

ORIGINAL ARTICLE

Randomized controlled trial of the effect of regular paracetamol on influenza infection

SARAH JEFFERIES,¹ IRENE BRAITHWAITE,¹ STEVEN WALKER,¹ MARK WEATHERALL,^{2,3}
LANCE JENNINGS,⁴ MICHELLE LUCK,⁴ KEVIN BARRETT,⁴ ROBERT SIEBERS,² TIMOTHY BLACKMORE,³
RICHARD BEASLEY^{1,3} AND KYLE PERRIN^{1,2,3} On behalf of the Pi Study Group*

¹Medical Research Institute of New Zealand, ²Department of Medicine, University of Otago Wellington, ³Capital & Coast District Health Board, Wellington, and ⁴Canterbury Health Laboratories, Canterbury District Health Board, Christchurch, New Zealand

ABSTRACT

Background and objective: Anti-pyretic treatment is recommended in the management of influenza infection. In animal models anti-pyretic treatment increases mortality from influenza. We investigated the effects of paracetamol on viral and clinical outcomes in adults with influenza infection.

Methods: This is a randomized, double-blind, placebo-controlled trial of adults aged 18–65 years with influenza-like illness and positive influenza rapid antigen test. Treatments were 1 g paracetamol four times a day, or matching placebo, for 5 days. Pernal swabs were taken for influenza quantitative RT-PCR at Baseline and Days 1, 2 and 5. Temperature and symptom scores were recorded for 5–14 days or time of resolution respectively. The primary outcome variable was area under the curve (AUC) for quantitative PCR log₁₀ viral load from Baseline to Day 5.

Correspondence: Irene Braithwaite, Medical Research Institute of New Zealand, Private Bag 7902, Newtown, Wellington 6242, New Zealand. Email: irene.braithwaite@mri.nz

Disclosure statement: RB has been a member of the GlaxoSmithKline (GSK) New Zealand advisory board and has received research grants, payments for lectures and/or attended meetings from GSK, a manufacturer of paracetamol. LJ has received unrestricted research funding from F. Hoffman-La Roche, and honoraria and travel assistance from F. Hoffman-La Roche, GlaxoSmithKline and Sanofi Pasteur for participating on advisory groups or in scientific meetings.

*Pi Study Group: Medical Research Institute of New Zealand: Irene Braithwaite, Richard Beasley, James Fingleton, Sarah Jefferies, Mark Holliday, Claire Munro, Mitesh Patel, Kyle Perrin, Janine Pilcher, Alison Pritchard and Steve Walker; Capital & Coast District Health Board: Jonathon Barrett, Tim Blackmore, Marina Dzheleli, Leeanne Olsen, Serena Rooker and Helen White; University of Otago, Wellington: Rob Siebers and Mark Weatherall; Canterbury Health Laboratories: Kevin Barratt, Lance Jennings and Michelle Luck.

Received 8 April 2015; invited to revise 21 May and 3 July 2015; revised 26 May and 14 July 2015; accepted 31 August 2015 (Associate Editor: Marcos Restrepo).

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

SUMMARY AT A GLANCE

Despite recommendations to administer paracetamol for symptom relief in influenza and influenza-like-illnesses, this study has found that regular administration of paracetamol has no effect on viral or clinical outcomes in this setting.

Results: A total of 80 participants were randomized: no one was lost to follow up, and one withdrew after 4 days. There were 22 and 24 participants who were influenza PCR-positive in placebo and in paracetamol groups respectively. Mean (SD) AUC PCR log₁₀ viral load was 4.40 (0.91) in placebo and 4.64 (0.88) in paracetamol; difference was -0.24, 95% CI: -0.78 to 0.29, $P = 0.36$. In all participants there were no differences in symptom scores, temperature, time to resolution of illness and health status, with no interaction between randomized treatment and whether influenza was detected by PCR.

Conclusion: Regular paracetamol had no effect on viral shedding, temperature or clinical symptoms in patients with PCR-confirmed influenza. There remains an insufficient evidence base for paracetamol use in influenza infection.

Clinical trial registration: ACTRN12611000497909 at the Australian New Zealand Clinical Trials Registry.

Key words: anti-pyresis, influenza, influenza-like illness, paracetamol, randomized controlled trial.

Abbreviations: °C, degrees Celsius; AUC, area under the curve; CI, confidence interval; CTU, clinical trials unit; IFN- γ , interferon γ ; IL, interleukin; Log, logarithm; mg, milligrams; NSAID, non-steroidal anti-inflammatory drug; PCR, polymerase chain reaction; RNA, ribonucleic acid; RT-PCR, reverse transcriptase polymerase chain reaction; SD, standard deviation; VAS, visual analogue scale.

INTRODUCTION

Seasonal and pandemic influenza infection is an important public health issue.^{1,2} Effective strategies to

reduce the morbidity and mortality associated with influenza are a global health priority.³ International guidelines recommend fever treatment with anti-pyretics during influenza infection with the qualification that they 'may help and are unlikely to cause harm'.⁴ However fever is a beneficial adaptive physiological response to infection that may confer a survival benefit so that, in fact, treating fever with anti-pyretics could be harmful.⁵

In animals, treatment with anti-pyretic drugs increases mortality in viral,⁶ bacterial⁷ and parasitic⁸ infections. A meta-analysis of the effect of anti-pyretic drug therapy in animal models of influenza infection found an increased risk of mortality, with an odds ratio of 1.34 (95% CI: 1.04–1.73).⁹ In humans paracetamol prolongs infection in varicella zoster,¹⁰ malaria¹¹ and rhinovirus,¹² and impairs immune responses.^{12,13} There have been no previous randomized, double-blind, placebo-controlled trials of the effect of anti-pyretic therapy on human influenza infection.

