Managing Common Infections

Impetigo antimicrobial prescribing

Stakeholder comments table

14/08/2019 – 11/09/2019

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1	Irwell Medical Practice	Draft Guideline	2	9-10	We are concerned about the challenges that this recommendation would pose. Particular concerns raised in the educational meeting were about impetigo being more common in children, and often peri-orally. It was felt that hydrogen peroxide may not be suitable in a large number of cases due to this. In addition to this there were felt to be problems with staining, use on certain skin types and colours and also issues with regards to cost. Although the evidence has been found for hydrogen peroxide specifically, the guideline states that "an antiseptic" can be used, and the team felt that there were other antiseptics that were more financially viable, such as chlorhexidine, or those that were available over the counter such as cetrimide/chlorhexidine creams that these may also be considered in a wider variety of patients.	Thank you for your comment. The recommendation for hydrogen peroxide 1% cream is based on evidence showing that this is as effective as topical fusidic acid. The evidence also shows there are no differences between these treatments in the number of adverse events or mild side effects. The committee discussed the use of hydrogen peroxide 1% cream peri-orally in children and use on dark skin. Based on its experience, it agreed that this low concentration was unlikely to be harmful. The committee also discussed the cost associated with hydrogen peroxide 1% cream. Although this can be purchased over the counter, it can be prescribed. Current practice to treat impetigo with an antibiotic (topical or oral) would require a consultation with a health professional. No evidence was identified for other topical antiseptics, and some common preparations are not licensed for superficial skin infections. The committee concluded that they could make a recommendation for hydrogen peroxide 1% cream only, but this is now a consider recommendation to reflect stakeholder comments. A recommendation to be aware that other topical antiseptics are available for

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						superficial skin infections, but no evidence was found has also been added.
2	Leeds North Clinical Commissioning Group	Draft for consultation guideline	5	8 onwards Table 1	Even though a topical antiseptic is first line treatment we are concerned that prescribers will see the antibiotics table and do not note that antiseptic is indeed first line. We think adding a note advising on antiseptic use above the table in the guideline and visual summary would be helpful.	Thank you for your comment. The antimicrobial prescribing table has been amended to include hydrogen peroxide 1% cream.
3	Leeds North Clinical Commissioning Group	Draft for consultation guideline	2	16	'Offer a topical or oral antibiotic for people with non bullous impetigo who are not systemically unwell'. We are considering if oral antibiotics should only be reserved for those patients who are systemically unwell, given the increasing concerns of resistance, and so topical use should be encouraged.	Thank you for your comment. The committee agreed that the risk of antimicrobial resistance is a concern with both oral and topical antibiotics and can develop rapidly with topical antibiotics. Therefore, it agreed that including a choice for route of administration was appropriate.
4	The British Society for Antimicrobial Chemotherapy (BSAC)	Guideline	2	19	Both' may give impression of combination. Please re-word	Thank you for your comment. It is considered that it is clear from the recommendation that either a topical or oral antibiotic should be offered. There is also a recommendation stating that combination treatment with a topical and oral antibiotic should not be offered. Therefore, no changes have been made to the wording of this recommendation.
5	The British Society for Antimicrobial Chemotherapy (BSAC)	Guideline	9	5	Please insert some reference to prolonged use of topical antibiotics being associated with resistance developing. Generally we advise using these antibiotic creams for more than 10 days in a row (so your recommendation of 5-7 days is great). If we could have some comment in here re the 10 days max, it would help deter the frequent prescriptions we see that have been in place for a month or more! Resistance to these topical agents has repercussions for MRSA decolonisation (suppression) treatment regime	Thank you for your comment. The committee discussed that antimicrobial resistance can develop rapidly with repeated use of topical antibiotics and agreed to include reference to this in the points that should be taken account of when choosing an antibiotic. The committee agreed that a 5- to 7-day course length should be recommended, and therefore it is not appropriate to include further detail on a different maximum course length in the antimicrobial prescribing tables. However, the medicines safety section of the guideline does state that extended or recurrent use of topical

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						fusidic acid or mupirocin may increase the risk of developing antimicrobial resistance.
6	The British Society for Antimicrobial Chemotherapy (BSAC)	Guideline	15	2-12	I may be reading this wrong (in which case possibly needs clarity in wording) but is the rationale suggesting that topical antibiotics were no better than topical steroids or topical antifungals? This brings the need for antibiotics at all into question, doesn't' it? I figure it is more likely to be comparison between the different antibiotics, but this needs to be made clear.	Thank you for your comment. The evidence described in the guideline for topical antibiotics compared to antiseptics, steroids and antifungals (page 15 of the draft guideline) states that there were no differences in clinical effectiveness between: • topical antibiotics and topical antiseptics • topical antibiotics and topical steroids, or • topical antibiotics and topical antifungals. The committee agreed that as impetigo is highly infectious, a form of treatment should be offered to all people with impetigo to help limit the spread of infection, to hasten recovery and to limit deterioration. Based on this evidence as well as its experience of using antiseptics, the committee agreed that people with localised non-bullous impetigo who are not systemically unwell or at high risk of complications should consider using hydrogen peroxide 1% cream. However, the committee agreed that for some people, hydrogen peroxide 1% cream would not be suitable, and these people should be offered a topical antibiotic instead.
7	The British Society for Antimicrobial Chemotherapy (BSAC)	Guideline	19	23-25	Can we have mention of mupirocin having the same issue and consideration please?	Thank you for your comment. Reference to mupirocin has been added to the medicines safety section of the guideline.
8	The British Society for Antimicrobial Chemotherapy (BSAC)	Main guideline and Visual summary	6 2	10 Table: Choice of antibiotic: children and young people	We agree with the role of topical disinfectants / topical Abs for localised, non-bullous impetigo but feel strongly that if oral therapy is required in a young child, it needs to be a palatable anti-staph suspension such a cephalexin. Flucloxacillin suspension is poorly tolerated by children due to the taste (Baguley D et al. Prescribing for children - taste and palatability affect adherence to	Thank you for your comment. The committee agreed that flucloxacillin will usually be the most appropriate oral antibiotic for people with impetigo. However, noting the issues with palatability, the committee agreed to recommend that children aged 2 to 9 should be offered flucloxacillin capsules (if tolerated), and children and young people aged 10 to 17 should be

