eTABLE 1. Relative and absolute desirable and undesirable effects (95% CI) from randomized controlled tirals and certainty in the evidence for systemic antibiotics compared to no systemic antibiotic for symptomatic irreversible pulpitis with or without symptomatic apical periodontitis in immunocompetent adults

Systemic antibiotics compared to no systemic antibiotic for symptomatic irreversible pulpitis with or without symptomatic apical periodontitis in immunocompetent adults

Patient or population: immunocompetent adults with symptomatic irreversible pulpitis with or without symptomatic apical periodontitis
Setting: dental settings where definitive, conservative dental treatment is not immediately available
Intervention: systemic antibiotics
Comparison: no systemic antibiotic

Outcomes[*]	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect[†] (95% Confidence Interval)	Anticipated absolute effects	
				Risk with no systemic antibiotic[‡]	Risk difference with systemic antibiotics[§]
Pain intensity at 24 hours	40 (1 RCT) [¶]	⨁⨁◯◯ LOW [#]	-	The mean pain intensity at 24 hours was **1.35**	MD **0.35 higher** (0.21 lower to 0.91 higher)
Pain experience at 24 hours	40 (1 RCT) [¶]	⨁⨁◯◯ LOW [**]	**RR 1.20** (0.68 to 2.11) [††]	500 per 1,000	**100 more per 1,000** (160 fewer to 555 more) [††]
Pain intensity at 48 hours	40 (1 RCT) [¶]	⨁⨁◯◯ LOW [#]	-	The mean pain intensity at 48 hours was **1.35**	MD **0.2 higher** (0.35 lower to 0.75 higher)
Pain experience at 48 hours	40 (1 RCT) [¶]	⨁⨁◯◯ LOW [**]	**RR 1.22** (0.65 to 2.29) [††]	450 per 1,000	**99 more per 1,000** (158 fewer to 581 more) [††]
Pain intensity at 72 hours	40 (1 RCT) [¶]	⨁⨁◯◯ LOW [#]	-	The mean pain intensity at 72 hours was **1.35**	MD **0** (0.5 lower to 0.5 higher)
Pain experience at 72 hours	40 (1 RCT) [¶]	⨁⨁◯◯ LOW [**]	**RR 1.00** (0.47 to 2.14) [††]	400 per 1,000	**0 fewer per 1,000** (212 fewer to 456 more) [††]
Pain intensity at 7 days	40 (1 RCT) [¶]	⨁⨁◯◯ LOW [#]	-	The mean pain intensity at 7 days was **1.35**	MD **0.15 lower** (0.75 lower to 0.45 higher)
Pain experience at 7 days	40 (1 RCT) [¶]	⨁⨁◯◯ LOW [**]	**RR 0.89** (0.43 to 1.83) [††]	450 per 1,000	**49 fewer per 1,000** (257 fewer to 374 more) [††]
Total number of NSAID (tablets) used	40 (1 RCT) [¶]	⨁⨁◯◯ LOW [#]	-	The mean total number of NSAID (tablets) used was **9.6**	MD **0.4 lower** (4.23 lower to 3.43 higher)
Total number of acetaminophen with codeine (tablets) used	40 (1 RCT) [¶]	⨁⨁◯◯ LOW [‡‡]	-	The mean total number of acetaminophen with codeine (tablets) used was **4.45**	MD **2.45 higher** (1.23 lower to 6.13 higher)

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes:

[*] No studies meeting our selection criteria reported data on malaise, trismus, fever, cellulitis, additional dental visit, additional medical visit, allergic reaction, endodontic flare-up, diarrhea, *Clostridium difficile* infection, or repeat procedure for this population. Fouad 1996 did report intra-oral swelling, but due to symptom inconsistencies with a clinical diagnosis of symptomatic irreversible pulpitis with or without symptomatic apical periodontitis, we did not extract this data.

[†] RR: Risk ratio.

[‡] For dichotomous outcomes, we calculated absolute treatment effects by using the control group's baseline risk as the assumed control intervention risk.

[§] MD: Mean difference

[¶] Nagle 2000.

[#] Serious issues of imprecision due to small sample size.

[**] Very serious issues of imprecision due to small sample size and the confidence interval suggests a large benefit and a large harm.

[††] For Nagle 2000, the data for the outcome of pain was dichotomized (VAS from 0-3) as follows: "no pain" and "mild pain" were coded as "no pain," and "moderate pain" and "severe pain" were coded as "pain."

[‡‡] Very serious issues of imprecision due to small sample size and the confidence interval suggests both a small benefit and a large harm.

eTABLE 2. Magnitude of undesirable effects related to antibiotic use from observational studies and certainty in the evidence.