There are a number of potential mechanisms by which treatment with anti-pyretics such as paracetamol may influence outcomes in influenza infection. Temperatures within the human febrile range enhance the activity of cytotoxic T lymphocytes and cytokines such as interferon (IFN).^{14,15} Paracetamol inhibits polymorphonuclear leucocyte function *in vitro*^{16,17} with this effect augmented at human febrile temperatures.¹⁸ Prophylactic paracetamol at the time of vaccination impairs the humoral immune response and opsonophagocytic activity in infants, apparently independent of an effect on fever.¹⁹ Human-tropic influenza viruses replicate in the upper respiratory tract at 33–37°C. Most naturally occurring influenza A strains that infect humans are temperature sensitive, with inhibition of replication at temperatures within the physiological febrile range of 38–41°C.^{20,21} The degree of temperature sensitivity is one of the characteristics that determine virulence.²²

This trial investigates the effects of paracetamol on viral shedding and clinical symptoms in adults with community-acquired influenza infection. We hypothesized that regular administration of paracetamol during confirmed influenza infection is associated with prolonged viral shedding, worse symptoms, and prolonged illness duration.

METHODS

We conducted a randomized, double-blind, placebo-controlled, parallel-group trial in the clinical trials unit (CTU), Wellington Regional Hospital, Wellington, New Zealand, between July 2011 and September 2012, spanning two southern hemisphere winter influenza seasons. Participants were referred by doctors in the Wellington region or presented directly to the study site following public advertising and telephone screening. This trial was prospectively registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12611000497909, URL <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=336870>

This study received NZ Health & Disability Ethics Committee Approval: CEN/10/12/057.

More detailed methodology is available in Supplementary Appendix S1. Eligible participants were aged 18–65 years and had symptoms of an influenza-like illness (a history of fever (or documented temperature of $\geq 37.8^\circ\text{C}$), and at least one of cough, sore throat, rhinorrhoea, headache, myalgia, fatigue or malaise) for less than 48 h. After obtaining written informed consent, a rapid immunoassay test for influenza A and/or B (Xpect Flu A&B, Remel, Lenexa, KS, USA) was used to screen participants.²³ Only those who tested positive were eligible for recruitment. Key exclusion criteria included were the need for hospital admission and the regular use of paracetamol or non-steroidal anti-inflammatory drugs (NSAID) (excluding low dose aspirin).

Participants were simple-randomized 1:1 to receive two 500-mg paracetamol tablets, or placebo tablets, four times daily for 5 days (Sigma Pharmaceuticals Ltd, Rowville, Vic., Australia). Double-blinding was maintained by the use of identical paracetamol and placebo tablets. In addition to the study medication, all participants received a course of oral oseltamivir 75 mg one tablet twice daily with food for 5 days. Low dose oral codeine was available as required for pain.

All participants were admitted to the CTU for 48 h, during which they received directly observed randomized treatments and underwent standardized clinical assessments. Baseline data were collected.

Following randomization the following study assessments were performed: Pernal nasal flocked swabs (Copan Diagnostics, Murietta, CA, USA) were collected into Universal Transport Medium (Roche Diagnostics, Basel, Switzerland) taken for influenza quantitative viral load reverse transcriptase-polymerase chain reaction (RT-PCR) analysis at Baseline (before the first medication dose), 24 h (Day 1), 48 h (Day 2) and 120 h (Day 5). All baseline samples were tested for the presence of human ribonucleic acid (RNA) to ensure that samples had obtained human tissue; these were positive in all instances. A multiplex polymerase chain reaction (PCR) (Fast-Track Diagnostics, Junglinster, Luxembourg) was also performed on Baseline samples for other respiratory viruses.²⁴ Additional pernasal swabs were taken for viral culture at Baseline, Day 1 and Day 5. Blood samples were taken for analysis of serum cytokines (tumour necrosis factor α , IFN- γ and interleukin (IL)-6) at Baseline, Day 2 and Day 5. Details of virology methodology and cytokine analysis are provided in Supplementary Appendix S1.

Symptom scores were recorded daily from Baseline to Day 14 or until the total daily symptom score was ≤ 1 (defined as the resolution of illness). Participants rated their health on a 100-mm visual analogue scale (VAS) between 'worst possible health' and 'my health is normal for me', at Baseline, Day 2 and Day 5. Temperature was recorded using an infrared tympanic thermometer (Liberty Health Products, Melbourne, Vic., Australia) every 4 h for the duration of the CTU admission. After discharge from the CTU, participants used the same thermometer to continue

recording temperature in their study diary four times daily until a final reading was recorded on Day 5 at the scheduled CTU appointment.

Adverse events were recorded by staff during the CTU admission, on medical review on Day 5, and as documented in patient diaries up until Day 14. Adherence to randomized treatment for Days 3–5 was calculated by tablet count from returned medication bottles.