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				under 18 years.	antibiotics: a review. Arch Dis Child. 2012 Mar;97(3):293-7). Although we appreciate the need to advocate for the narrowest agent possible, this needs to be balanced with pragmatic prescribing in terms of avoiding agents that children will refuse to take. This risks progression of infection / risk of sepsis.	offered capsules. A link to the Medicines for Children, Helping your child to swallow leaflet has been included in the footnotes to table 2 to aid implementation. The committee also noted that alternative oral antibiotics (clarithromycin or erythromycin in pregnancy) were suitable for use when flucloxacillin is not suitable, including when it's not tolerated due to poor palatability. The article highlighted (Baguley et al 2012) will not be included in the evidence review based on study type (narrative literature review).
9	Royal College of General Practitioners	Guideline	13	23	The committee should consider stating 5 days as the length of course of oral and topic antibiotics in view of antimicrobial resistance and the evidence presented. (Line 27, page 13 agrees that the shortest effective dose should be prescribed). The draft recommends 5-7 days of treatment which is longer than the current recommended 5 days of topical treatment without evidence to support this extension other than "expert opinion". If 5-7 days is left in the guideline, the default position for GPs is likely to be a 7 day prescription, therefore increasing, rather than decreasing the topical antimicrobial use for impetigo going against all antimicrobial resistance guidance we currently have. Can the committee consider rewording this to read: "5 days of antibiotics (oral or topical) is recommended but can be extended to 7 days if the impetigo has not fully resolved after 5 days of treatment". This would then be consistent with other NICE guidance e.g. community acquired pneumonia, which encourages a 5 day course of antibiotics in uncomplicated infections, increased	Thank you for your comment. The committee agreed that a 5-day course would be appropriate for most people with impetigo, however, some people may need a longer course because of the severity or number of lesions. The committee agreed that the option of prescribing antibiotics for 7 days should be available for these people. A footnote has been added to the antimicrobial prescribing tables to reflect this.

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					to 7 if needed. The main evidence on length of course, presented as the committee's choice for 5-7 days, compares 3 days or oral co-trimoxazole.	
10	Royal College of General Practitioners	Visual summary			The committee should consider removing the statement "offer topical antibiotic if a topical antiseptic is not suitable" from the top square blue box. The written guidance states topical antiseptic is first choice and the visual summary should concur with this. The worsening instructions in the right hand boxes are clear on alternative treatments if the topical antiseptic does not work. Taking a firmer stance on topical non-antimicrobial prescribing would be welcomed since the evidence presented shows antiseptics are not inferior to topical antimicrobial.	Thank you for your comment. The visual summary is a representation of the recommendations in the guideline and has been updated in line with the changes in the final guideline. The committee agreed that hydrogen peroxide 1% cream should be considered for people with localised non-bullous impetigo who are not systemically unwell or at high risk of complications. However, the committee agreed that the option of offering a topical antibiotic should also be available for when hydrogen peroxide 1% cream is not suitable.
11	Royal College of General Practitioners	Visual summary			The committee should remove the wording 5-7 days in each box and replace it with "5 days in the first instance, extending to 7 days if the infection has not completely resolved", as described in comment 1.	Thank you for your comment. The committee agreed that a 5-day course would be appropriate for most people with impetigo, however, some people may need a longer course because of the severity or number of lesions. The committee agreed that the option of prescribing antibiotics for 7 days should be available for these people. A footnote has been added to the antimicrobial prescribing tables to reflect this.
12	Royal College of General Practitioners	Visual summary + guideline	5 + visual summary	13 + visual summary	The committee should consider increasing the recommended dose of erythromycin and clarithromycin to 500mg, or justifying the lower dose of these drugs used in treatment. If "based on experience" (as quoted in the guideline), 500mg of flucloxacillin (the higher dose) is recommended from the BNF, then the equivalent strength of erythromycin and clarithromycin should also be used (500mg), unless there is evidence against this.	Thank you for your comment. The committee agreed that based on its experience the higher end of the dose range of flucloxacillin recommended in the BNF was appropriate for treatment of impetigo. Also based on its experience, the committee agreed that the standard dose as recommended in the BNF was appropriate for clarithromycin and erythromycin but added a footnote to the table that a higher dose of clarithromycin could be used if required for severe infections.
13	Royal College of Paediatrics and Child Health	Draft guideline	1.1.10	4	The advice is only to "consider" taking an antimicrobial sample if the condition is not improving or worsening following topical or oral	Thank you for your comment. The committee agreed that sending a skin swab for microbiological testing at first presentation was

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					antibiotics. This seems too cautious/late in view of increasing antibiotic resistance. A swab should be taken at the first encounter and decision to treat made. If the condition is not improving or worsening at review despite topical or oral antibiotics then results should be available to guide treatment choice at that stage. There is additional risk of a false negative swab taken after application of topical antiseptic or antibiotic. Better to swab first and then start initial treatment.	unlikely to be a good use of resources as most cases of impetigo will be resolved with empirical treatment. Therefore, no changes to the recommendations on microbiological testing have been made.
14	Royal College of Paediatrics and Child Health	Draft guideline	1.1.11	4	For people in whom impetigo recurs frequently the advice is to "consider" taking a nasal swab and start decolonisation therapy. No mention of decolonisation of family contacts. If recurrence is frequent, skin and nasal swab should be done to look at antibiotic susceptibility of the pathogen, decolonisation should be recommended, and family contact decolonisation should be considered.	Thank you for your comment. The committee discussed family decolonisation and it recognised that this may be appropriate in some cases. However, it did not make a recommendation as this decision should be based on specialist advice. The rationale has been updated to include information on this point.
15	Royal College of Paediatrics and Child Health	Draft guideline	1.2	5 and 6	In secondary care the reviewer always uses oral antibiotics. In their experience most, infants and preschool children spit out flucloxacillin because of the taste. Therefore, in this group co-amoxiclav is used as first line treatment.	Thank you for your comment. The committee agreed that flucloxacillin will usually be the most appropriate oral antibiotic for people with impetigo. However, noting the issues with palatability, the committee agreed to recommend that children aged 2 to 9 should be offered flucloxacillin capsules (if tolerated), and children and young people aged 10 to 17 should be offered capsules. A link to the Medicines for Children, Helping your child to swallow leaflet has been included in the footnotes to table 2 to aid implementation. The committee also noted that alternative oral antibiotics (clarithromycin or erythromycin in pregnancy) are suitable for use when flucloxacillin is not suitable, including when it's not tolerated due to poor palatability.

