The early use of Antibiotics for At-risk children with InfluEnza in Primary Care (the ARCHIE programme)

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Disclosure of interests

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Scientific summary

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Scientific summary

Background

Influenza circulates annually, predominantly in the winter months, creating a burden on health services, families and individuals. Although for most children influenza-like illness (ILI) is a mild and relatively short illness, it is widely considered to be a predisposing factor for secondary complications, including bacterial infections such as otitis media and pneumonia. These complications often result in children consulting a health-care professional more than once during the same illness episode owing to clinical deterioration, putting additional strain on the NHS during the winter months. At-risk children are children who are more prone to clinical deterioration from ILI (e.g. bacterial infections and hospitalisation) and include children with underlying health conditions such as asthma, diabetes mellitus and Down syndrome.

Although vaccination against influenza is widely available, the uptake and efficacy of the vaccine is variable from season to season, meaning alternative strategies remain necessary. It is widely acknowledged that antibiotics should not routinely be given to treat viral illness owing to a lack of efficacy and the risk of fuelling antibiotic resistance. However, there is exploratory evidence indicating that treatment with an antibiotic early in an episode of ILI may reduce the risk of clinical deterioration by preventing additional complications and may help children feel better more quickly. In order to ensure antibiotics stockpiles are managed responsibly and appropriate strategies are in place, both for seasonal ILI and any future influenza pandemics, the potential effectiveness of antibiotics to treat at-risk children presenting with ILI is a key research question.

Objectives

The overall objective of the programme was to provide an evidence base to inform the use of antibiotics in at-risk children with ILI. Our nine specific objectives were as follows:

1. to identify risk factors and assess the reliability of published prognostic models for influenza-related complications in children (work package A)
2. to understand what factors influence general practitioners' (GPs') decisions about antibiotic prescribing for at-risk children with influenza/ILI (work package B)
3. to explore the experiences of parents of at-risk children who have previously become unwell due to influenza/ILI (work package B)
4. to explore parental consulting attitudes in relation to influenza/ILI (work package B)
5. to determine the effectiveness of early co-amoxiclav (Augmentin®, GlaxoSmithKline UK) use in at-risk children with influenza/ILI (work package C)
6. to examine the impact on antibiotic resistance of early co-amoxiclav use in at-risk children with influenza/ILI (work package D)
7. to determine the impact on long-term respiratory bacterial carriage of early co-amoxiclav use in at-risk children with influenza/ILI (work package D)
8. to develop and validate risk scores for influenza-related clinical deterioration and complications for use in children with influenza/ILI (work package E1)
9. to explore the cost-effectiveness of different potential strategies for early antibiotic use in at-risk children with influenza/ILI (work package E2).

Work package methods and results

Objectives were addressed through five separate work packages.

Work package A

Methods

A systematic review of the existing literature was carried out, which met objective 1 (identify risk factors and assess existing models).

Results

The systematic review identified premature birth as a new risk factor for clinical deterioration, particularly in children aged <2 years, where the most data relating to this risk factor were available. Other identified risk factors were neurological disorders, sickle cell disease, immunosuppression and diabetes mellitus. Obesity and reactive airway diseases such as asthma were not found to be significant risk factors, although data on clinical severity were not available to examine. The presence of multiple co-morbidities was associated with increased risk of hospitalisation.

Work package B

Methods

Qualitative research was conducted via interviews with both GPs and parents/guardians of children with underlying medical conditions who had experienced an influenza/ILI episode to address objectives 2–4.

Results

Objective 2

There is considerable variation in how GPs decide to treat at-risk children presenting with ILI. However, their assessments are primarily based on their overall impression of the child's condition, including familial circumstances (i.e. trust in parent/guardian) and local arrangements for out of hours care, and rarely on vaccination status and type of infection (influenza vs. other infection) outside influenza pandemic settings.

Objective 3

Parents of children with underlying risk factors noticed that their children tended to deteriorate quickly if they developed ILI and would take longer to recover than otherwise healthy children. In some cases, the management of the child's underlying condition also changed and took time to return to normal. ILI episodes resulting in serious illness caused significant disruption and challenges in relation to parents' work, children's attendance at school or day care and managing household arrangements and finances.

Objective 4

Parents valued being able to seek advice from clinicians who knew their children well. Some would make contact with the child's specialist team directly if the child developed ILI or stay in telephone contact with their GP. Factors that prompted parents to seek medical advice included high temperatures not resolving despite repeated doses of paracetamol and ibuprofen, reduced oral fluid intake or symptoms persisting for a longer time than they felt comfortable with managing at home.