Outcome variables

The primary outcome variable was area under the curve (AUC) for quantitative PCR influenza \log_{10} viral load from Baseline to Day 5 for those participants who were PCR influenza-positive, adjusted for Baseline temperature and paracetamol use in the 48 h prior to randomization. This was chosen as the primary outcome variable as it may be a predictor of the severity of influenza infection and a predictor of risk of hospital admission.²⁵ Secondary viral outcome variables, also only applicable to participants who were PCR influenza-positive, were the proportion with a $>2 \log_{10}$ decrease in viral load at Day 2, the proportion with an undetectable viral load by RT-PCR on Days 2 and 5, and viral culture at Days 1 and 5.

Secondary clinical outcomes, applicable to all participants regardless of influenza status, were temperature profile (daily maximum, daily mean, AUC temperature in the first 48 h), time to resolution of illness, total daily symptom score, and AUC of health status VAS over 5 days.

Power calculation

Past research reports the standard deviation (SD) for AUC for quantitative PCR influenza viral load for Days 1–5 between 1.4 and 2.2 \log_{10} units.²⁶ We used the mean of these SDs for our analysis. A randomized controlled trial of anti-viral therapy in influenza reports a difference from placebo therapy of 2.2 \log_{10} units,²⁷ and we anticipated that the effect of paracetamol may be half the difference found with anti-viral therapy, (1.1). A total sample size of 80, with 40 in each of the two treatment arms, had 80% power to detect this difference, with a type I error rate of 5%.

Statistical analysis

Statistical analysis was by intention-to-treat without interim analysis. The primary outcome variable was analyzed by Student's *t*-test. The adjusted analysis was carried out by analysis of covariance. Categorical variables were analyzed by calculation of relative risks or risk differences together with appropriate CI. The analysis of temperature, symptom score and AUC VAS was by analysis of variance with randomized group, PCR influenza status and the interaction between the two as predictor variables. The individual temperature profiles were plotted together with locally weighted scatter plot smoothers. Cox proportional hazards survival analysis was used to compare time with symptom resolution. SAS version 9.3 (SAS Institute Inc, Cary, NC, USA) was used.

RESULTS

A total of 80 participants positive on influenza rapid antigen testing were randomized, 40 each to placebo and paracetamol. None was lost to follow up; one participant withdrew after 4 days due to a serious adverse event (acute kidney injury). Demographic and clinical characteristics of participants are shown in Table 1. The majority had taken anti-pyretics in 48 h prior to randomization (median dose 1 g/day of paracetamol and 400 mg/day of NSAID in 50 and 29 participants respectively). Most patients (54/80) were referred by their general practitioner following attendance with an influenza-like illness.

There were 46 participants who were PCR influenza-positive (A/H3N2 $n = 33$, A/H1N1 $n = 4$, A not typed $n = 1$, B $n = 8$): 22 in the placebo group and 24 in the paracetamol group (Fig. 1). In 20 participants a non-influenza respiratory virus only was identified by PCR, and in 14 participants no virus was identified by PCR.

Virology outcomes

The difference between the randomized groups (placebo minus paracetamol) for the primary outcome measure of AUC for quantitative influenza PCR \log_{10} viral load from Baseline to Day 5 was -0.24 (95% CI: -0.78 to 0.29), $P = 0.36$ (Table 2a). The estimate of the difference after adjustment for paracetamol use in the past 48 h and temperature at Baseline was -0.30 (95% CI: -0.87 to 0.27), $P = 0.30$. Table 2a shows viral load comparisons at each individual time point. There were no differences in the secondary viral outcome variables (Table 2b) or the cytokine measurements (Supplementary Tables S1 and S2).

Clinical outcomes

For all participants with influenza-like illness ($N = 80$) there was no difference between the paracetamol and placebo groups in the maximum daily temperature (Table 3 and Supplementary Fig. S1), mean daily temperature (Supplementary Table S3) or AUC temperature in the first 48 h (Supplementary Table S4). There was no difference in total daily symptom scores between the two groups over 5 days or in the AUC of health status VAS over 5 days (Table 3). The hazard ratio for time to resolution of illness in the placebo versus paracetamol groups was 0.89 (95% CI: 0.52–1.53), $P = 0.67$ (Fig. 2).

There was no interaction between randomized treatment and whether influenza was detected by PCR for maximum daily temperature, total daily symptom scores, time to resolution of illness and VAS (Table 3). The maximum daily temperature on Day 1 was higher for PCR influenza-positive versus -negative participants, 38.1 versus 37.4°C, mean difference 0.7°C (95% CI: 0.4–1.0), $P < 0.001$. There were no significant differences between PCR influenza-positive versus -negative participants in maximum daily temperature (Days 2–5), symptom scores, time to resolution of illness and VAS.