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16	Royal College of Paediatrics and Child Health	Draft guideline			The reviewer is happy with the recommendations.	Thank you for your response.
17	Royal Pharmaceutical Society	Guideline			Use of hydrogen peroxide 1% cream as topical antiseptic. We have a concern about the proposal to promote the use of hydrogen peroxide 1% cream as topical antiseptic. Given most impetigo occurs in children, for whom prescriptions are free, we are unsure how acceptable this proposal will be to both NHS England, who are promoting self-purchase for OTC and P products, and to parents of children who may be told to purchase this product which, as far as we can ascertain, is quite expensive. Our concern is that it may result in poor adherence and consequently poor care to children; and with possible treatment failure that may lead to use of inappropriate use of oral antibiotics at a second consultation.	Thank you for your comment. The committee discussed the cost associated with hydrogen peroxide 1% cream. Although this can be purchased over the counter, it can be also be prescribed. Current practice to treat impetigo with an antibiotic (topical or oral) would require a consultation with a health professional. No evidence was identified for other topical antiseptics, and not all products are licensed for treating superficial skin infections. Based on the evidence of no difference in effectiveness between hydrogen peroxide and fusidic acid, the committee agreed that this topical antiseptic should be considered for people with localised non-bullous impetigo. This is based on the principles of antimicrobial stewardship. Considering the evidence available and the cost of hydrogen peroxide, the committee agreed to amend the recommendation in the final guideline to 'consider' rather than 'offer' hydrogen peroxide 1% cream, with a subsequent recommendation to offer a topical antibiotic for when hydrogen peroxide 1% cream is not suitable.
18	Royal Pharmaceutical Society	Guideline			Use of hydrogen peroxide 1% cream as topical antiseptic. It may be a suitable option, but it is unclear why specifically hydrogen peroxide 1% has been promoted when there are other similar products that parents may have available at home or that could be purchased/supplied on prescription.	Thank you for your comment. The only evidence identified for antiseptics in treating impetigo was for hydrogen peroxide 1% cream. Furthermore, not all products are licensed for treating superficial skin infections. As no evidence was identified for other antiseptics, the committee could not make a recommendation on these. However, a recommendation to be aware that other topical antiseptics are available for

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						superficial skin infections, but no evidence was found has been added.
19	Royal Pharmaceutical Society	Guideline			Course lengths for both topical and oral antibiotics. Saying 5-7 days is not helpful. Suggest choosing either 5 or 7 days, preferably 5 days as longer courses have more risk of resistance.	Thank you for your comment. The committee agreed that a 5-day course would be appropriate for most people with impetigo, however, some people may need a longer course because of the severity or number of lesions. The committee agreed that the option of prescribing antibiotics for 7 days should be available for these people. A footnote has been added to the antimicrobial prescribing tables to reflect this.
20	Royal Pharmaceutical Society	Guideline			Flucloxacillin suspension has poor palatability. Should there be an alternative first line agent that has better potential for adherence?	Thank you for your comment. The committee agreed that flucloxacillin will usually be the most appropriate oral antibiotic for people with impetigo. However, noting the issues with palatability, the committee agreed to recommend that children aged 2 to 9 should be offered flucloxacillin capsules (if tolerated), and children and young people aged 10 to 17 should be offered capsules. A link to the Medicines for Children, Helping your child to swallow leaflet has been included in the footnotes to table 2 to aid implementation. The committee also noted that alternative oral antibiotics (clarithromycin or erythromycin in pregnancy) are suitable for use when flucloxacillin is not suitable, including when it's not tolerated due to poor palatability.
21	Royal Pharmaceutical Society	Guideline			The inclusion of a dose range for flucloxacillin and erythromycin is understandable, but we have received feedback about our regional guidelines that GPs sometimes are unsure when to choose lower or upper end of dose range. There could be a tendency to use the higher dose in all cases. This point is applicable to all NICE guidelines with dose ranges.	Thank you for your comment. The committee agreed that it was appropriate to recommend the dose ranges stated in the BNF for most of the recommended antibiotics. The exception to this is flucloxacillin for which the committee agreed based on its experience the higher end of the dose range of flucloxacillin recommended in the BNF was appropriate for treatment of impetigo.

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22	Royal Pharmaceutical Society	Guideline			It is important that if/when this guideline is adopted that there is clear information distributed to community pharmacists to raise awareness of the potential use of hydrogen peroxide cream in impetigo since the products are not commonly promoted.	Thank you for your comment. The committee recognises the importance of raising awareness to support implementation of the guidelines.
23	Ferrer Internacional S.A.	Draft	5	8	As the resistance rate to fusidic acid of MRSA in the community has been increasing in direct relation with the increase in prescriptions (increase of a 3% from 2016; APRAHAI April 2017-Dec 2018) achieving currently already a 20% (Ellington 2015) there is a high risk of increasing it still more by using it empirically for impetigo treatment, even using short courses of therapy. For that reason, we would suggest that the guideline includes the recently approved Ozenoxacin 1% topical cream as it would be available in the UK in the early future. Ozenoxacin has shown to be bactericidal with and eradication rate of sensitive and resistant strains of *S aureus* of over an 80% already after 2 days of therapy and more than a 90% after 5 days, twice a day therapy, as mentioned on the therapeutic schedule. The fast activity of a topical antibiotic is closely related to the reduction of spread of pathogens and decrease of transmission of the infection. *(**Gropper S,** Albareda N, Chelius K, Kruger D, Mitha I, Vahed Y, Gani M, García-Alonso F; Ozenoxacin in Impetigo Trial Investigators Group. Ozenoxacin 1% cream in the treatment of impetigo: a multicenter, randomized, placebo- and retapamulin-controlled clinical trial. **Future Microbiol. 2014**;9(9):1013-23.; **Rosen T,** Albareda N, Rosenberg N, Alonso FG, Roth S, Zsolt I, Hebert AA. Efficacy and Safety of Ozenoxacin Cream for Treatment of Adult and*	Thank you for your comment. The committee discussed the concerns around fusidic acid resistance. However, it agreed that fusidic acid is still the most appropriate first-choice topical antibiotic if hydrogen peroxide 1% cream is unsuitable or ineffective, based on the evidence of its effectiveness and fewer adverse events compared with other antibiotics as well as experience of its use in practice. The committee agreed to include a recommendation highlighting that antimicrobial resistance can develop rapidly with repeated use of topical antibiotics, and it discussed that the recommendation to consider a topical antiseptic may reduce fusidic acid use. The pooled analysis of Gropper et al. 2014 and Rosen et al. 2018 (Hebert et al. 2018) has been prioritised and included in the final evidence review. The committee discussed this evidence for ozenoxacin topical cream as an option for impetigo. However, no evidence was identified which compared ozenoxacin to other antibiotics, therefore the committee could not comment on the benefits or harms relative to the antibiotics recommended in the draft guideline. It was also noted that ozenoxacin is not available in the UK at the time of guideline publication. Therefore, the committee did not make any recommendations for ozenoxacin.