Systemic antibiotics compared to no systemic antibiotics for dental conditions

Patient or population: any person of any age presenting in any dental setting in the United States
Setting: any dental setting in the United States
Exposure: any systemic antibiotics
Non-exposure: no systemic antibiotic

Outcome[*]	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
Community-associated *Clostridium difficile (C. difficile)* infections	(2 observational studies) [†,‡]	⊕⊕⊕◯ MODERATE [§]	Out of 10,000 people with a community-associated *C. difficile* infection in 2011, approximately 6,400 were probably exposed to antibiotics.[¶]
Community-associated *C. difficile* infection related to a dental prescription for antibiotics	(3 observational studies) [†,‡,#]	⊕◯◯◯ VERY LOW [**]	Out of 10,000 people with a community-associated *C. difficile* infection in 2011, approximately 640 may have been exposed to antibiotics received from a dentist. [¶,††,‡‡]
Mortality due to community-associated *C. difficile* infections	(2 observational studies) [†,‡]	⊕⊕⊕◯ MODERATE [§]	Out of 10,000 people with a community-associated *C. difficile* infection in 2011, approximately 80 people probably died due to exposure to antibiotics. [¶]
Antibiotic-resistant infections	(1 observational study) [§§]	⊕⊕◯◯ LOW	At least 2 million people may experience an antibiotic-resistant infection annually in the United States.
Mortality due to antibiotic-resistant infections	(1 observational study) [§§]	⊕⊕◯◯ LOW	Annually, there may have been approximately 23,000 deaths due to antibiotic-resistant infections.
Community-associated *C. difficile* infection related costs	(2 observational studies) [†,¶¶]	⊕⊕⊕◯ MODERATE [§]	In 2011, the mean community-associated *C. difficile*-attributable cost was likely $3 billion.
Community-associated *C. difficile* infection costs associated with a dental prescription for antibiotics	(2 observational studies) [†,#,¶¶]	⊕◯◯◯ VERY LOW [**]	We approximated that in 2011 $300 million may have been related to community-associated *C. difficile* infections that were associated with a dental prescription for antibiotics.[††,‡‡,##]
Antibiotic-resistant infection related costs	(1 observational study) [§§]	⊕⊕◯◯ LOW	In 2008, antibiotic resistance may have caused $20 billion direct costs with an additional $35 billion associated with productivity losses.
Antibiotic-resistant infection related costs associated with a dental prescription for antibiotics	(2 observational studies) [#,§§]	⊕◯◯◯ VERY LOW [**]	We approximate that $2 billion in direct costs with an additional $3.5 billion associated with productivity losses may have been related to antibiotic resistance associated with a dental prescription for antibiotics.[††,‡‡,##]
Admission to hospital due to community-associated *C. difficile* infection	(2 observational studies) [†,‡]	⊕⊕⊕◯ MODERATE [§]	Out of 10,000 people with a community-associated *C. difficile* infection, probably 1,270 patients probably listed community-associated *C. difficile* infection as the primary reason for admission to the hospital.
Admission to hospital due to antibiotic-resistant infection	(1 observational study) [***]	⊕⊕◯◯ LOW	In 2006, infection related hospitalizations associated with antibiotic-resistant infections may have accounted for 2.4% of all infection related hospitalizations.
Admission to hospital due to antibiotic-resistant infection associated with a dental prescription for antibiotics	(1 observational study) [#,***]	⊕◯◯◯ VERY LOW [**]	We approximated that in 2006, 0.24% of infection related hospitalizations due to antibiotic-resistant infections may have been associated with a dental prescription for antibiotics.[††,‡‡,##]
Length of hospital stay due to community-associated *C. difficile* infection	(1 observational study) [¶¶]	⊕⊕◯◯ LOW	The average community-associated *C. difficile*-attributable length of stay due to community-associated *C. difficile* infection may be 5.7 days (Range 2.1 – 33.4).
Length of hospital stay due to antibiotic-resistant infections	(1 observational study) [†††]	⊕⊕◯◯ LOW	In 2014, the average length of hospital stay due to bacterial infections and infections associated with multidrug-resistant organisms (i.e. Methicillin-resistance *Staphylococcus aureus* and other multidrug-resistant organisms) may range from 9.45 days (SD 11.81) – 9.47 days (SD 11.59).