Table 1 Demographic and clinical characteristics

Characteristic	Placebo N = 40	Paracetamol N = 40	All N = 80
Age [†]	24.2 (7.0)	27.2 (11.9)	25.7 (9.8)
Male sex [‡]	14 (35)	14 (35)	28 (35)
Previous or current smoker [‡]	11 (27.5)	10 (25)	21 (26.3)
Respiratory comorbidity [‡]	17 (42.5)	4 (10)	21 (26.3)
Cardiovascular comorbidity [‡]	2 (5)	3 (7.5)	5 (6.3)
Ethnicity			
European [‡]	32 (80)	28 (70)	60 (75)
Māori [‡]	5 (12.5)	5 (12.5)	10 (12.5)
Pacific [‡]	1 (2.5)	3 (7.5)	4 (4)
Asian [‡]	2 (5)	4 (10)	6 (7.5)
Current influenza vaccination [‡]	9 (22.5)	3/39 [§] (7.7)	12/79 (15.2)
Anti-pyretic use in previous 48 hours [‡]			
Paracetamol	21 (52.5)	29 (72.5)	50 (62.5)
NSAID	14 (35)	10 (25)	24 (30)
Influenza A H3N2	15	18	33
Influenza A H1N1	4	0	4
Influenza A not typed	0	1	1
Influenza B	3	5	8
Non-influenza respiratory virus [¶]	9	11	20
No virus on PCR [¶]	8	6	14

[†]Mean (SD).

[‡]Number (%).

[§]Data not collected from one participant.

[¶]Six participants who were influenza A-positive and two participants who were influenza B-positive had other respiratory viruses identified: rhinovirus ($n = 2$), coronavirus ($n = 3$), parainfluenza ($n = 1$), respiratory syncytial virus ($n = 1$) and both rhinovirus and coronavirus ($n = 1$). In 20 participants a non-influenza respiratory virus only was identified by PCR: rhinovirus ($n = 8$), coronavirus ($n = 6$), parainfluenza ($n = 3$), respiratory syncytial virus ($n = 1$), enterovirus ($n = 1$) and both rhinovirus and parainfluenza ($n = 1$). In 14 participants no virus was identified by PCR.

NSAID, non-steroidal anti-inflammatory drug; PCR, polymerase chain reaction; SD, standard deviation.

In PCR influenza-positive participants, the mean (SD) maximum daily temperatures were 38.1°C (0.8) and 37.4°C (0.8) on Days 1 and 2 respectively (Supplementary Table S5).

Adverse events

One participant in the placebo group suffered a serious adverse event and withdrew from the study on Day 4. One subject in the placebo group suffered an exacerbation of asthma requiring oral prednisone. Four participants received oral antibiotics: three in the placebo group, (sinusitis ($n = 2$) and asthma ($n = 1$)), and one in the paracetamol group (tonsillitis). Oseltamivir was discontinued in 17 participants due to intolerance (7 in placebo group, 10 in paracetamol group). The median (interquartile range) codeine use in the first 48 h was 30 mg (0–60) in both placebo and paracetamol groups.

Adherence

There was a directly observed adherence of 100% to the investigational medicines during the initial 48-h inpatient stay. Two participants in the placebo group and four participants in the paracetamol group failed to return their bottles on Day 5. Adherence for Days 3–5 was 92.8% in the placebo group and 88.4% in the paracetamol group.

DISCUSSION

To our knowledge this is the first randomized, double-blind, placebo-controlled trial on the effect of paracetamol in patients with confirmed influenza infection. Regular daily administration of the maximum recommended dose of paracetamol for 5 days had no effect on viral shedding, temperature or clinical symptoms in participants with PCR-proven influenza infection. It is difficult to infer benefit or harm given the lack of effect of regular paracetamol administered early in the course of an influenza-like illness in this trial; thus, recommendations for or against this practice in the community cannot be made based on these findings.

There are a number of methodological issues to consider in the interpretation of our findings. Participants were randomized within 48 h of symptom onset to ensure treatment was initiated early in the course of the illness. The small amount of paracetamol or NSAID used by most participants before randomization is unlikely to have had a clinically significant effect on the natural course of their illness. Additionally, there was variable time between symptom onset and study entry; however, this is likely to mirror what will happen should patients seek medical advice for flu-like symptoms. Despite a pre-determined randomization schedule, there was a

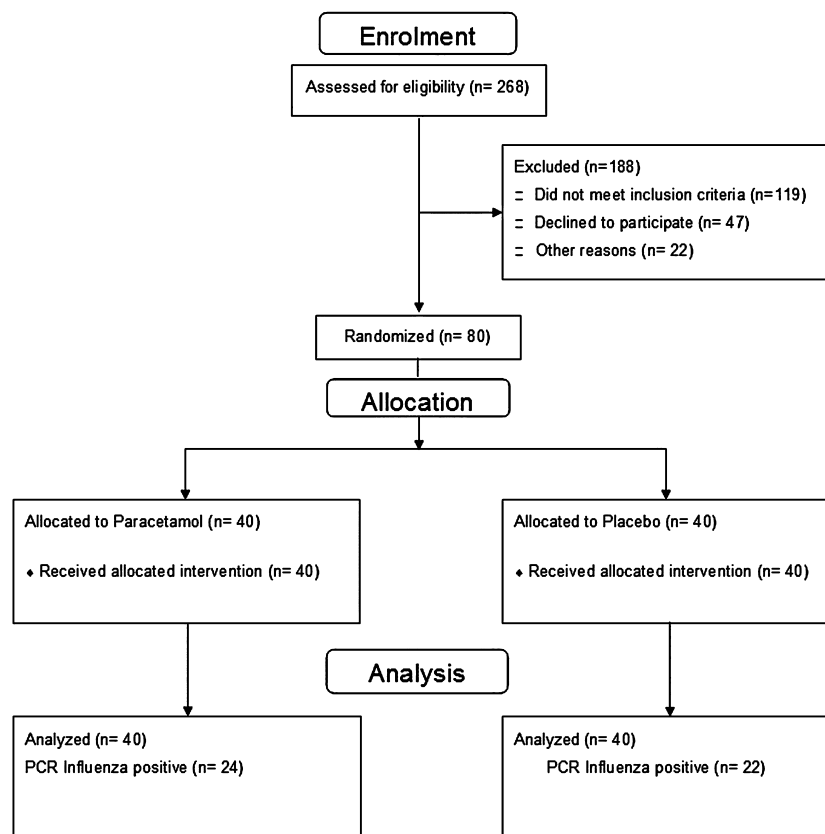


Figure 1 Flow of participants through the study.