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					Pediatric Patients With Impetigo: A Randomized Clinical Trial. ***JAMA Dermatol. 2018*** *Jul 1;154(7):806-813;* ***SmPC OZEDUB (OZENOXACIN) FERRER 10 MG/G CREAM****. Ferrer Internacional 25/5/2017. Revised 21/06/2018*	Gropper et al. 2014 was identified in the search for this guideline and was excluded as it is included in the prioritised pooled analysis (Hebert et al. 2018). Rosen et al. 2018 was not identified in the search for this guideline, however, it was not included as it is included in the prioritised pooled analysis (Hebert et al. 2018).
24	Ferrer Internacional S.A.	Evidence review	10	10	The recommendation to use fusidic acid and mupirocin is based on the results of a very well-conducted systematic review (Koning 2012) but it doesn't considers that the included studies were carried out mainly in the 80's and because of that, the present efficacy rates are doubtful according to the current resistance rates to fusidic acid and mupirocin recently published. *(**Ellington MJ**, Reuter S, Harris SR, Holden MT, Cartwright EJ, Greaves D, Gerver SM, Hope R, Brown NM, Török ME, Parkhill J, Köser CU, Peacock SJ. Emergent and evolving antimicrobial resistance cassettes in community-associated fusidic acid and meticillin-resistant Staphylococcus aureus.* ***Int J Antimicrob Agents. 2015*** *May;45(5):477-84.;* ***Poovelikunnel T,*** *Gethin G, Humphreys H. Mupirocin resistance: clinical implications and potential alternatives for the eradication of MRSA.* ***J Antimicrob Chemother. 2015*** *Oct;70(10):2681-92.)*	Thank you for your comment. The committee discussed the limitations of the evidence for fusidic acid and mupirocin. However, the committee agreed that based on its experience and knowledge of current practice, in combination with the evidence showing the effectiveness of fusidic acid and mupirocin compared with other antibiotics, that these antibiotics are the most appropriate for treatment of impetigo. Ellington et al. 2015 is not included based on population (not impetigo). Poovelikunnel et al. 2015 is not included based on population (not impetigo).
25	Ferrer Internacional S.A.	Draft	3	17	When reassessing people with impetigo, take account of:…."possibility of antibiotic resistance" should be added.	Thank you for your comment. The recommendation for reassessment for people with impetigo has been amended to suggest taking account of previous antibiotic use *which may have led to resistant bacteria*.

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26	Ferrer Internacional S.A.	Evidence review	6	31	The NICE guidelines on antimicrobial stewardship and processes for effective antimicrobial medicine use (2015) states that one of the recommendations for drug prescribers is to use the shortest effective course length of an antibiotic. Ozenoxacin has shown to be effective and safe after 5 days, twice a day therapy. This fact would be relevant for doctors to know once it would be available in the UK. *(**Gropper S**, Albareda N, Chelius K, Kruger D, Mitha I, Vahed Y, Gani M, García-Alonso F; Ozenoxacin in Impetigo Trial Investigators Group. Ozenoxacin 1% cream in the treatment of impetigo: a multicenter, randomized, placebo- and retapamulin-controlled clinical trial. **Future Microbiol. 2014**;9(9):1013-23.; **Rosen T**, Albareda N, Rosenberg N, Alonso FG, Roth S, Zsolt I, Hebert AA. Efficacy and Safety of Ozenoxacin Cream for Treatment of Adult and Pediatric Patients With Impetigo: A Randomized Clinical Trial. **JAMA Dermatol. 2018** Jul 1;154(7):806-813; **SmPC OZEDUB (OZENOXACIN) FERRER 10 MG/G CREAM**. Ferrer Internacional 25/5/2017 25. Revised 21/06/2018)*	Thank you for your comment. The committee agreed that a 5-day course would be appropriate for most people with impetigo, however, some people may need a longer course because of the severity or number of lesions. The committee agreed that the option of prescribing antibiotics for 7 days should be available for these people. A footnote has been added to the antimicrobial prescribing tables to reflect this. The pooled analysis of Gropper et al. 2014 and Rosen et al. 2018 (Hebert et al. 2018) has been prioritised and included in the final evidence review. The committee discussed this evidence for ozenoxacin topical cream as an option for impetigo. However, no evidence was identified which compared ozenoxacin to other antibiotics, therefore the committee could not comment on the benefits or harms relative to the antibiotics recommended in the draft guideline. It was also noted that ozenoxacin is not available in the UK at the time of guideline publication. Therefore, the committee did not make any recommendations for ozenoxacin. Gropper et al. 2014 was identified in the search for this guideline and was excluded as it is included in the prioritised pooled analysis (Hebert et al. 2018). Rosen et al. 2018 was not identified in the search for this guideline, however, it was not included as it is included in the prioritised pooled analysis (Hebert et al. 2018).

