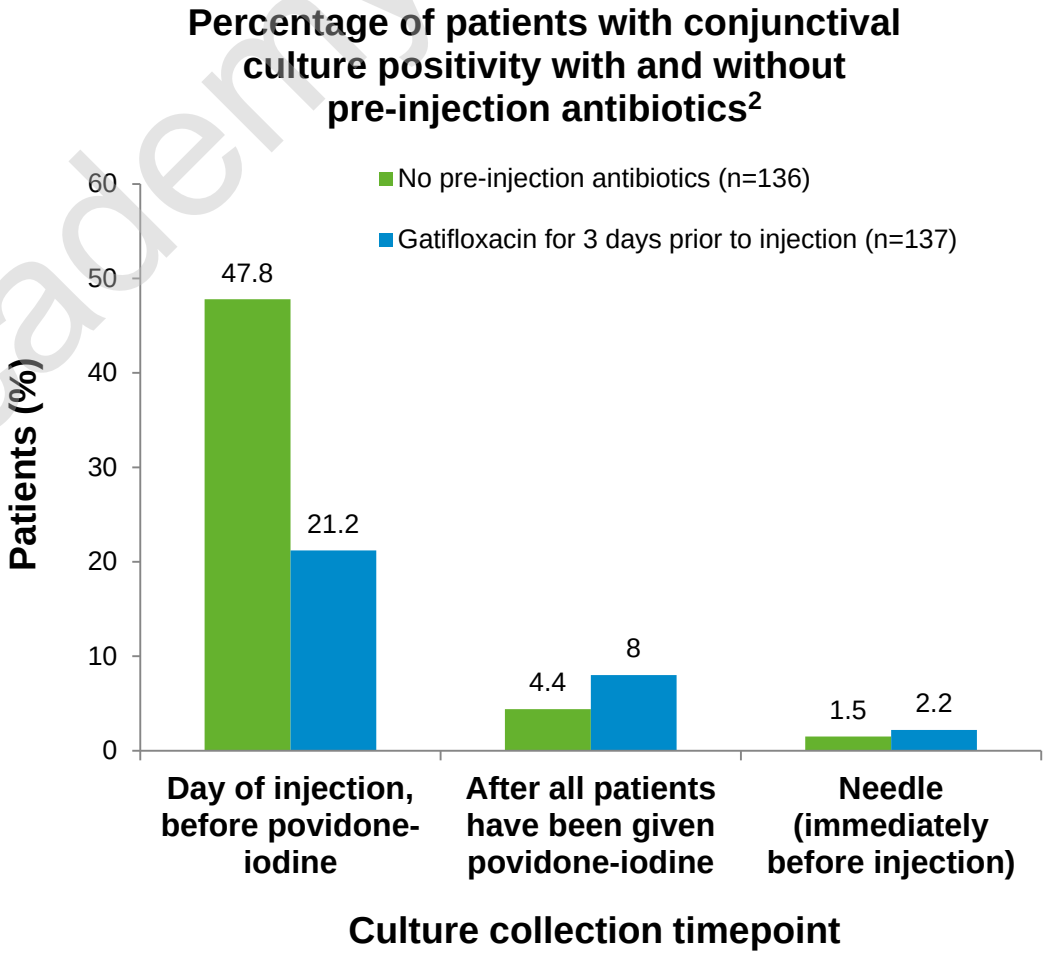
Pre-injection antibiotics are not associated with lower bacterial loads at the injection site*

- The use of topical antibiotics (combined with povidone-iodine) before cataract surgery has been shown to result in reduced colony counts[1]
- This benefit does not appear to translate to the use of topical antibiotics administered before an intravitreal injection
- **There is no additional benefit of pre-injection antibiotic use** when combined with povidone-iodine
  - Povidone-iodine reduces the number of bacterial colonies by 91%[3]
  - Povidone-iodine lowers the risk of endophthalmitis to 0.06% (vs. 0.24%)[4]



*When given in addition to povidone-iodine.