Systemic antibiotics compared to no systemic antibiotics for dental conditions

Patient or population: any person of any age presenting in any dental setting in the United States
Setting: any dental setting in the United States
Exposure: any systemic antibiotics
Non-exposure: no systemic antibiotic

Outcome[*]	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
Anaphylaxis due to antibiotics	(1 observational study) [‡‡‡]	⊕⊕◯◯ LOW	Out of 10,000 hospitalizations between 1995 and 2013, approximately 46 patients may have reported anaphylaxis due to a penicillin drug class.[¶] Out of 10,000 hospitalizations between 1995 and 2013, approximately 2 patients may have reported anaphylaxis due to amoxicillin.[¶] Out of 10,000 hospitalizations between 1995 and 2013, approximately 6 patients may have reported anaphylaxis due to a cephalosporin drug class.[¶] Out of 10,000 hospitalizations between 1995 and 2013, approximately 1 patient may have reported anaphylaxis due to cephalexin.[¶]
Anaphylaxis due to antibiotics associated with a dental prescription	(2 observational studies) [#,‡‡‡]	⊕◯◯◯ VERY LOW [**]	Out of 100,000 hospitalizations between 1995 and 2013, approximately 46 patients may have reported anaphylaxis due to a penicillin drug class and received the antibiotic from a dentist.[¶,††,‡‡] Out of 100,000 hospitalizations between 1995 and 2013, approximately 2 patients may have reported anaphylaxis due to amoxicillin and received the antibiotic from a dentist.[¶,††,‡‡] Out of 100,000 hospitalizations between 1995 and 2013, approximately 6 patients may have reported anaphylaxis due to a cephalosporin drug class and received the antibiotic from a dentist.[¶,††,‡‡] Out of 100,000 hospitalizations between 1995 and 2013, approximately 1 patient may have reported anaphylaxis due to cephalexin and received the antibiotic from a dentist.[¶,††,‡‡]

Footnotes

[*] No studies meeting our selection criteria reported data on mortality due to community-associated *C. difficile* infections related to a dental prescription for antibiotics, mortality due to antibiotic-resistant infections associated with a dental prescription for antibiotics, cost-effectiveness of antibiotics to treat symptomatic irreversible pulpitis with or without symptomatic apical periodontitis, pulp necrosis and symptomatic apical periodontitis, or pulp necrosis and localized acute apical abscess, admission to hospital due to community-associated *C. difficile* infections related to a dental prescription for antibiotics, length of hospital stay due to community-associated *C. difficile* infection related to a dental prescription for antibiotics, length of hospital stay due to antibiotic-resistant infections associated with a dental prescription for antibiotics, allergic reaction due to antibiotics, allergic reaction due to antibiotics associated with a dental prescription, fatal anaphylaxis due to antibiotics, or fatal anaphylaxis due to antibiotics associated with a dental prescriptions.

[†] Considerations for Lessa 2015: 1) the case definition of *C. difficile* infection relying only on positive test results for *C. difficile* toxin or molecular assay from unformed samples sent to laboratories may lead to an underestimation of the true burden (i.e. partially formed samples being untested), 2) there is the possibility for an underestimation of "both recurrence and mortality, given that [they] assessed only first recurrences and deaths that were documented in the medical record," 3) there is a potential over diagnosis or an overestimation of the burden of *C. difficile* infection due to diagnostic tests being highly sensitive (i.e. a poor distinction between colonization and the disease), and 4) authors estimated the recurrence of and mortality due to *C. difficile* infection by using a random sample of cases that may or may not be representative of the United States rates.

[‡] Considerations for Chitnis 2013: 1) Potential issues of generalizability to the United States population given that patients included in the analysis with community-associated *C. difficile* infection were more likely to be white and female, 2) only a convenience sample of stools were sent for definitive testing (40%), 3) although antibiotic use within 12 weeks was adjudicated based on a telephone interview (self-reported) and medical records it is unclear as to how many cases were confirmed using both methods, and 4) hospitalization in which *C. difficile* infection was primary reason for admission was ascertained through medical records.

[§] Upgraded due to a large effect based on observational studies without important risk of bias or other limitations.

[¶] This is likely an overestimation of the effect of dental prescriptions for antibiotics because the provided information/data did not differentiate between inpatient and outpatient antibiotic prescriptions. We assume that prescribing for dental conditions rarely occurs in inpatient settings.

[#] Considerations for Hicks 2015: 1) Dentistry accounts for 10% of the total outpatient antibiotic prescriptions in the United States, 2) the magnitude of antibiotic prescriptions may not necessarily represent the magnitude of antibiotic consumption by patients, 3) possible underestimation due to the total number of prescriptions from other non-dental professionals (e.g., emergency medicine services, etc.) for any dental condition not being included in the estimate, and 4) according to Roberts et al , estimates related to antibiotic prescribing practices reported by Hicks et al correspond to that of general dentists and not all dental specialties combined.

[**] Downgraded due to serious issues of indirectness related to estimates being extrapolated to illustrate the burden in a dental setting.