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27	Ferrer Internacional S.A.	Evidence review	7	18	The NICE guidelines on antimicrobial stewardship and processes for effective antimicrobial medicine use (2015) states that one of the recommendations for drug prescribers is to use a narrow spectrum antibiotic. We would suggest to add that Ozenoxacin, a non-fluorinated topical quinolone, in an in vitro surveillance study that included 10.054 isolates from 128 centers worldwide was highly active on sensitive and resistant Gram-positive microorganisms (MRSA, quinolone-resistant S.aureus) and the most effective on S. pyogenes, while the activity on Enterobacteriaceae was 2 dilutions higher than the one shown by fluorquinolones. ***(Morrissey I**, Cantón R, Vila J, Gargallo-Viola D, Zsolt I, Garcia-Castillo M, López Y. Microbiological profile of ozenoxacin. **Future Microbiol. 2019** May 28.)*. Ozenoxacin's specificity on *S. pyogenes* and sensitive and resistant strains of *S. aureus* together with its bactericidal effect should be taken into account when trying to stick to an antibiotic stewardship program.	Thank you for your comment. The committee discussed ozenoxacin as an option for impetigo, including its potential for specificity and bactericidal effect. However, no evidence was identified which compared ozenoxacin to other antibiotics, therefore the committee could not comment on the benefits or harms relative to the antibiotics recommended in the draft guideline. It was also noted that ozenoxacin is not available in the UK at the time of guideline publication. Therefore, the committee did not make any recommendations for ozenoxacin. Morrissey et al. 2019 is not included as it is an *in vitro* study.
28	Ferrer Internacional S.A.	Evidence review	7	26	The ESPAUR report 2018 does not include information about the trend of prescription of fusidic acid nor mupirocin. According to Ellington 2015, the prescription of fusidic acid is decreasing in hospitals but increasing in primary care. ***(Ellington MJ**, Reuter S, Harris SR, Holden MT, Cartwright EJ, Greaves D, Gerver SM, Hope R, Brown NM, Török ME, Parkhill J, Köser CU, Peacock SJ. Emergent and evolving antimicrobial resistance cassettes in community-associated fusidic acid and meticillin-resistant Staphylococcus aureus. **Int J Antimicrob Agents. 2015** May;45(5):477-84; **Shallcross LJ**, Petersen I, Rosenthal J, Johnson AM, Freemantle N, Hayward AC. Use of primary care data for detecting impetigo trends, United Kingdom, 1995-*	Thank you for your comment. The committee discussed the concerns around fusidic acid and mupirocin resistance. However, it agreed that fusidic acid is the most appropriate first choice topical antibiotic and mupirocin the most appropriate alternative topical antibiotic if hydrogen peroxide 1% cream is unsuitable or ineffective. This is based on the evidence of effectiveness and the committee's experience of their use in practice. The committee agreed to include a recommendation highlighting that antimicrobial resistance can develop rapidly with repeated use of topical antibiotics, and it discussed that the recommendation to consider hydrogen peroxide 1% cream may reduce topical antibiotic use.

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					2010. ***Emerg Infect Dis. 2013*** *Oct;19(10):1646-8.).* The recommendation of prescription of fusidic acid as a first line treatment in impetigo could lead to mutation pressure and the risk of emergence of some fusidic resistant clone of *S. aureus* could occur as it happened in the past with the EEFIC clone in the UK and other Northern countries in the EU *(**O'Neill** AJ, Larsen AR, Skov R, Henriksen AS, Chopra I. Characterization of the epidemic European fusidic acid-resistant impetigo clone of Staphylococcus aureus**. J Clin Microbiol. 2007** May;45(5):1505-10.).* A mupirocin and fusidic acid resistant *S. aureus* clone has newly emerged in Greece, increasing 9 times the resistance rate to mupirocin and 2 times the resistance rate to fusidic acid from 2013 to 2016**. *(Doudoulakakis A,** Spiliopoulou I, Spyridis N, Giormezis N, Kopsidas J, Militsopoulou M, Lebessi E, Tsolia M. Emergence of a Staphylococcus aureus Clone Resistant to Mupirocin and Fusidic Acid Carrying Exotoxin Genes and Causing Mainly Skin Infections. **J Clin Microbiol. 2017** Aug;55(8):2529-2537.)* That is the reason why it would be good to include Ozenoxacin in the guideline as it would represent an alternative to fusidic acid. Ozenoxacin has shown a very low probability of resistance generation due to its bactericidal activity as it targets with great affinity concomitantly DNA gyrase and Topoisomerase IV, both enzymes involved in bacterial DNA replication and repair. On the other hand, several studies have shown that it is very difficult to generate resistant mutants in vitro compared with other quinolones. *(**Yamakawa T**, Mitsuyama J, Hayashi K. In vitro and in vivo antibacterial activity of T-3912, a novel non-fluorinated topical quinolone. **J Antimicrob Chemother. 2002** Mar;49(3):455-65.; **López Y**,*	The committee discussed ozenoxacin topical cream as an option for impetigo, including the issues highlighted regarding resistance. However, no evidence was identified which compared ozenoxacin to other antibiotics, therefore the committee could not comment on the benefits or harms relative to the antibiotics recommended in the draft guideline. It was also noted that ozenoxacin is not available in the UK at the time of guideline publication. Therefore, the committee did not make any recommendations for ozenoxacin. Ellington et al. 2015 is not included based on population (not impetigo). Shallcross et al. 2013 is not included based on study type (observational study). O'Neill 2007 is not included based on study type (doesn't include clinical data; molecular evidence only) Doudoulakakis et al. 2017 is not included based on study type (observational study) Yamakawa et al. 2002 is not included as it is an *in vitro* and animal study. López et al. 2015 is not included as it is an *in vitro* study. López et al. 2019 is not included as it is an *in vitro* study.

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					Tato M, Espinal P, Garcia-Alonso F, Gargallo-Viola D, Cantón R, Vila J. In vitro selection of mutants resistant to ozenoxacin compared with levofloxacin and ciprofloxacin in Gram-positive cocci. ***J Antimicrob Chemother. 2015*** *Jan;70(1):57-61.)* and the concentration achieved on the skin is over the mutant prevention concentration what means that it will be effective not only on the resistant isolates but also on the new resistant mutants that could emerge.*(**Lopez Y**, Tato M, Canton R, Vila J. Mutant prevention concentration of Ozenoxacin compared to other quinolones for quinolone-susceptible and resistant Gram-positive cocci clinical isolates. 53rd Interscience Conference on Antimicrobial Agents* ***(ICAAC) 2013,*** *Sept 10th-13th Denver, Colorado, USA. Abst Nr C1-522b.* ***López Y. Plos One 2019****, in press).*	
29	Ferrer Internacional S.A.	Evidence review	10	11	Although the methodology followed by Koning et al for the systematic review is very robust it has to be taken into account that the 6 included studies for efficacy of mupirocin and fusidic acid vs placebo are as follows: Mupirocin: Eels 1986: n=38pts; evaluation: day 7-9. Gould 1984: n=129, evaluation "until cleared". Rojas 1985: n=NR (50?); evaluation at 7-12 days. Fusidic acid: Koning 2002: n=160; evaluation day 7. Some patients combined with povidone. Bacitracin: Ruby 1973: n=177; evaluation at day 8. Nevertheless, the evidence with Ozenoxacin therapy is based in two randomized pivotal clinical trials vs vehicle conducted in 723 patients with impetigo (>60% children population from 2 months on), 361 treated with Ozenoxacin, in which the efficacy was evaluated after 5 days of therapy (twice a day application) obtaining significant greater clinical and microbiological improvement over vehicle. For this reason we would suggest the	Thank you for your comment. The committee discussed the limitations of the evidence for fusidic acid and mupirocin. However, the committee agreed that based on its experience and knowledge of current practice, in combination with the evidence showing the effectiveness of fusidic acid and mupirocin compared with other antibiotics, that these antibiotics are the most appropriate for treatment of impetigo. The pooled analysis of Gropper et al. 2014 and Rosen et al. 2018 (Hebert et al. 2018) has been prioritised and included in the final evidence review. The committee discussed this evidence for ozenoxacin topical cream as an option for impetigo. However, no evidence was identified which compared ozenoxacin to other antibiotics, therefore the committee could not comment on the benefits or harms relative to the antibiotics