Summary

Parents were on the whole aware of the dangers of antibiotic resistance and that antibiotics should not typically be used to treat viral illness. However attitudes towards antibiotics were positive, including their use as prophylactic treatment. Parents interviewed discussed rapid, and sometimes unexpected, deterioration in their child when unwell with ILI owing to their child's underlying health condition.

Work package C

Some text in this section has been adapted with permission Wang K, Semple MG, Moore M, Hay AD, Tonner S, Galal U, *et al*. The early use of Antibiotics for at Risk CHildren with InfluEnza-like illness (ARCHIE): a double-blind randomised placebo-controlled trial. *Eur Respir J* 2021;**58**:2002819. The text below includes minor additions and formatting changes to the original text.

Methods

Objective 5 was addressed through a randomised double-blind placebo-controlled clinical trial to determine if early treatment with co-amoxiclav versus placebo reduces the risk of reconsultation owing to clinical deterioration in at-risk children who present with ILI. Reconsultation was defined in our trial protocol as any subsequent visit to a primary care or other equivalent ambulatory care setting including but not limited to out of hours primary care centres, accident and emergency departments, day assessment units and specialist clinics. We defined clinical deterioration as the worsening of symptoms, development of new symptoms or development of complications requiring medication or hospitalisation.

Results

A total of 271 participants were recruited to the clinical trial (co-amoxiclav *n* = 136, placebo *n* = 135) with primary outcome data being available for 265 participants (co-amoxiclav *n* = 133, placebo *n* = 132). At least one reconsultation owing to clinical deterioration was recorded in 33/133 children randomised to co-amoxiclav (24.8%) and 28/132 children randomised to placebo (21.2%). There was no evidence of a difference in clinical deterioration between groups after adjustment for stratification and minimisation factors [adjusted risk ratio (RR) 1.16, 95% confidence interval (CI) 0.75 to 1.80; unadjusted RR 1.17, 95% CI 0.75 to 1.82; unadjusted risk difference 3.6%, 95% CI −6.5% to 13.7%]. An exploratory subgroup analysis of participants with laboratory-confirmed influenza showed that the proportion of children who reconsulted owing to clinical deterioration was lower in the co-amoxiclav group (*n* = 5/21, 23.8%) than in the placebo group (*n* = 6/16, 37.5%). However, this result was not shown to be statistically significant and should be interpreted with caution owing to the limited number of children in this subgroup. Unadjusted analyses comparing durations of symptoms and fever between groups found that participants randomised to the co-amoxiclav arm reported a shorter duration of disturbed sleep [co-amoxiclav: median 4 days, interquartile range (IQR) 2–6; placebo: median 7 days, IQR 3–11; $p = 0.021$]. However, after adjustment, a statistically significant difference in duration of disturbed sleep was no longer observed between the co-amoxiclav and placebo groups. Instead, duration of shortness of breath was found to be significantly shorter in the co-amoxiclav group (adjusted median difference −2.00 days, 95% CI −3.89 to −0.11 days; $p = 0.038$).

Work package D

Methods

To address objectives 6–7, a nested substudy was conducted within the clinical trial to assess if there was an impact on antibiotic resistance or long-term respiratory bacterial carriage in participants randomised to co-amoxiclav versus placebo. Participants who were consented to the substudy were invited for additional throat swabs at 3, 6 and 12 months.

Results

We obtained a baseline throat swab for 225/271 participants. However, there was a 66% attrition rate and a 12-month swab was obtained for 93 participants only. As a result of this limited data, only descriptive statistics were possible for the majority of the data gathered.

Objective 6

No evidence was found to suggest that the additional course of antibiotics led to suppression of mixed flora or emergence of other resistant species methicillin-resistant *Staphylococcus aureus* Rosenbach 1884 (MRSA).

Objective 7

Haemophilus influenzae (Lehmann and Neumann 1896) Winslow *et al*. 1917 was the most common pathogen isolated (23% of all isolates). A chi-squared test was applied to these data in regards to co-amoxiclav versus placebo (29% vs. 18%, respectively, $\chi^2 = 4.03$; $p < 0.05$) and there were no statistically significant differences in prevalence of *H. influenzae* at 3, 6 or 12 months between the two arms.

Work package E

Methods

To address objective 8, data collected during the clinical trial were used to compile risk reduction scores where sufficient data were available. To address objective 9, a within-trial health economics cost analysis was conducted.