Table 2 Influenza PCR log₁₀ viral load by randomized treatment and viral load secondary outcome variables in the 46 participants who were PCR-positive for influenza

(a) Influenza PCR log₁₀ viral load by randomized treatment

	Placebo mean (SD) N = 22	Paracetamol mean (SD) N = 24	Placebo minus paracetamol (95% CI)	P
AUC	4.4 (0.91)	4.64 (0.88)	-0.24 (-0.78 to 0.29)	0.36
Baseline	6.63 (0.92)	6.44 (1.46)	0.19 (-0.53 to 0.91)	0.61
Day 1	5.26 (1.6)	5.6 (1.32)	-0.33 (-1.20 to 0.54)	0.44
Day 2	4.57 (1.06)	5.07 (1.31)	-0.50 (-1.21 to 0.20)	0.16
Day 5	2.85 (1.21)	2.83 (1.21)	0.02 (-0.70 to 0.73)	0.97

(b) Viral load secondary outcome variables in the 46 participants who were PCR-positive for influenza

	Placebo n/22 (%)	Paracetamol n/24 (%)	Relative risk (95% CI)	P
Day 2: >2 log ₁₀ decrease in viral load	13 (59)	11 (46)	1.29 (0.74 to 2.25)	0.37
Day 2: Undetectable viral load	1 (5)	1 (4)	1.09 (0.07 to 16.4)	0.95
Day 5: Undetectable viral load	9 (49)	7 (29)	1.40 (0.63 to 3.12)	0.40
Day 1: Positive viral culture	20 (91)	21 (88)	1.04 (0.85 to 1.27)	0.71
Risk difference (95% CI)				
Day 5: Positive viral culture	0 (0)	2 (8)	-7.6 (-17.9 to 2.5)	0.18

AUC, area under the curve; CI, confidence interval; PCR, polymerase chain reaction; SD, standard deviation.

Table 3 The maximum daily temperature, total daily symptom score and AUC of health status VAS according to randomized treatment in 80 randomized participants, and interaction between influenza PCR status and randomized treatment

	Mean (SD)		Mean difference (95% CI)		Adjusted mean difference (95% CI), <i>P</i>		
	Placebo	Paracetamol	Placebo minus paracetamol	<i>P</i> value	PCR-confirmed influenza minus non-influenza [†]	Placebo minus paracetamol	Interaction <i>P</i>
Maximum temperature							
Day 1	37.8 (0.8)	37.7 (0.7)	0.1 (−0.3 to 0.4)	0.64	0.7 (0.4 to 1.0), <0.001	0.1 (−0.2 to 0.4), 0.44	0.35
Day 2	37.2 (0.6)	37.5 (0.8)	−0.3 (−0.6 to 0.1)	0.10	0.2 (−0.2 to 0.5), 0.31	−0.3 (−0.6 to 0.06), 0.11	0.48
Day 3	37.0 (0.6)	37.1 (0.5)	−0.02 (−0.3 to 0.2)	0.88	0.1 (−0.2 to 0.3), 0.57	−0.02 (−0.3 to 0.2), 0.18	0.14
Day 4	36.8 (0.6)	37.0 (0.4)	−0.2 (−0.4 to 0.1)	0.17	0.03 (−0.2 to 0.3), 0.79	−0.2 (−0.4 to 0.1), 0.18	0.13
Day 5	36.8 (0.6)	37.0 (0.5)	−0.2 (−0.4 to 0.1)	0.19	0.2 (−0.1 to 0.4), 0.18	−0.2 (−0.4 to 0.1), 0.19	0.27
Symptom score							
Day 1	10.7 (4.0)	10.6 (3.7)	0.07 (−1.7 to 1.8)	0.93	0.3 (−1.4 to 2.1), 0.70	0.1 (−1.7 to 1.9), 0.91	0.74
Day 2	8.2 (3.8)	8.5 (4.4)	−0.3 (−2.1 to 1.5)	0.75	1.0 (−0.9 to 2.8), 0.29	−2.0 (−2.1 to 1.6), 0.80	0.46
Day 3	7.5 (4.0)	7.2 (3.9)	0.30 (−1.5 to 2.1)	0.74	0.2 (−1.6 to 2.0), 0.84	0.3 (−1.5 to 2.1), 0.73	0.39
Day 4	6.2 (4.0)	6.2 (4.1)	−0.04 (−1.9 to 1.8)	0.96	−0.05 (−1.9 to 1.8), 0.96	−0.04 (−1.9 to 1.8), 0.96	0.86
Day 5	4.3 (3.4)	5.2 (4.0)	−0.9 (−2.5 to 0.8)	0.30	−0.9 (−2.6 to 0.8), 0.30	−0.9 (−2.6 to 0.8), 0.29	0.68
AUC visual analogue score Days 1–5	56.7 (13.2)	54.2 (11.2)	2.5 (−3.1 to 8.1)	0.37	−1.8 (−7.5 to 3.8), 0.52	2.4 (−3.2 to 8.0), 0.39	0.96

[†]A total of 46 participants had PCR-confirmed influenza, 34 did not have PCR-confirmed influenza.