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					need to include the evidence concerning Ozenoxacin in the present guideline *(**Gropper S**, Albareda N, Chelius K, Kruger D, Mitha I, Vahed Y, Gani M, García-Alonso F; Ozenoxacin in Impetigo Trial Investigators Group. Ozenoxacin 1% cream in the treatment of impetigo: a multicenter, randomized, placebo- and retapamulin-controlled clinical trial. **Future Microbiol. 2014**;9(9):1013-23.; **Rosen T**, Albareda N, Rosenberg N, Alonso FG, Roth S, Zsolt I, Hebert AA. Efficacy and Safety of Ozenoxacin Cream for Treatment of Adult and Pediatric Patients With Impetigo: A Randomized Clinical Trial. **JAMA Dermatol. 2018** Jul 1;154(7):806-813; **SmPC OZEDUB (OZENOXACIN) FERRER 10 MG/G CREAM**. Ferrer Internacional 25/5/2017 25. Revised 21/06/2018)*	recommended in the draft guideline. It was also noted that ozenoxacin is not available in the UK at the time of guideline publication. Therefore, the committee did not make any recommendations for ozenoxacin. Gropper et al. 2014 was identified in the search for this guideline and was excluded as it is included in the prioritised pooled analysis (Hebert et al. 2018). Rosen et al. 2018 was not identified in the search for this guideline, however, it was not included as it is included in the prioritised pooled analysis (Hebert et al. 2018).
30	Ferrer Internacional S.A.	Evidence review	55	Appendix E. Hebert et al. 2018	This analysis should not be considered as a post-hoc analysis as it followed a study protocol to pool all the individual data from the two randomized vehicle-controlled pivotal clinical trials ***(Gropper S**, Albareda N, Chelius K, Kruger D, Mitha I, Vahed Y, Gani M, García-Alonso F; Ozenoxacin in Impetigo Trial Investigators Group. Ozenoxacin 1% cream in the treatment of impetigo: a multicenter, randomized, placebo- and retapamulin-controlled clinical trial. **Future Microbiol. 2014**;9(9):1013-23.; **Rosen T**, Albareda N, Rosenberg N, Alonso FG, Roth S, Zsolt I, Hebert AA. Efficacy and Safety of Ozenoxacin Cream for Treatment of Adult and Pediatric Patients With Impetigo: A Randomized Clinical Trial. **JAMA Dermatol. 2018** Jul 1;154(7):806-813)*. Then we would suggest to please change it to "pooled analysis" instead. *(**Hebert AA**, Albareda N, Rosen T, Torrelo A, Grimalt R, Rosenberg N et al. Topical Antibacterial Agent for Treatment of Adult and Pediatric Patients*	Thank you for your comment. Reference to Hebert et al. 2018 has been amended throughout the evidence review and guideline to refer to it as a pooled analysis.

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					With Impetigo: Pooled Analysis of Phase 3 Clinical Trials. ***Drugs Dermatol. 2018****;17(10):1046-1052.*	
31	Ferrer Internacional S.A.	Evidence Review	87	Study reference. Gropper 2014.	Please, as in previous comment 8, we suggest to please change it to "included in a pooled analysis".	Thank you for your comment. Reference to Hebert et al. 2018 has been amended throughout the evidence review and guideline to refer to it as a pooled analysis.
32	Ferrer Internacional S.A.	Equality impact information			Although neither fusidic acid nor mupirocin have driven big concerns about safety, another point to take into account to include Ozenoxacin into this guideline is its safety profile. As the transcutaneous absorption rate of Ozenoxacin is negligible, it might be applied in all patient populations from 6 months on, including pregnant women. The adverse event rate during the clinical studies with Ozenoxacin was lower than 1% and no adverse reaction was reported in the paediatric population. ***(SmPC OZEDUB (OZENOXACIN) FERRER 10 MG/G CREAM****. Ferrer Internacional 25/5/2017.Revised 21/06/2018)*	Thank you for your comment. No evidence was identified which compared ozenoxacin to other antibiotics, therefore the committee could not comment on the benefits or harms relative to the antibiotics recommended in the draft guideline. It was also noted that ozenoxacin is not available in the UK at the time of guideline publication. Therefore, the committee did not make any recommendations for ozenoxacin.
33	Neonatal and Paediatric Pharmacists Group (NPPG)	Visual summary			NPPG welcome the production of this clear summary which will act as a quick reference guide.	Thank you for your comment.
34	Neonatal and Paediatric Pharmacists Group (NPPG)	Guideline	2	9/10	We welcome the recommendation of first line use of an antiseptic cream rather than an antibiotic supporting our commitment to reduce prescribing of antimicrobials and prevent the furthering of antimicrobial resistance.	Thank you for your comment.
35	UK Clinical Pharmacy Association (UKCPA)	Guideline			There is no consideration of the previous microbiology result **before** starting treatment (and no option if MRSA). Locally our MRSA susceptibility to fusidic acid is only ~40% (vs 78% in MSSA or vs mupiricin which is >99% for both).	Thank you for your comment. The committee agreed that sending a skin swab for microbiological testing at first presentation was unlikely to be a good use of resources as most cases of impetigo will be resolved with empirical treatment. No recommendations have been made to take into account previous microbiology results, so as not to encourage inappropriate additional microbiological tests. However, the