[††] Data was adjusted considering that dentistry accounts for 10% of total outpatient antibiotic prescriptions in the United States.

[‡‡] The presented estimate assumes that dental prescriptions for any antibiotic has the same potential of inducing antibiotic resistance as non-dental related prescriptions.

[§§] Considerations for Centers for Disease Control and Prevention 2013: 1) No reports containing methods or results is linked to this report, 2) estimates used from this report are likely an underestimation of the true burden of antibiotic resistance related outcomes, and 3) the magnitude of antibiotic resistance related outcomes may not necessarily represent the magnitude of antibiotics prescribed for and consumed by patients.

[¶¶] Considerations for Zhang 2016: 1) All included studies in the Zhang review reported direct medical costs from a hospital perspective; indirect costs to patients and society, and costs of additional care after hospital discharge have not been captured (e.g., productivity loss due to work day losses, costs in long-term care facilities, etc.). About 9% of *C. difficile* infection patients were discharged to a long-term care facility for an average of 24 days of after-care, which would result in an additional $141 million burden on the healthcare system and society due to long-term care facility transfers, 2) primary *C. difficile* infections were not separated for the estimation of recurrent *C. difficile* infection costs, 3) discrepancy in case definitions in cost studies versus surveillance/epidemiological studies (e.g., community- vs health care-associated *C. difficile* infections), and 4) the total costs of *C. difficile* infection in the United States may be higher than the reported estimate.

[##] This is likely an overestimation of the effect of dental prescriptions for antibiotics due to the primary study not measuring or reporting antibiotic exposure.

[***] Considerations for Mainous 2011: 1) the methods did not allow us to determine whether the infection arose in the hospital or if patients were colonized or infected prior to admission, 2) ICD-9-CM diagnosis codes were used instead of laboratory results on bacterial cultures ,and 3) “greater awareness of drug resistance among hospital coding departments may have prompted more attention to adding these codes to discharge records of patients who were relatively healthy and discharged without incident.”

[†††] Considerations for Johnston 2019: 1) ICD-9-CM diagnosis codes were used instead of laboratory results on bacterial cultures, 2) authors were unable to distinguish between hospital-acquired and community-acquired infections, and 3) 10% of the eligible population was excluded due to missing data.

[‡‡‡] Considerations for Dhopeshwarkar 2019: 1) the estimates presented in this study only include penicillin and cephalosporin drug classes and amoxicillin and cephalexin drugs, and does not include other individual drugs commonly prescribed by dentists such as clindamycin (Durkin et al), 3) there may be issues of generalizability as only patients from two Boston-area hospitals were included in this analysis and may not be representative of inpatient populations admitted to other United States hospitals, 4) there is a potential overestimate of the occurrence of anaphylaxis due to reported cases not being confirmed by tryptase tests, 5) possible underestimation due to exclusion of codes listed in electronic health records not directly linking to anaphylaxis, and 6) there is uncertainty surrounding if the estimates of the reported or observed cases of anaphylaxis resulted in death.

eTABLE 3. Calculations of the magnitudes of harms related to antibiotic use.

Systemic antibiotics compared to no systemic antibiotics for dental conditions

Patient or population: any person of any age presenting in any dental setting in the United States
Setting: any dental setting in the United States
Exposure: any systemic antibiotics
Non-exposure: no systemic antibiotic