1. Isenberg SJ *et al*. *Arch Ophthalmol* 1985; 103 (9): 1340–1342. 2. Moss JM *et al*. *Ophthalmology* 2009; 116 (8): 1498–1501. 3. Apt L *et al*. *Arch Ophthalmol* 1984; 102 (5): 728–729.
4. Speaker MG *et al*. *Ophthalmology* 1991; 98 (12): 1769–1775.

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Use of antibiotics can interfere with models of care

- For patients on a PRN regimen with monthly monitoring, a requirement for pre-injection antibiotics would mean that intravitreal injections could not take place during the monitoring visit[1]
  - Increased burden of appointments for patients and clinics
- Post-injection antibiotics have been estimated to increase the financial burden to the US healthcare system by an additional $64 million per year[2]

Burden on the patient

Additional clinic visits may affect adherence to treatment

Burden on clinic capacity

Increased clinic visits require resources and clinician time

Burden on the healthcare system

Increased costs of delivering intravitreal therapy

PRN, *pro re nata* (as needed).

1. Hunyor AP *et al. Acta Ophthalmologica* 2016. Review: Topical antibiotics and intravitreal injections – manuscript in press. 2. Chen RW *et al. JAMA Ophthalmol* 2013; 131 (7): 840–842.

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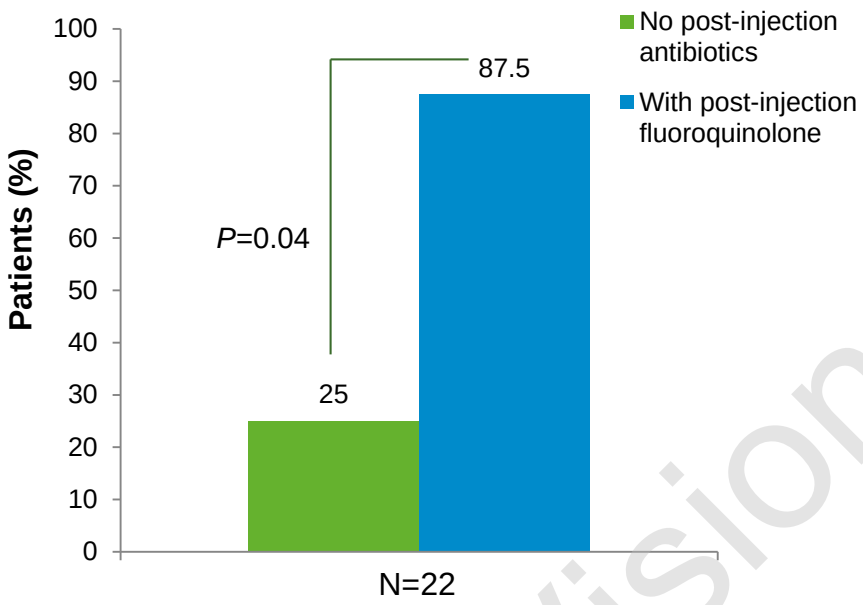
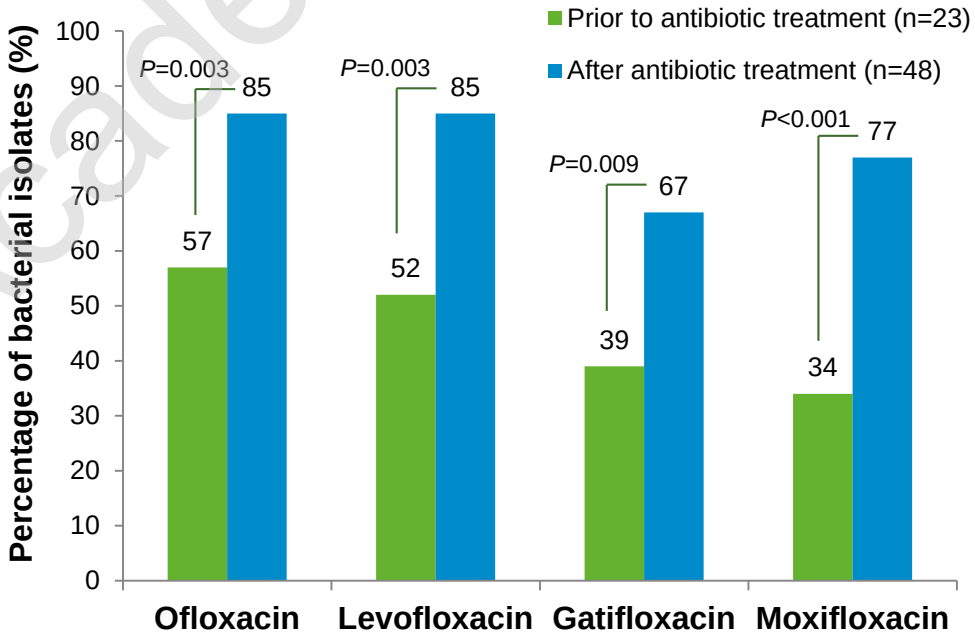
Use of topical antibiotics increases antibiotic resistance