Maximum daily temperature data were available for 80, 80, 79, 78 and 77 participants on Days 1, 2, 3, 4, 5 respectively. Total daily symptom score data were available for 77, 80, 80, 78 and 78 participants on Days 1, 2, 3, 4, 5 respectively. AUC VAS data were available for 77 participants over the 5-day period. AUC, area under the curve; CI, confidence interval; PCR, polymerase chain reaction; SD, standard deviation; VAS, visual analogue score.

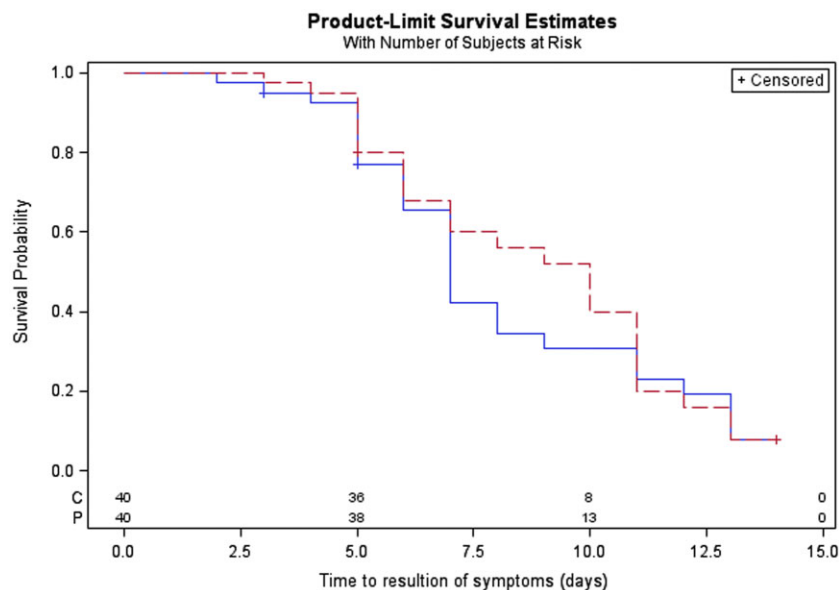


Figure 2 Survival analysis of time to resolution of illness in the 80 randomized participants. The median time to resolution of illness was 7 days (95% CI: 6–9) in the placebo (C) group and 10 days (95% CI: 6–11) in the paracetamol (P) group. The hazard ratio for placebo versus paracetamol was 0.89 (95% CI: 0.52–1.53), *P* = 0.67. Randomization: — C, - - - P.

larger number of participants in the placebo group who had chronic respiratory conditions and/or had the seasonal influenza vaccine compared with the control group. It is unclear to what extent these characteristics may have influenced participant symptom scores, if at all. All participants were admitted to the CTU for the first 48 h of the trial period. Consequently for that period, there was full compliance with the study drug and temperature recordings were complete and accurate. Adherence with medication after discharge was approximately 90% in both groups. All

participants were administered a 5-day course of oseltamivir in accordance with international recommendations for management of influenza infection at the time of protocol development.²⁸ Although this may have reduced the illness severity and viral load, the effect of oseltamivir would have been the same across both the paracetamol and placebo groups.²⁹ However, it is possible that its use may have reduced our ability to detect a significant difference between randomized treatments for the primary outcome. Most patients were recruited following attendance at

their primary healthcare clinic with an influenza-like illness and so the findings are generalizable to both the management of otherwise healthy adults with an influenza-like illness, and to those with proven influenza infection in the community.

There are a number of alternative explanations for our finding of no difference between randomized groups apart from that, in fact, paracetamol does not affect influenza outcomes. The study did not recruit 80 PCR-confirmed cases despite screening with a rapid antigen testing kit with a reported diagnostic specificity of 96–100% for both influenza A and B.²³ All Baseline pernasal samples contained human RNA, indicating that this lower than expected result was unlikely to be due to poor sampling technique. It is possible that the specificity of the rapid antigen test was reduced in this study due to cross reactivity with other respiratory viruses.²³ The lower than anticipated number of PCR-positive influenza cases might be expected to reduce statistical power to detect differences, but the SD of the primary outcome variable was substantially less than anticipated from past research. The CI for the difference excluded the difference we expected to detect, that is half the magnitude of that seen with anti-viral treatment of influenza,²⁷ but it may be that a smaller difference in the primary outcome variable is still clinically relevant. In terms of the clinical outcome variables, paracetamol did not have any significant anti-pyretic effect whether measured as daily maximum, daily mean or AUC of temperature over 48 h. This may be due in part to the modest febrile response in the participants, the mean maximum temperature on Day 1 in the influenza PCR-positive group was 38.1°C, falling to 37.4°C by Day 2. Due to its lack of anti-pyretic efficacy in our sample, we were unable to test our hypothesis that the suppression of fever with paracetamol in influenza infection may be harmful.