Outcome[*]	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Calculation of impact
Community-associated *Clostridium difficile (C. difficile*) infections	(2 observational studies) [†,‡]	⊕⊕⊕◯ MODERATE [§]	Of the estimated cases of community-associated *C. difficile* infections, approximately 64% were exposed to antibiotics in 2011. This represents 102,409 cases out of 159,700 total *C. difficile* infections (95% CI 85,056 – 119,040).[¶]
Community-associated *C. difficile* infection related to a dental prescription for antibiotics	(3 observational studies) [†,‡,#]	⊕◯◯◯ VERY LOW [**]	We approximated that 6.4% of people with community-associated *C. difficile* infections who were exposed to antibiotics received the prescription from a dentist. This represents 10,221 cases out of 159,700 total *C. difficile* infections in 2011 (95% CI 8,506 – 11,904). [¶,††,‡‡]
Mortality due to community-associated *C. difficile* infections	(2 observational studies) [†,‡]	⊕⊕⊕◯ MODERATE [§]	In 2011, approximately 2000 out of 159,700 people infected with community-associated *C. difficile* infection died within 30 days of diagnosis (95% CI 1,200 –2,800). Of the estimated cases of community-associated *C. difficile* infection, approximately 64% were exposed to antibiotics. 1,280 people died due to community-associated C. difficile infection related to exposure to antibiotics (95% CI 768 – 1792). This represents a 0.8% mortality rate due to community-associated *C. difficile* infection related to exposure to antibiotics.[¶]
Antibiotic-resistant infections	(1 observational study) [§§]	⊕⊕◯◯ LOW	Estimate taken directly from report.
Mortality due to antibiotic-resistant infections	(1 observational study) [§§]	⊕⊕◯◯ LOW	Estimate taken directly from report.
Community-associated *C. difficile* infection related costs	(2 observational studies) [†,¶¶]	⊕⊕⊕◯ MODERATE [§]	The estimated cost due to community-associated *C. difficile* infection in 2015, reported in Zhang 2016, was $20,085. The estimated cases of community-associated *C. difficile* infection in 2011, as reported in Lessa 2015, was 159,700 cases. The United States Department of Labor inflation calculator (https://www.bls.gov/data/inflation_calculator.htm) was used to convert the value of a 2015 United States dollar to the value of a 2011 United States dollar, which equates to $19,163.40. $19,163.40 * 159,700 cases of *C. difficile* infection in 2011 = $3,060,394,980
Community-associated *C. difficile* infection costs associated with a dental prescription for antibiotics	(2 observational studies) [†,#,¶¶]	⊕◯◯◯ VERY LOW [**]	The total cost due to community-associated *C. difficile* infections was adjusted by 10%.[††,‡‡,##]
Antibiotic-resistant infection related costs	(1 observational study) [§§]	⊕⊕◯◯ LOW	Estimate taken directly from report.
Antibiotic-resistant infection related costs associated with a dental prescription for antibiotics	(2 observational studies) [#,§§]	⊕◯◯◯ VERY LOW [**]	The total cost related to antibiotic-resistance infections was adjusted by 10%.[††,‡‡,##]
Admission to hospital due to community-associated *C. difficile* infection	(2 observational studies) [†,‡]	⊕⊕⊕◯ MODERATE [§]	Of the estimated cases of community-associated C. difficile infections in 2011, approximately 12.7% of people were admitted to the hospital due to community-associated *C. difficile* infections being the primary reason for admission. This represents 20,287 out of 159,700 total cases with community-associated *C. difficile* infections (95% CI 16,878 – 23,622).
Admission to hospital due to antibiotic-resistant infection	(1 observational study) [***]	⊕⊕◯◯ LOW	Estimate taken directly from report.
Admission to hospital due to antibiotic-resistant infection associated with a dental prescription for antibiotics	(1 observational study) [#,***]	⊕◯◯◯ VERY LOW [**]	Admissions to the hospital due to antibiotic-resistant infections was adjusted by 10%.[††,‡‡,##]

Systemic antibiotics compared to no systemic antibiotics for dental conditions

Patient or population: any person of any age presenting in any dental setting in the United States
Setting: any dental setting in the United States
Exposure: any systemic antibiotics
Non-exposure: no systemic antibiotic

Outcome[*]	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Calculation of impact
Length of hospital stay due to community-associated *C. difficile* infection	(1 observational study) [¶¶]	⊕⊕◯◯ LOW	Estimate taken directly from report.
Length of hospital stay due to antibiotic-resistant infections	(1 observational study) [†††]	⊕⊕◯◯ LOW	Estimate taken directly from report.
Anaphylaxis due to antibiotics	(1 observational study) [‡‡‡]	⊕⊕◯◯ LOW	Estimates taken directly from report.[¶]
Anaphylaxis due to antibiotics associated with a dental prescription	(2 observational studies) [#,‡‡‡]	⊕◯◯◯ VERY LOW [**]	Reported anaphylaxis due to antibiotics occurrences was adjusted by 10%.[¶,††,‡‡]

Footnotes

[*] No studies meeting our selection criteria reported data on mortality due to community-associated *C. difficile* infections related to a dental prescription for antibiotics, mortality due to antibiotic-resistant infections associated with a dental prescription for antibiotics, cost-effectiveness of antibiotics to treat symptomatic irreversible pulpitis with or without symptomatic apical periodontitis, pulp necrosis and symptomatic apical periodontitis, or pulp necrosis and localized acute apical abscess, admission to hospital due to community-associated *C. difficile* infections related to a dental prescription for antibiotics, length of hospital stay due to community-associated *C. difficile* infection related to a dental prescription for antibiotics, length of hospital stay due to antibiotic-resistant infections associated with a dental prescription for antibiotics, allergic reaction due to antibiotics, allergic reaction due to antibiotics associated with a dental prescription, fatal anaphylaxis due to antibiotics, or fatal anaphylaxis due to antibiotics associated with a dental prescriptions.