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						committee agreed that based on good clinical practice, it is likely that results from previous tests would be taken into account when available. The committee agreed that if MRSA is suspected or confirmed, a local microbiologist should be consulted. This has been reflected in the antimicrobial prescribing tables.
36	UK Clinical Pharmacy Association (UKCPA)	Guideline			If previous MRSA+ve no clear oral option recommended.	Thank you for your comment. MRSA infection is uncommon in impetigo. The committee agreed that if MRSA is suspected or confirmed, a local microbiologist should be consulted. This has been reflected in the antimicrobial prescribing tables.
37	UK Clinical Pharmacy Association (UKCPA)	Guideline			It is unclear why specifically hydrogen peroxide 1% has been promoted when there are other similar antiseptic products that parents may have available in the home or could be purchased/supplied on prescription.	Thank you for your comment. The only evidence identified for topical antiseptics in treating impetigo was for hydrogen peroxide 1% cream. Current practice to treat impetigo with an antibiotic (topical or oral) would require a consultation with a health professional. Furthermore, some common preparations are not licensed for superficial skin infections. As no evidence was identified for other antiseptics, the committee could not make a recommendation on these. A recommendation to be aware that other topical antiseptics are available for superficial skin infections, but no evidence was found has also been added.
38	UK Clinical Pharmacy Association (UKCPA)	Guideline			The suggested course lengths for both topical and oral antibiotics are 5-7 days and it would be clearer for users to choose either 5 or 7 days, preferably 5 days as longer courses have more risk of resistance.	Thank you for your comment. The committee agreed that a 5-day course would be appropriate for most people with impetigo, however, some people may need a longer course because of the severity or number of lesions. The committee agreed that the option of prescribing antibiotics for 7 days should be available for these people. A footnote has been added to the antimicrobial prescribing tables to reflect this.

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39	British Association of Dermatologists				Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. Reducing overuse of topical antibiotic steroid combinations, particularly in primary care but also in secondary care. Relative benefits of topical vs systemic antibiotics and topical antibiotics vs antiseptics. Optimal length of treatment/dosage. Differences between management in children and adults. Hazards of topical antiseptics (e.g. potassium permanganate ingestion). Evidence of topical antiseptics vs saline in impetigo.	Thank you for your answer to our question asked at consultation.
40	British Association of Dermatologists				What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) There is a lot of information out there and some good reviews, but this knowledge is not that widely known.	Thank you for your answer to our question asked at consultation.
41	British Association of Dermatologists				Are there any recommendations that will be a significant change to practice or will be difficult to implement? If so, please give reasons why. All above. Influence of pharma marketing over the years. Possibility that MHRA might recommend potassium permanganate should be discontinued in community.	Thank you for your answer to our question asked at consultation.
42	British Association of Dermatologists				What are the key issues or learning points for professional groups? Don't use topical antibiotic steroid combinations long-term. Don't use topical antibiotics except in some very specific situations.	Thank you for your answer to our question asked at consultation. Please note that the effectiveness of an antibiotic compared with an antibiotic and steroid combination was not covered by this guideline. Therefore, the committee did not make any recommendations on the use of topical antibiotic and steroid combinations.
43	Royal College of Physicians				The RCP would like to endorse the response submitted by the British Association of Dermatologists (BAD).	Thank you for your comment.

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44	Scottish Antimicrobial Prescribing Group	Visual summary and guideline			Good in general, however more detail is needed for mild cases, in particular, on the antiseptic cream. The summary only says 'such as hydrogen peroxide cream 1%'. Does that mean that the much more common proprietary or OTC creams that many families with young children will have in the home don't work/don't work as well, e.g. savlon (chlorhexidine based) and sudocrem (zinc)? It is not helpful to specify one particular product. Is Hydrogen peroxide cream likely to be irritant? Hydrogen peroxide cream is not commonly used so NHS 24/NHS 111 need to be made aware to be able to suggest self-care/consulting a pharmacy. Community pharmacies also need to be aware of recommended antiseptic products to ensure they keep them as stock.	Thank you for your comment. The only evidence identified for topical antiseptics in treating impetigo was for hydrogen peroxide 1% cream. Current practice to treat impetigo with an antibiotic (topical or oral) would require a consultation with a health professional. Furthermore, some common preparations are not licensed for superficial skin infections. As no evidence was identified for other antiseptics, the committee could not make a recommendation on these. A recommendation to be aware that other topical antiseptics are available for superficial skin infections, but no evidence was found has also been added. The evidence for hydrogen peroxide compared with fusidic acid shows there are no differences between these treatments in the number of adverse events or mild side effects. The committee also agreed, based on its experience, that hydrogen peroxide 1% cream was not likely to be an irritant. The committee recognises the importance of raising awareness to support implementation of the guidelines.
45	Scottish Antimicrobial Prescribing Group	Visual summary and guideline			The main reason GPs are pressured into antibiotics (usually topical) is when a child has a very small crusty lesion, and they are excluded from school or nursery for 48hrs (and thus parents can't go to work) until after they get antibiotics as per PHE guidelines. Extract from a link in this NICE consult document: *Inform the person of Public Health England exclusion recommendations:*	Thank you for your comment. This antimicrobial prescribing guideline was developed in collaboration with Public Health England and advice regarding school and work exclusion guidelines will be reviewed by PHE.

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					• *Children and adults should stay away from school and other childcare facilities or work until lesions are healed, dry and crusted over or 48 hours after initiation of antibiotics.* This needs to be changed at PHE level if antiseptic cream is an acceptable treatment.	
46	Scottish Antimicrobial Prescribing Group	Visual summary and guideline			Recommendation for 5-7 days for creams or antibiotics may be confusing. Suggest specify 5 days and review if no improvement rather than overtreat the majority of patients who only need 5 days.	Thank you for your comment. The committee agreed that a 5-day course would be appropriate for most people with impetigo, however, some people may need a longer course because of the severity or number of lesions. The committee agreed that the option of prescribing antibiotics for 7 days should be available for these people. A footnote has been added to the antimicrobial prescribing tables to reflect this.
47	Scottish Antimicrobial Prescribing Group	Visual summary and guideline			Oral antibiotic choices. Practice in Scotland would be to use doxycycline as an alternative to flucloxacillin (in patients 12 years and over) rather than macrolides.	Thank you for your comment. The committee discussed the alternative choices for oral antibiotics if flucloxacillin is unsuitable and agreed that clarithromycin and erythromycin (in pregnancy) are suitable as they are effective against the common pathogens that cause impetigo and evidence indicated that macrolides are as effective as penicillins for treating impetigo. No evidence was identified for doxycycline. Therefore, no changes have been made to the choices of alternative oral antibiotics.
48	Scottish Antimicrobial Prescribing Group	Implementation questions			While the addition of an option to use antiseptic cream is welcome as a means of using less antibiotics this represents a change to current practice. Clear messaging about suggested products is required for GPs and community pharmacists as well as for patients and parents.	Thank you for your comment. The recommendation has been amended to specify the choice of topical antiseptic and this has also been added to the prescribing table.
49	NHS England	Guideline			The revised guidelines are not too dissimilar to what is currently standard practice but clarifies some areas which I think will be very helpful for	Thank you for your comment. The committee agreed that by recommending mupirocin as an alternative choice antibiotic if fusidic acid