These findings raise questions about the anti-pyretic efficacy of paracetamol in influenza and other respiratory infections. There are no previous studies of paracetamol in proven influenza infection in adults or children. We have found two studies of paracetamol in adults with upper respiratory tract infections. One study reported a non-significant 0.43°C reduction in temperature with regular paracetamol compared with placebo in presumed non-bacterial upper respiratory tract infections.³⁰ The other study compared a single 1000-mg dose of paracetamol with placebo in acutely febrile adults with upper respiratory tract symptoms and reported a significant reduction in temperature of 1.08°C.³¹

In summary, this study has found that regular administration of paracetamol had no effect on viral shedding, temperature, symptoms or illness duration in patients with PCR-confirmed influenza infection or influenza-like illness that were also treated with oseltamivir. It is a priority to undertake further studies to ascertain the risk–benefit profile of the routine use of paracetamol alone in the treatment of presumed or PCR-confirmed influenza infection in otherwise healthy adults in the community.

Acknowledgements

The Pi Study Group would like to acknowledge the assistance of the staff at the following General Practices and Medical Centres: Island Bay Medical Centre, Karori Medical Centre, Kenepuru Accident and Medical Clinic, Massey University Student Health, Miramar Medical Centre, Newlands Medical Centre, Onslow Medical Centre, Peninsula Medical Centre, Ropata Medical Centre, Victoria University Student Health and Wellington Hospital Emergency Department.

We would also like to thank all study participants for their time contributed to the study and their diligence in adhering to study procedures.

This study was funded by the Health Research Council of New Zealand (HRC). The HRC had no role in the design and conduct of the study; the collection, management, analysis and interpretation of data; and preparation, review or approval of the manuscript, nor in the decision to submit the paper for publication. The full data set is available on request to the corresponding author at irene.braithwaite@mri.nz.ac.nz. Consent was not obtained from participants for data sharing, but the presented data are anonymized and the risk of identification is minimal.

REFERENCES

- Molinari N-AM, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Pascale MW, Weintraub E, Bridges CB. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 2008; **25**: 5086–96. doi: 10.1016/j.vaccine.2007.03.046.
- Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH, Schonberger LB. The impact of influenza epidemics on mortality: introducing a severity index. *Am. J. Public Health* 1997; **87**: 1944–50. doi: 10.2105/AJPH.87.12.1944.
- Tran TH, Ruiz-Palacios GM, Hayden FG, Farrar J. Patient-oriented pandemic influenza research. *Lancet* 2009; **373**: 2085–6. doi: http://dx.doi.org/10.1016/S0140-6736(09)61131-4.
- Lim WS. Pandemic flu: clinical management of patients with an influenza-like illness during an influenza pandemic. Provisional guidelines from the British Infection Society, British Thoracic Society, and Health Protection Agency in collaboration with the Department of Health. *Thorax* 2007; **62**(Suppl. 1): 1–46. doi: 10.1136/thx.2006.073080.
- Kluger MJ, Kozak W, Conn CA, Leon LR, Soszynski D. The adaptive value of fever. *Infect. Dis. Clin. North Am.* 1996; **10**: 1–20.
- Kurosawa S, Kobune F, Okuyama K, Sugiura A. Effects of antipyretics in rinderpest virus infection in rabbits. *J. Infect. Dis.* 1987; **155**: 991–7. doi: 10.1093/infdis/155.5.991.
- Vaughn LK, Veale WL, Cooper KE. Antipyresis: its effect on mortality rate of bacterially infected rabbits. *Brain Res. Bull.* 1980; **5**: 69–73. doi: 10.1016/0361-9230(80)90285-3.
- van der Zee CE, van Dam RH, Dwinger RH, Nieuwenhuijs J, Zwart D. Flurbiprofen and immunosuppression of *Trypanosoma brucei* infection in the goat. *Vet. Immunol. Immunopathol.* 1985; **8**: 341–50.
- Eyers S, Weatherall M, Shirtcliffe P, Perrin K, Beasley R. The effect on mortality of antipyretics in the treatment of influenza infection: systematic review and meta-analysis. *JRSM* 2010; **103**: 403–11. doi: 10.1258/jrsm.2010.090441.
- Doran TF, De Angelis C, Baumgardner RA, Mellitts ED. Acetaminophen: more harm than good for chickenpox? *J. Pediatr.* 1989; **114**: 1045–8. doi: 10.1016/S0022-3476(89)80461-5.
- Brandts CH, Ndjave M, Graninger W, Kremsner PG. Effect of paracetamol on parasite clearance time in *Plasmodium falciparum* malaria. *Lancet* 1997; **350**: 704–9. doi: 10.1016/S0140-6736(97)02255-1.
- Graham NM, Burrell CJ, Douglas RM, Debelle P, Davies L. Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. *J. Infect. Dis.* 1990; **162**: 1277–82. doi: 10.1093/infdis/162.6.1277.