[†] Considerations for Lessa 2015: 1) the case definition of *C. difficile* infection relying only on positive test results for *C. difficile* toxin or molecular assay from unformed samples sent to laboratories may lead to an underestimation of the true burden (i.e. partially formed samples being untested), 2) there is the possibility for an underestimation of "both recurrence and mortality, given that [they] assessed only first recurrences and deaths that were documented in the medical record," 3) there is a potential over diagnosis or an overestimation of the burden of *C. difficile* infection due to diagnostic tests being highly sensitive (i.e. a poor distinction between colonization and the disease), and 4) authors estimated the recurrence of and mortality due to *C. difficile* infection by using a random sample of cases that may or may not be representative of the United States rates.

[‡] Considerations for Chitnis 2013: 1) Potential issues of generalizability to the United States population given that patients included in the analysis with community-associated *C. difficile* infection were more likely to be white and female, 2) only a convenience sample of stools were sent for definitive testing (40%), 3) although antibiotic use within 12 weeks was adjudicated based on a telephone interview (self-reported) and medical records it is unclear as to how many cases were confirmed using both methods, and 4) hospitalization in which *C. difficile* infection was primary reason for admission was ascertained through medical records.

[§] Upgraded due to a large effect based on observational studies without important risk of bias or other limitations.

[¶] This is likely an overestimation of the effect of dental prescriptions for antibiotics because the provided information/data did not differentiate between inpatient and outpatient antibiotic prescriptions. We assume that prescribing for dental conditions rarely occurs in inpatient settings.

[#] Considerations for Hicks 2015: 1) Dentistry accounts for 10% of the total outpatient antibiotic prescriptions in the United States, 2) the magnitude of antibiotic prescriptions may not necessarily represent the magnitude of antibiotic consumption by patients, 3) possible underestimation due to the total number of prescriptions from other non-dental professionals (e.g., emergency medicine services, etc.) for any dental condition not being included in the estimate, and 4) according to Roberts et al , estimates related to antibiotic prescribing practices reported by Hicks et al correspond to that of general dentists and not all dental specialties combined.

[**] Downgraded due to serious issues of indirectness related to estimates being extrapolated to illustrate the burden in a dental setting.

[††] Data was adjusted considering that dentistry accounts for 10% of total outpatient antibiotic prescriptions in the United States.

[‡‡] The presented estimate assumes that dental prescriptions for any antibiotic has the same potential of inducing antibiotic resistance as non-dental related prescriptions.

[§§] Considerations for Centers for Disease Control and Prevention 2013: 1) No reports containing methods or results is linked to this report, 2) estimates used from this report are likely an underestimation of the true burden of antibiotic resistance related outcomes, and 3) the magnitude of antibiotic resistance related outcomes may not necessarily represent the magnitude of antibiotics prescribed for and consumed by patients.

[¶¶] Considerations for Zhang 2016: 1) All included studies in the Zhang review reported direct medical costs from a hospital perspective; indirect costs to patients and society, and costs of additional care after hospital discharge have not been captured (e.g., productivity loss due to work day losses, costs in long-term care facilities, etc.). About 9% of *C. difficile* infection patients were discharged to a long-term care facility for an average of 24 days of after-care, which would result in an additional $141 million burden on the healthcare system and society due to long-term care facility transfers, 2) primary *C. difficile* infections were not separated for the estimation of recurrent *C. difficile* infection costs, 3) discrepancy in case definitions in cost studies versus surveillance/epidemiological studies (e.g., community- vs health care-associated *C. difficile* infections), and 4) the total costs of *C. difficile* infection in the United States may be higher than the reported estimate.

[##] This is likely an overestimation of the effect of dental prescriptions for antibiotics due to the primary study not measuring or reporting antibiotic exposure.

[***] Considerations for Mainous 2011: 1) the methods did not allow us to determine whether the infection arose in the hospital or if patients were colonized or infected prior to admission, 2) ICD-9-CM diagnosis codes were used instead of laboratory results on bacterial cultures ,and 3) “greater awareness of drug resistance among hospital coding departments may have prompted more attention to adding these codes to discharge records of patients who were relatively healthy and discharged without incident.”

[†††] Considerations for Johnston 2019: 1) ICD-9-CM diagnosis codes were used instead of laboratory results on bacterial cultures, 2) authors were unable to distinguish between hospital-acquired and community-acquired infections, and 3) 10% of the eligible population was excluded due to missing data.