Percentage of patients with ocular colonies resistant to fluoroquinolones[1]



Percentage of conjunctival bacterial isolates resistant to fluoroquinolones, before and after 3 intraocular injections with post-injection antibiotics[2]



Use of povidone-iodine alone with intravitreal injections does **NOT** lead to bacterial resistance[3]

1. Milder E *et al*. *Ophthalmology* 2012; 119 (7): 1420–1424. 2. Kim SJ *et al. Ophthalmology* 2011; 118 (7): 1358–1363. 3. Hsu J *et al. Am J Ophthalmol* 2014; 157 (3): 514–518.e1.

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Lack of antibiotic penetration into the vitreous

- A prospective randomized study demonstrated that topical antibiotic administration leads to effective levels in the aqueous but not in the vitreous
  - The concentrations in the vitreous did not exceed the MIC_{90} for the most common bacterial pathogens causing acute postoperative endophthalmitis

Topical antibiotic	Mean vitreous concentration ± SD (µg / mL)		MIC_{90} (µg / mL)		
	3-day pre-surgery regimen* (n=3)	1 hour pre-surgery regimen† (n=3)	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*Staphylococcus pneumoniae*
Moxifloxacin 0.5%	0.011 ± 0.008	0.012 ± 0.011	0.064	0.047	0.125
Gatifloxacin 0.3%	0.008 ± 0.006	0.001 ± 0.0003	0.11	0.09	0.22

*4 doses per day for three days prior to surgery (patient administered; 100% patient compliance); †1 drop every 15 minutes for a total of 3 doses administered 1 hour prior to surgery.
MIC_{90}, minimum inhibitory concentration for 90% of isolates; SD, standard deviation.
Costello P *et al*. *Retina* 2006; 26 (2): 191–195.

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Debate:

Is there a case FOR topical antibiotics with intravitreal injections?

Professor Anat Loewenstein
Tel Aviv Sourasky Medical Center, Israel

Risk of endophthalmitis with intravitreal injections

- Endophthalmitis is an uncommon, potentially devastating, complication of intravitreal injection[1]
  - Occurrence ranges from 1 in 1,000 to 1 in 5,000 injections[2]
  - Despite appropriate prompt therapy, visual outcomes are often poor[3]
- Risk reduction strategies for prevention of endophthalmitis are particularly important for improving overall patient outcomes[3]

1. Sachdeva MM *et al*. *J Ophthalmic Inflamm Infect* 2016; 6 (1): 2. 2. Sigford DK *et al*. *Clin Ophthalmol* 2015; 9: 773–781. 3. Schwartz SG *et al*. *Curr Pharm Des* 2015; 21 (32): 4703–4706.