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					primary care teams dealing with impetigo (this can be GP's, ANP's, AED and ?pharmacists) I found the emphasis on topical antiseptic as an effective first line treatment as very helpful. (I will change my practice as a consequence) If this was more broadly adopted it may help with AMR. Fucidin should rightly be advised as first line after topical antiseptic and it may be worth adding that we are trying to limit mupirocin use as it can be used for MRSA and resistance is being seen to it and there isn't another topical treatment to use after it (that I know of). (P15 24-27 emphasises no difference in effectiveness) I also found the advice to use oral antibiotics for bullous impetigo due to possible lack of effectiveness of topical treatments on bullous lesions helpful. When published I wonder if these 2 points (topical/bullous treatments), which seem to me to be the main changes, be emphasised in any published summary?	resistance suspected or confirmed, it was limiting mupirocin use as much as appropriate. The committee also noted that by recommending that hydrogen peroxide 1% cream should be considered for people with localised non-bullous impetigo, it was helping to limit topical antibiotic use, including mupirocin use. We have discussed the main changes in practice - as highlighted by stakeholders and by the committee - with the NICE communications team. We are not able to provide a summary of the main changes to practice within the guideline.
50	NHS England	Guideline	2	13/14	This didn't read well and initially confused me, do you think lines 13/14 should be before 9/10 (in red below) Treatment 7 1.1.2 For people with localised non-bullous impetigo who are not systemically unwell or at high risk of complications • a topical antiseptic such as hydrogen peroxide 1% cream (applied two to three times a day for 5 to 7 days), or	Thank you for your comment. The treatment recommendations for people with localised non-bullous impetigo who are not systemically unwell or at high risk of complications have been separated for clarity.

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					a topical antibiotic (see recommendations on choice of antibiotic) if a topical antiseptic is not suitable.	
51	NHS England	Guideline	3	6	I appreciate that combination treatment should not be offered and this would not be common practice but would it be worth mentioning the role of a deferred prescription? It may be reasonable when treating topically if it looks borderline for topical treatment and/or there are extenuating circumstances (eg Friday..) to treat topically and give a deferred prescription for oral antibiotics should it not improve/worsen in the next few days. The reason being to reduce burden on already stretched services and improve the patient journey.	Thank you for your comment. The committee discussed the use of delayed prescriptions for management of impetigo. However, the committee noted that recommendations on reassessment include reassessing people with impetigo if their symptoms worsen rapidly or significantly at any time or have not improved after completing a course of treatment. Appropriate treatment options for these people are also recommended in the section on reassessment. Therefore, the committee agreed that it was not appropriate to recommend delayed prescriptions for management of impetigo.
52	NHS England	Guideline	3	12/15	I was a little confused on the advice to seek medical help if "do not start to improve after completing a course of treatment" This could be 5-7 days, generally I would advise that they should see improvement on treatment after 48-72hrs and if not to seek a review.	Thank you for your comment. The committee agreed that it was appropriate for people with impetigo who have not improved to seek help at the end of treatment, and not earlier, as improvement of symptoms before this time may not be expected. It also noted that the recommendation on reassessment covered earlier reassessment of people with impetigo if their symptoms worsen rapidly or significantly at any time.
53	NHS England	Guidelines	3	18	Possibly include herpes simplex as a possible differential diagnosis if localised to area around lips/nose?	Thank you for your comment. Herpes simplex has been included as another possible diagnosis to consider when reassessing people with impetigo.
54	NHS England	Guidelines	4	6	It is unusual for patients to not improve on treatment but would it be useful to suggest a second line oral antibiotic to use whilst awaiting skin swab results? Generally not treating whilst waiting the few days for results isn't an option, so	Thank you for your comment. The committee agreed that it could not make recommendations on second-line antibiotics to use while waiting for skin swab results, and that the choice to offer an antibiotic in this case should be based on clinical judgement. The committee noted that second-line

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					another antibiotic will be tried, so guidance may help rationalise that choice.	antibiotic choices are included in the antimicrobial prescribing tables and that these would likely be appropriate.
55	NHS England	Guidelines	8	8	It would be helpful to stipulate when they can return to work/school etc. Currently after 48hrs of treatment or when lesions crusted over. If that is still the case then it would be helpful to re-state to help advise patients (more often working parent desperate to get child back into school/nursery and unable to unless can get advice on exclusion duration).	Thank you for your comment. The school and work restrictions for impetigo are recommended by Public Health England and are not covered by this guideline. This antimicrobial prescribing guideline was developed in collaboration with PHE and advice regarding school and work exclusion guidelines will be reviewed by PHE.
56	NHS England	Guidelines			Specific questions: Are there any recommendations that will be a significant change to practice or will be difficult to implement? • As above no significant changes and no difficulty to implement. What are the key issues or learning points for professional groups? • As above, highlighting learning points as mentioned but none that have an impact on practice or challenging to implement. There is more likely a positive impact with a potential reduction in AMR risk.	Thank you for your response to our questions asked at consultation.
57	Royal College of Nursing	General			The Royal college of Nursing (RCN) welcomes proposals by NICE to develop guidelines for the antimicrobial prescribing for impetigo.	Thank you for your comment.
58	Royal College of Nursing	General			The draft guideline is clear and comprehensive. We are pleased to note reference to the importance of clinicians using clinical judgement where appropriate to tailor treatment for individual patients.	Thank you for your comment.