[‡‡‡] Considerations for Dhopeshwarkar 2019: 1) the estimates presented in this study only include penicillin and cephalosporin drug classes and amoxicillin and cephalexin drugs, and does not include other individual drugs commonly prescribed by dentists such as clindamycin (cite Durkin), 3) there may be issues of generalizability as only patients from two Boston-area hospitals were included in this analysis and may not be representative of inpatient populations admitted to other United States hospitals, 4) there is a potential overestimate of the occurrence of anaphylaxis due to reported cases not being confirmed by tryptase tests, 5) possible underestimation due to exclusion of codes listed in electronic health records not directly linking to anaphylaxis, and 6) there is uncertainty surrounding if the estimates of the reported or observed cases of anaphylaxis resulted in death.

eTABLE 4. Relative and absolute desirable and undesirable effects (95% CI) from randomized controlled trials and certainty in the evidence for systemic antibiotics as adjuncts to definitive, conservative dental treatment compared to no systemic antibiotic as adjuncts to definitive, conservative dental treatment for pulp necrosis and symptomatic apical periodontitis and pulp necrosis and localized acute apical abscess in immunocompetent adults

Systemic antibiotics as adjuncts to definitive dental treatment compared to no systemic antibiotic as adjunct to definitive dental treatment for pulp necrosis and symptomatic apical periodontitis or pulp necrosis and localized acute apical abscess in immunocompetent adults

Patient or population: immunocompetent adults with pulp necrosis and symptomatic apical periodontitis or pulp necrosis and localized acute apical abscess
Setting: dental setting where definitive, conservative dental treatment is immediately available
Intervention: systemic antibiotics as adjuncts to definitive, conservative dental treatment
Comparison: no systemic antibiotic as adjunct to definitive, conservative dental treatment

Outcomes[*]	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect[†] (95% Confidence Interval)	Anticipated absolute effects	
				Risk with no systemic antibiotic as adjuncts to definitive, conservative dental treatment[‡]	Risk difference with systemic antibiotics as adjuncts to definitive, conservative dental treatment[§]
Pain intensity at 24 hours	72 (2 RCTs) ¶,#	⨁◯◯◯ VERY LOW **,††	-	The mean pain intensity at 24 hours ranged from **0.67 to 1.68**	MD **0.09 higher** (0.37 lower to 0.55 higher)
Pain experience at 24 hours	72 (2 RCTs) ¶,#	⨁◯◯◯ VERY LOW **,‡‡	**RR 0.80** (0.49 to 1.30) §§	442 per 1,000	**88 fewer per 1,000** (225 fewer to 133 more)
Pain intensity at 48 hours	72 (2 RCTs) ¶,#	⨁◯◯◯ VERY LOW **,††	-	The mean pain intensity at 48 hours ranged from **0.52 to 0.96**	MD **0.39 higher** (0.13 lower to 0.91 higher)
Pain experience at 48 hours	72 (2 RCTs) ¶,#	⨁◯◯◯ VERY LOW **,‡‡	**RR 1.55** (0.75 to 3.21) §§	233 per 1,000	**128 more per 1,000** (58 fewer to 514 more)
Pain intensity at 72 hours	72 (2 RCTs) ¶,#	⨁◯◯◯ VERY LOW **,††	-	The mean pain intensity at 72 hours ranged from **0.29 to 0.82**	MD **0.12 higher** (0.32 lower to 0.56 higher)
Pain experience at 72 hours	72 (2 RCTs) ¶,#	⨁◯◯◯ VERY LOW **,‡‡	**RR 1.38** (0.50 to 3.82) §§	116 per 1,000	**44 more per 1,000** (58 fewer to 328 more)
Pain intensity at 7 days	41 (1 RCT) ¶	⨁⨁◯◯ LOW ††	-	The mean pain intensity at 7 days was **0.32**	MD **0.05 lower** (0.41 lower to 0.3 higher)
Pain experience at 7 days	41 (1 RCT) ¶	⨁⨁◯◯ LOW ‡‡	**RR 5.75** (0.29 to 112.83) §§	23 per 1,000	**108 fewer per 1,000** (16 fewer to 2,542 more)
Intra-oral swelling at 24 hours	67 (2 RCTs) ¶,#,¶¶	⨁◯◯◯ VERY LOW **,‡‡	**RR 1.70** (0.55 to 5.24) ##,***	250 per 1,000	**175 more per 1,000** (112 fewer to 1,060 more)
Intra-oral swelling at 48 hours	66 (2 RCTs) ¶,#,†††	⨁◯◯◯ VERY LOW **,‡‡	**RR 1.36** (0.62 to 2.98) ##,***	282 per 1,000	**102 more per 1,000** (107 fewer to 558 more)
Intra-oral swelling at 72 hours	59 (2 RCTs) ¶,#,†††	⨁◯◯◯ VERY LOW **,‡‡‡	**RR 1.00** (0.05 to 20.81) ##,***	189 per 1,000	**0 fewer per 1,000** (180 fewer to 3,748 more)

