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CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

APPENDIX A: THE BRADFORD HILL CRITERIA FOR CAUSALITY

Criteria	Meaning
Strength of association	A strong association is more likely to have a causal component than is a modest association. Strength of the association is determined by the types of existing studies. The highest level studies from the evidence pyramid would represent the strongest associations (i.e., RCTs and systematic reviews with meta-analyses) Results from these studies must demonstrate an odds ratio or relative risk of at least 2.0 or above in order to be meaningful. Anything between 1 and 2 is weak while >2 is moderate and >4 is considered strong.
Consistency	A relationship is repeatedly observed in all available studies.
Specificity	A factor influences specifically a particular outcome or population. The more specific an association between a factor and an effect, the greater the probability that it is causal.
Temporality	The cause must precede the outcome it is assumed to affect (e.g., smoking before the appearance of lung cancer). Outcome measured over time (longitudinal study).
Biological gradient (dose–response)	The outcome increases monotonically with increasing dose of exposure or according to a function predicted by a substantive theory (e.g., the more cigarettes one smokes, the greater the chance of the cancer occurring).
Plausibility	The observed association can be plausibly explained by substantive matter (i.e., biologically possible).
Coherence	A causal conclusion should not fundamentally contradict present substantive knowledge. (Studies must not contradict each other.)
Experiment	Causation is more likely if evidence is based on randomized experiments or a systematic review of randomized experiments. However, these RCTs may not be ethically possible and thus prospective rather than experimental studies, such as cohort studies, may be the highest level of evidence available.
Analogy	For analogous exposures & outcomes an effect has already been shown (e.g., effects first demonstrated on animals or an effect previously occurring on humans such as the effects of thalidomide on a fetus during pregnancy).

Source: Lavigne SE. From Evidence to Causality: How Do We Determine Causality? [Online course]. 2018. Available from: www.dentalcare.com/en-us/professional-education/ce-courses/ce530

APPENDIX B: EXCLUDED STUDIES AND REASONS FOR EXCLUSION

	Author	Year	Study type	Reason for exclusion
1	Abariga SA ³⁵	2016	SR of observational studies	RCTs not included
2	Borell LN ³⁶	2011	Critical summary	Summary, not an actual study
3	Borgnakke WS ²	2013	SR of observational studies	RCTs not included
4	Boyd L ³⁷	2012	Literature review	Not a SR or MA
5	Cao R ³⁸	2019	SR, network MA	Network study and included antibiotics
6	Darré L ³⁹	2008	MA of interventional studies	Mixture of controlled and non-controlled studies and were too old
7	Engebretson S ¹⁶	2013	SR/MA	Included a mixture of treatment modalities not just NSPT
8	Grellmann AP ⁴⁰	2016	MA	Adjuvant antimicrobials main focus
9	Hsu Y-T ⁴¹	2019	SR of cohort studies	RCTs not included and outcome measure not HbA1c
10	Janket S-J ⁴²	2014	Critical summary	Summary, not an actual study
11	Liccardo D ⁴³	2019	Literature review	Not a SR or MA
12	Liew AKC ⁴⁴	2013	MA	Included mixed interventions/ antimicrobials
13	Lima RPE ⁴⁵	2018	SR	Different outcome measures
14	Lira Junior R ⁴⁶	2017	SR	All studies combined SRP with antibiotics
15	Madianos PN ⁴⁷	2018	Review of MAs	Mixture of T1 and T2; antibiotics