Results

Objective 8

Limited available data meant that the planned risk score calculations could not be completed in full. From the data available there was no evidence of increased risk of clinical deterioration associated with treatment arm (co-amoxiclav vs. placebo), respiratory risk factors versus other risk factors, or recruitment in secondary care versus primary care. An increased risk of clinical deterioration was observed for a higher respiratory rate at baseline and a decreased risk observed if there was a smoker in the household. Owing to the limited number of clinical deterioration events, however, these findings should be interpreted with caution.

Objective 9

The pre-trial cost-effectiveness decision model highlighted the need for a trial to be undertaken, owing to the lack of published evidence to inform the parameters of a pre-trial cost analysis model. Despite extensive consultation with parents and young people regarding preferred outcome measures prior to the trial, only 27% of day 28 diaries were received. A statistically non-significant trend towards lower non-medication costs and total costs for participants randomised to co-amoxiclav than those randomised to placebo was observed. However, larger studies would be needed to confirm this trend. The mean total cost per patient was £94 [standard deviation (SD) £480] in the co-amoxiclav group, and £122 (SD £539) in the placebo group (adjusted between group difference –£25, 95% CI –£113 to £62; $p = 0.566$).

Strengths and limitations

Work conducted as part of work packages A and B has contributed evidence towards identifying which comorbidities may make children more susceptible to clinical deterioration when consulting with ILI. It has also contributed towards our understanding of the decision-making process of clinicians treating at-risk children and the concerns of parents of at-risk children. This is an essential component in determining the acceptability of any change in treatment guidance.

The most significant limitation was the lower than anticipated recruitment into our clinical trial. Recruitment was hindered by low levels of influenza circulating in the UK during the recruiting seasons of 2015–8. Logistical and capacity issues also occurred at recruiting sites, making opportunistic recruitment difficult. Lower than anticipated recruitment into the clinical trial and a lower than anticipated proportion of children reconsulting owing to clinical deterioration impacted on our microbiology (work package D), risk reduction score calculation (work package E1) and health economic (work package E2) strands as they were reliant on follow-up and data collected from work package C. We did not nest any qualitative research within the trial. This might have helped us gain a better understanding of the factors that drive parents to reconsult and the potential impact of taking part in the trial on health-care professional behaviours. The qualitative work conducted within this programme primarily involved parents of younger children. This may have implications for the generalisability of our findings to older children with known risk factors. The case vignette we devised for our interview study with GPs also described a young child with potential risk factors for clinical deterioration. This may have elicited different responses from interview participants from those that may have been elicited had we presented a scenario involving an older child alongside or instead of the scenario we devised.

Conclusions

Our clinical trial results showed no evidence that early co-amoxiclav treatment in at-risk children presenting in primary or ambulatory care with ILI is effective in reducing reconsultation owing to clinical deterioration. However exploratory subgroup analysis results suggest that, for at-risk children with laboratory-confirmed influenza, early co-amoxiclav treatment may be effective. No evidence of increased incidence of antibiotic resistance being associated with the 5-day course of co-amoxiclav was observed in work package D. Our within-trial economic evaluation did not find evidence that early co-amoxiclav treatment improves quality of life or reduces health-care use and costs in at-risk children with ILI. A statistically non-significant trend towards lower non-medication and total costs in the co-amoxiclav arm than the placebo arm was observed in work package E2 but larger trials would be necessary to confirm this.

Future work

Owing to only a small subset (n = 37/271) of clinical trial participants testing positive for influenza at baseline, the question of whether or not at-risk children with influenza (rather than ILI) would benefit from antibiotic treatment early on in their illness remains open. More research is needed to determine the clinical effectiveness and cost-effectiveness of early antibiotic treatment during periods of high influenza activity, such as influenza pandemics, and to explore strategies for identifying children with ILI who would potentially gain the most clinical benefit from early antibiotic treatment. These strategies may include consideration of local surveillance data on influenza and other respiratory infections, point-of-care testing for influenza and other potentially pathogenic respiratory infections, and risk prediction scores to identify children at the greatest risk of serious complications from acute respiratory tract infections. Most acute respiratory tract infections presenting in primary care have initially been assessed remotely since the start of the COVID-19 pandemic. Further research to inform remote assessment of risk would also be informative in guiding clinical decisions about when early antibiotic treatment should be considered and parental decisions about when to seek the advice of a health-care professional when their child has ILI. Future qualitative research should potentially explore the views of parents, children and health-care professionals on such strategies and aim to understand clinical decision-making and health-care-seeking behaviour across a wider range of groups and clinical scenarios.

Trial registration

This trial is registered as ISRCTN70714783 and EudraCT 2013-002822-21.

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