- 13 Roberts NJ Jr. Impact of temperature elevation on immunologic defenses. *Rev. Infect. Dis.* 1991; **13**: 462–72. doi: 10.1093/clinids/13.3.462.
- 14 Mullbacher A. Hyperthermia and the generation and activity of murine influenza-immune cytotoxic T cells in vitro. *J. Virol.* 1984; **52**: 928–31.
- 15 Ron Y, Dougherty JP, Duff GW, Gershon RK. The effect of febrile temperatures on biologic actions of interferons: abrogation of suppression of delayed-type hypersensitivity and antibody production. *J. Immunol.* 1984; **133**: 2037–42.
- 16 Shalabi EA. Acetaminophen inhibits the human polymorphonuclear leukocyte function in vitro. *Immunopharmacology* 1992; **24**: 37–46. doi: 10.1016/0162-3109(92)90068-N.
- 17 van Zyl JM, Basson K, van der Walt BJ. The inhibitory effect of acetaminophen on the myeloperoxidase-induced antimicrobial system of the polymorphonuclear leukocyte. *Biochem. Pharmacol.* 1989; **38**: 161–5. doi: 10.1016/0006-2952(89)90163-9.
- 18 Shalabi EA, al-Tuwaijri AS. The thermal potentiation of acetaminophen-inhibited PMN oxidative metabolism in vitro. *Biopharm. Drug Dispos.* 1996; **17**: 501–9. doi: 10.1002/(SICI)1099-081X(199608)17:6<501::AID-BDD968>3.0.CO;2-1.
- 19 Prymula R, Siegrist CA, Chlibek R, Zemlickova H, Vackova M, Smetana J, Lommel P, Kaliskova E, Borys D, Schuerman L. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet* 2009; **374**: 1339–50. doi: 10.1016/S0140-6736(09)61208-3.
- 20 Dalton RM, Mullin AE, Amorim MJ, Medcalf E, Tiley LS, Digard P. Temperature sensitive influenza A virus genome replication results from low thermal stability of polymerase-cRNA complexes. *Virol. J.* 2006; **3**: 58. doi: 10.1186/1743-422X-3-58.
- 21 Giesendorf B, Bosch F, Wahn K, Rot R. Temperature sensitivity in maturation of mammalian influenza A viruses. *Virus Res.* 1984; **1**: 655–67. doi: 10.1016/0168-702(84)90056-X.
- 22 Chu CM, Tian SF, Ren GF, Zhang YM, Liu GQ. Occurrence of temperature-sensitive influenza A viruses in nature. *J. Virol.* 1982; **41**: 353–9.
- 23 REMEL. X/pect™ FLU A&B Data Sheet IFU24600, revised August 2003.
- 24 Anderson TP, Werno AM, Barratt K, Mahagamasekera P, Murdoch DR, Jennings LC. Comparison of four multiplex PCR assays for the detection of viral pathogens in respiratory specimens. *J. Virol. Methods* 2013; **191**: 118–21. doi: 10.1016/j.jviromet.2013.04.005.
- 25 Lee N, Chan PK, Hui DS, Rainer TH, Wong E, Choi K-W, Lui GCY, Wong BCK, Wong RYK, Lam W-Y *et al.* Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J. Infect. Dis.* 2009; **200**: 492–500. doi: 10.1086/600383.
- 26 Hayden FG, Treanor JJ, Betts RF, Lobo M, Esinhart JD, Hussey EK. Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. *JAMA* 1996; **275**: 295–9. doi: 10.1001/jama.1996.03530280047035.
- 27 Nicholson KG, Aoki FY, Osterhaus AD, Trottier S, Carewicz O, Mercier CH, Rose A, Kinnersley N, Ward P. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. *Lancet* 2000; **355**: 1845–50. doi: 10.1016/S0140-6736(00)02288-1.
- 28 Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, McGeer AJ, Neuzil KM, Pavia AT, Tapper ML *et al.* Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin. Infect. Dis.* 2009; **48**: 1003–32. doi: 10.1086/598513.
- 29 Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst. Rev.* 2012; (4): CD008965. doi: 10.1002/14651858.CD008965.pub3.
- 30 Ryan PB, Rush DR, Nicholas TA, Graham DG. A double-blind comparison of fenoprofen calcium, acetaminophen, and placebo in the palliative treatment of common nonbacterial upper respiratory infections. *Curr. Ther. Res. Clin. Exp.* 1987; **41**: 17–23.
- 31 Bachert C, Chuchalin AG, Eisebitt R, Netayzhenko VS, Voelker M. Aspirin compared with acetaminophen in the treatment of fever and other symptoms of upper respiratory tract infection in adults: a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, single-dose, 6-hour dose-ranging study. *Clin. Ther.* 2005; **27**: 993–1003. doi: 10.1016/j.clinthera.2005.06.002.

Supplementary Information

Additional Supplementary Information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1 Methods.

Figure S1 The maximum daily temperature during the initial five day period in the 80 individual participants randomized to placebo (blue) and paracetamol (red).

Table S1 Mean (SD) and temperature (degrees Celsius) of study participants in Days 1–5 by placebo and paracetamol.

Table S2 Area under the curve (degrees Celsius) of study participants over the initial 48-h period of enrolment into the study by placebo and paracetamol.

Table S3 The maximum daily temperature in subgroups defined by influenza PCR status and randomized treatment.

Table S4 Relative risks and confidence intervals for the difference in proportions of detectable IFN- γ between placebo and paracetamol groups.

Table S5 Difference in logarithm cytokines IL-6 and TNF- α . The exponent of the logarithm is interpreted as the ratio of mean values.