Systemic antibiotics as adjuncts to definitive dental treatment compared to no systemic antibiotic as adjunct to definitive dental treatment for pulp necrosis and symptomatic apical periodontitis or pulp necrosis and localized acute apical abscess in immunocompetent adults

Patient or population: immunocompetent adults with pulp necrosis and symptomatic apical periodontitis or pulp necrosis and localized acute apical abscess
Setting: dental setting where definitive, conservative dental treatment is immediately available
Intervention: systemic antibiotics as adjuncts to definitive, conservative dental treatment
Comparison: no systemic antibiotic as adjunct to definitive, conservative dental treatment

Outcomes[*]	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect[†] (95% Confidence Interval)	Anticipated absolute effects	
				Risk with no systemic antibiotic as adjuncts to definitive, conservative dental treatment[‡]	Risk difference with systemic antibiotics as adjuncts to definitive, conservative dental treatment[§]
Intra-oral swelling at 7 days	40 (1 RCT) [¶]	⨁⨁◯◯ LOW [‡‡‡]	**RR 1.11** (0.07 to 16.47) [***]	48 per 1,000	**5 more per 1,000** (44 fewer to 737 more)
Total number of NSAID (tablets) used	41 (1 RCT) [¶]	⨁⨁◯◯ LOW [‡‡‡]	-	The mean total number of NSAIDS (tablets) used was **8.42**	MD **1.58 higher** (4.55 lower to 7.71 higher)
Total number of acetaminophen with codeine (tablets) used	41 (1 RCT) [¶]	⨁⨁◯◯ LOW [§§§]	-	The mean total number of acetaminophen with codeine (tablets) used was **5.58**	MD **0.31 lower** (3.94 lower to 3.32 higher)
Endodontic flare-up	30 (1 RCT) [#]	⨁◯◯◯ VERY LOW [**,‡‡]	**RR 0.28** (0.02 to 4.76)	182 per 1,000	**131 fewer per 1,000** (178 fewer to 684 more)
Diarrhea	31 (1 RCT) [#,¶¶¶]	⨁◯◯◯ VERY LOW [**,‡‡]	**RR 0.40** (0.02 to 7.63)	95 per 1,000	**57 fewer per 1,000** (93 fewer to 631 more)
Malaise	32 (1 RCT) [#,¶¶¶]	⨁◯◯◯ VERY LOW [**,‡‡]	**RR 6.79** (0.25 to 182.33)	24 per 1,000	**138 fewer per 1,000** (18 fewer to 4,317 more)

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes:

[*] No studies meeting our selection criteria reported data on trismus, fever, cellulitis, additional dental visit, additional medical visit, allergic reaction, *Clostridium difficile* infection, or repeat procedure for this population.

[†] RR: Risk ratio.

[‡] For dichotomous outcomes, we calculated absolute treatment effects by using the control group's baseline risk as the assumed control intervention risk.

[§] MD: Mean difference.

[¶] Henry 2001.

[#] Fouad 1996.

[**] Serious issues of risk of bias (attrition bias and selective reporting).

[††] Serious issues of imprecision due to small sample size.

[‡‡] Very serious issues of imprecision due to small sample size and the confidence interval suggests a large benefit and a large harm.

[§§] For included studies, the data for the outcome of pain was dichotomized (VAS from 0-3) as follows: “no pain” and “mild pain” were coded as “no pain,” and “moderate pain” and “severe pain” were coded as “pain.”

[¶¶] In Fouad 1996, 14 participants were excluded from the analysis because they either did not report their baseline swelling or they did not report swelling data at follow up.

[##] In Fouad 1996, the data for the outcome of intra-oral swelling was dichotomized (VAS from 0-4) as follows: “no swelling,” “much less swelling,” and “slightly less swelling,” when compared to swelling at baseline, were coded as “no swelling.” The options of “same swelling” and “more swelling,” when compared to swelling at baseline, were coded as “swelling.”

[***] In Henry 2001, the data for the outcome of swelling was dichotomized (VAS from 0-3) as follows: “no swelling” and “mild swelling” were coded as “no swelling” and “moderate swelling” and “severe swelling” were coded as “swelling.”

[†††] In Fouad 1996, 15 participants were excluded from the analysis because they either did not report their baseline swelling or they did not report swelling data at follow up.

[‡‡‡] Very serious issues of imprecision due to small sample size and the confidence interval suggests a small benefit and a large harm.

[§§§] Very serious issue of imprecision due to small sample size and the confidence interval suggests both a small benefit and a small harm.

[¶¶¶] Due to the total number of participants in Fouad 1996 informing this outcome, the total number of participants for the outcome of pain at 72 hours was used.