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Precautions for endophthalmitis prevention

General consensus on:

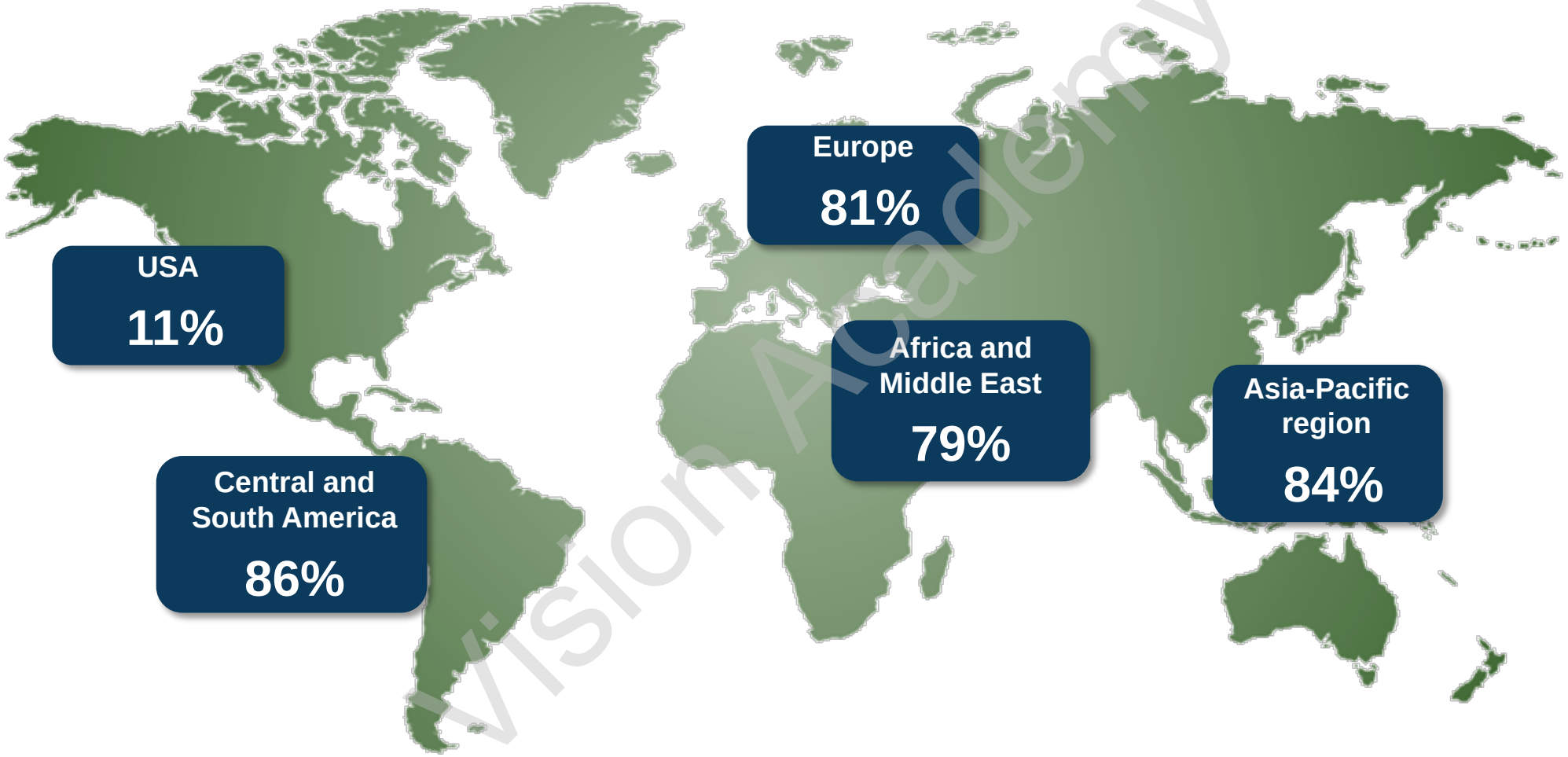
- Meticulous preparation
  - Avoidance of needle contact with eyelashes
  - Eyelid speculum
  - Drapes
- Careful attention to aseptic technique
- Povidone-iodine use
  - On ocular surface, in conjunctival cul-de-sac

Lack of consensus on:

- Use of sterile gloves
- Movement of conjunctiva over injection site
- **Use of pre-/post-injection antibiotics**

2014 ASRS PAT survey:

Percentage of physicians using topical antibiotics with intravitreal injections*



*Total percentage of physicians who prescribe topical antibiotics only in selected patients, or at any stage of the intravitreal injection process.
ASRS, American Society of Retina Specialists; PAT, Preferences and Trends.
Rezaei KA *et al*. 2014 Global Trends in Retina Survey. American Society of Retina Specialists; Chicago, IL, USA, 2014.

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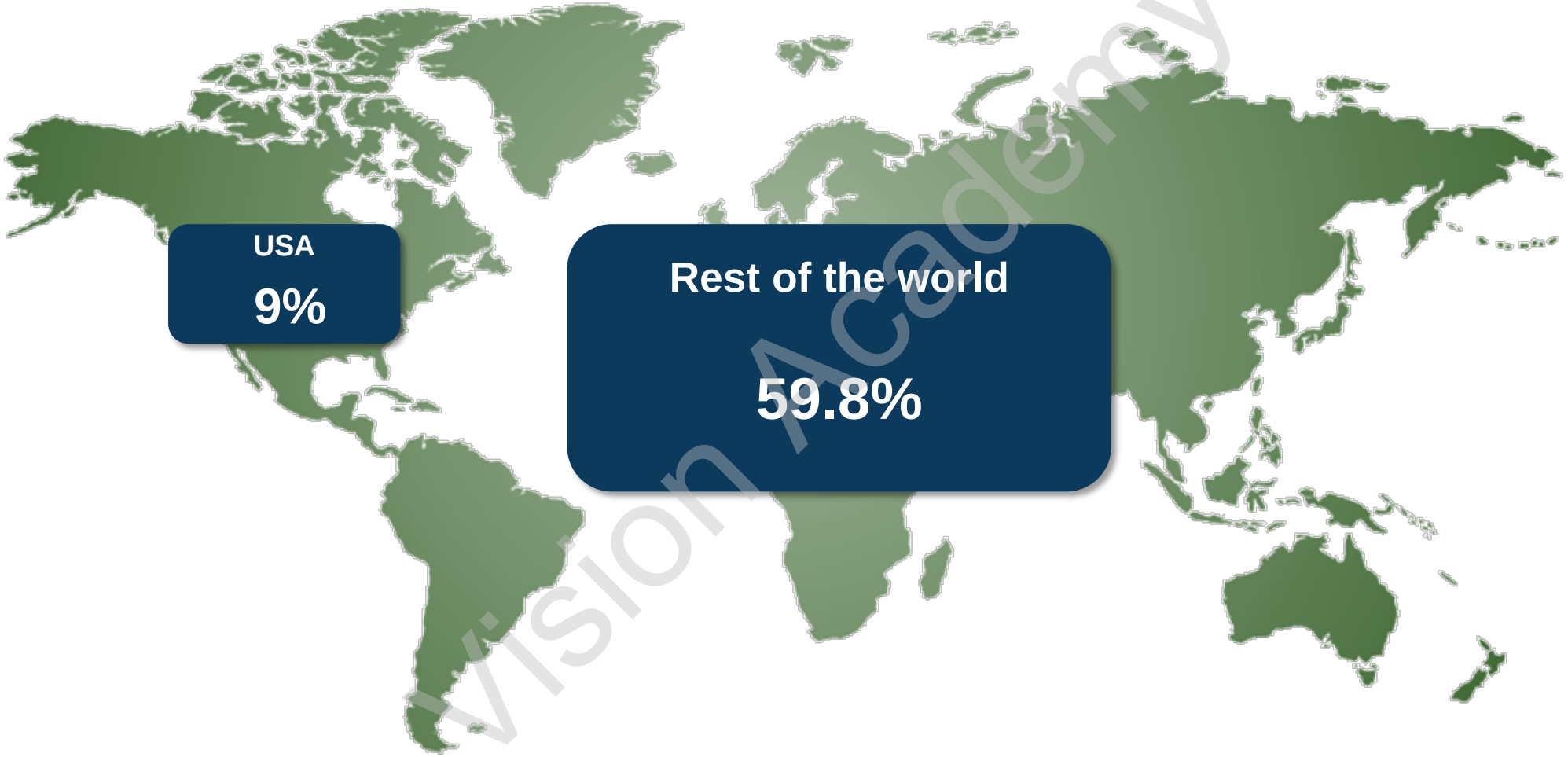
2015 ASRS PAT survey:

Percentage of physicians using topical antibiotics with intravitreal injections*



*Total percentage of physicians who prescribe topical antibiotics only in selected patients, or at any stage of the intravitreal injection process.
ASRS, American Society of Retina Specialists; PAT, Preferences and Trends.
Stone TW *et al*. 2015 Preferences and Trends Membership Survey. American Society of Retina Specialists; Chicago, IL, USA, 2015.

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Regional considerations

Possible reasons for regional variations:

- Perceived as ‘standard of care’ in some regions
- Personal preference
- Medico-legal considerations
- Mandated by label in some regions, e.g. Japan
- Resources and conditions vary between countries

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Intravitreal injection technique and monitoring: Updated guidelines of an expert panel

- The dramatic increase in the number of IVT injections has been accompanied by a comparable increase in evidence surrounding IVT practice patterns and techniques
- An expert panel of ophthalmologists performed a review of the literature regarding intravitreal injections and concluded that:

IVT, intravitreal.
R. L. Avery et al. *Retina* 2014; 34: S1–S18

Intravitreal injection technique and monitoring: Updated guidelines of an expert panel

- The dramatic increase in the number of IVT injections has been accompanied by a comparable increase in evidence surrounding IVT practice patterns and techniques
- An expert panel of ophthalmologists performed a review of the literature regarding intravitreal injections and concluded that:
  - There was a **lack of evidence** to support the routine use of pre-, peri-, and post-injection antibiotics to reduce the risk of endophthalmitis
  - There was a lack of evidence to support the role of aerosolized droplets containing oral contaminants from the patient and/or providers as a potential source of infection
- The panel emphasized the continued importance of applying povidone–iodine and avoiding eyelid contact with the intended injection site and needle

IVT, intravitreal.

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Intravitreal injection technique and monitoring: Updated guidelines of an expert panel

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Antibiotic Use

There is insufficient evidence to support the routine use of pre-, peri-, or postinjection antibiotics to reduce the rate of endophthalmitis.

They are not against antibiotics!

IVT, intravitreal.
R. L. Avery et al. *Retina* 2014; 34: S1–S18

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Is there a case FOR topical antibiotics with intravitreal injections?

Study	Injections	Retinal diseases treated	Endophthalmitis rate with topical antibiotics	Endophthalmitis rate without topical antibiotics	Statistical significance
Bhatt *et al.* 2011	4,767	Multiple	0.22%	0.20%	Not significant
Bhavsar *et al*. 2012	8,027	DME and PDR	0.13%	0.03%	Not significant
Cheung *et al*. 2012	15,895	Multiple	0.061–0.084%	0.038%	Not significant
Falavarjani *et al.* 2013	5,901	Multiple	0.10%	0%	Not significant
Park *et al.* 2013	17,332	Multiple	0%	0.035%	Not significant
Porteous *et al.* 2014	6,957	Not specified	Not applicable	0.04%	Not significant
Ramel *et al.* 2014	11,450	Not specified	0.03%	0.23%	*P*=0.024
Storey *et al.* 2014	117,171	Multiple	0.049%	0.032%	Not significant
Bhavsar *et al.* 2015	18,839	Multiple	0.005%	Not applicable	Not applicable
Meredith *et al.* 2015	18,509	Neovascular AMD	0.04–0.08%	0.15%	Not significant
Falavarjani *et al.* 2015	8,037	Multiple	0.01%	0%	Not significant

AMD, age-related macular degeneration; DME, diabetic macular edema; PDR, proliferative diabetic retinopathy.
Schwartz SG *et al*. *Curr Pharm Des* 2015; 21 (32): 4703–4706.

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What is the Vision Academy's position?

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Vision Academy Viewpoint:

Use of topical antibiotics with intravitreal injections

Based on an extensive literature search, the Vision Academy does not recommend the use of topical antibiotics alongside intravitreal injections

There is no evidence for prevention of infection[1]

There is no evidence for reduction of infection-related morbidity[2]

Repeated use is proven to increase the occurrence of antibiotic resistance and can potentially increase virulence[1]

There is an additional, unnecessary cost and burden to patients, physicians, and healthcare systems[1]

1. Merani R *et al*. *Int J Retina Vitreous* 2015; 1: 9. 2. Hunyor AP *et al. Acta Ophthalmologica* 2016. Review: Topical antibiotics and intravitreal injections – manuscript accepted.

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Vision Academy Viewpoint:

Use of topical antibiotics with intravitreal injections

Topical antibiotic use **prior to** intravitreal injection

- Most infections result from inoculation of organisms at the time of injection
- No prospective studies demonstrating that pre-injection antibiotics reduce the risk of endophthalmitis[1]

Topical antibiotic use **concurrent with** or **after** intravitreal injection

- No additional benefit of post-injection antibiotics in preventing endophthalmitis[2,3]

General consensus

Variation in opinion

1. Merani R *et al. Int J Retina Vitreous* 2015; 1: 9. 2. Li AL *et al. Retina* 2016; 36 (7): 1349–1356. 3. Storey P *et al. Ophthalmology* 2014; 121 (1): 283–289.

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Vision Academy Viewpoint:

Use of topical antibiotics with intravitreal injections

Antibiotic resistance

- Several studies have demonstrated increasing resistance of conjunctival flora to topical antibiotics[1,2]
- Resistance to fluoroquinolones, the most commonly used topical antibiotics in many regions, may have serious ramifications in other procedures, e.g. cataract surgery

Antibiotic penetration

- Topical administration leads to effective antibiotic levels in the aqueous but not in the vitreous[3]

General consensus

Variation in opinion

1. Merani R *et al. Int J Retina Vitreous* 2015; 1: 9. 2. Milder *et al. Ophthalmology* 2012; 119: 1420–1424. 3. Costello P *et al. Retina* 2006; 26 (2): 191–195.

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Vision Academy Viewpoint:

Use of topical antibiotics with intravitreal injections

Significant regional differences

- Reasons for continued use of topical antibiotics with intravitreal injections include:
  - Personal preference
  - Peer pressure
  - Medico-legal concerns

- Changes in practice habits may be achieved through the revision of drug labels and the amendment of local and professional society guidelines

General consensus

Variation in opinion

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Summary

The Vision Academy **does not recommend the use of topical antibiotics** alongside intravitreal injections

There is a **lack of evidence** supporting any benefit for topical antibiotic prophylaxis against post-injection endophthalmitis

There is a growing body of evidence detailing **increased antibiotic resistance** in patients receiving topical antibiotics

Product information for intravitreal medications should be updated to reflect this recommendation and to **remove barriers to clinicians wishing to change their practice**