Potential cardiovascular adverse events when phenylephrine is combined with paracetamol: simulation and narrative review

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Abstract

Background Increased bioavailability of phenylephrine is reported when combined with paracetamol in over-the-counter formulations for the symptomatic treatment of the common cold and influenza. Such formulations could increase phenylephrine-related cardiovascular adverse events particularly in susceptible individuals. Quantification of the effect of phenylephrine concentration on blood pressure allows simulation of potential adverse combination therapy effects.

Methods MEDLINE and EMBASE databases were searched for papers discussing or describing any adverse effect, hypersensitivity or safety concerns related to phenylephrine alone or in combination with other drugs.

The pharmacodynamic relationship between plasma phenylephrine concentration and mean arterial blood pressure was characterized using published observations of blood pressure changes after ophthalmic eye drops. The resulting pharmacokinetic and pharmacodynamic parameters were then used to predict mean arterial blood pressure (MAP) changes in that population if given an oral combination of phenylephrine and paracetamol.

Results There were 1172 papers identified for examination. Forty-seven reports fulfilled the inclusion criteria. Increases in blood pressure and decreases in heart rate have been reported with doses over 15 mg. It has been estimated that a 20-mmHg increase in systolic blood pressure would occur with an oral dose of 45 mg phenylephrine in normotensive healthy people. Those taking monoamine oxidase inhibitors report increased systolic blood pressure of greater than 60 mmHg. Blood pressure and heart rate changes are potentiated in patients with underlying hypertension. Simulation showed a modest increase in MAP when phenylephrine 10 mg was co-administered with paracetamol 1 g (4.2 vs 12.3 mmHg).

Conclusions Combination paracetamol phenylephrine oral therapy has potential to increase blood pressure more than phenylephrine alone in those with cardiovascular compromise.

Keywords Paracetamol · Phenylephrine · Interaction · Pharmacodynamics · Blood pressure

Introduction

Phenylephrine is a selective alpha-1 adrenoceptor agonist with powerful vasoconstrictive properties. Historically, its use had been restricted to the perioperative period and intensive care medicine for preparation of the surgical field and control of haemorrhage during ear nose and throat procedures, pupillary dilation and maintenance of blood pressure. Phenylephrine is commonly used now as a nasal decongestant in many over-the-counter (OTC) cold and influenza preparations.

When phenylephrine was combined with another commonly administered cold and flu medication, paracetamol, the plasma concentration of phenylephrine was, on average, twice that obtained when phenylephrine was given alone and
the peak concentration approximately four times higher [1]. It is suggested that the increase in phenylephrine bioavailability is due to a reduction in the amount of phenylephrine undergoing first-pass metabolism due to saturation of the sulfation pathways by paracetamol [1]. Formulation may also have impact. Phenylephrine bioavailability was reduced when administered as a paracetamol-guaifenesin-phenylephrine syrup compared to the same combination in tablet form [2]. These findings raise the concern that phenylephrine administered as a combination with paracetamol may increase the incidence of adverse effects attributable to phenylephrine, most notably cardiovascular adverse effects particularly those with preexisting cardiovascular conditions.

Here, we provide a systematic narrative review of cardiovascular adverse effects associated with phenylephrine. We quantify the effect of phenylephrine concentration on blood pressure using published data and simulate the potential impact paracetamol phenylephrine combination oral therapy may have on cardiovascular endpoints.

**Methods**

**Literature review of phenylephrine adverse events**

**Search strategy**

A broad search (search terms are detailed in the Supplementary Appendix) of both MEDLINE and EMBASE databases was undertaken followed by manual selection of relevant reports based on the inclusion and exclusion criteria described below. No specific time limits were applied to the search. The time frame of the search was limited only by the coverage of the database (MEDLINE: 1946 to April 2014; EMBASE: 1947 to April 2014).

Papers discussing or describing any adverse effect, hypersensitivity or safety concern related to phenylephrine alone or in combination were included. Papers were excluded if they (1) did not describe an adverse effect for phenylephrine; (2) related to children under 12 years of age; (3) were not written in English or a full-text version was not available for purchase; (4) was not a clinical trial [either prospective or retrospective], case report or series, or a meta-analysis; and (5) did not relate to the cardiovascular system. References of identified papers were reviewed for additional relevant reports.

**Simulation**

**Phenylephrine PKPD relationship analysis**

The relationship between plasma phenylephrine concentration and mean arterial blood pressure was characterized using those published data from Kumar and colleagues [3], who related the systemic absorption of phenylephrine eye drops to cardiovascular effects. Individual plasma concentrations and corresponding blood pressure changes at 0, 10, 20 and 60 min after 2.5 % \((n=10)\) and 10 % \((n=10)\) eye drops (two 32-μL drops at 5-min intervals) are contained in Tables 1 and 2 of that publication\((n=20)\). Further pharmacokinetic (PK) data were available from healthy volunteers given oral phenylephrine 10 mg alone, with blood for concentration assay taken at 5, 15, 30, and 45 min and 1, 2, 3, and 6 h \((n=28, \text{ data from [1, 4]}\)). Intravenous time-concentration data were available from a study by Hengstmann and colleagues [5]. Four healthy volunteers were given phenylephrine 1 mg, and blood was taken for assay on 17 occasions over the subsequent 4 h. Pooled data for that study are presented in Table 2 of that publication\((n=1)\). Technical methods for population parameter estimates using nonlinear mixed effects models (NONMEM) can be found in the Supplementary Appendix.

**Results**

**Literature search**

A total of 1172 papers were identified for examination. Forty-seven reports fulfilled the inclusion criteria. The majority of literature concerning phenylephrine and cardiovascular effects related to its use as a hypertensive agent for the management of hypotension associated with shock and spinal anaesthesia. These effects are therapeutic in these scenarios, and as they are not adverse effects, they are not discussed. Case reports and studies that described unexpected or unwanted cardiovascular effects following the use of phenylephrine are listed in Table 1.

The standard OTC 10-mg dose of phenylephrine appears to be well tolerated by the majority of people; however, increases in blood pressure and decreases in heart rate are reported with doses over 15 mg [6, 7]. It has been estimated that a 20-mmHg increase in systolic blood pressure would occur with an oral dose of 45 mg phenylephrine in normotensive healthy people [8]. This situation changes considerably in people taking medications such as monoamine oxidase inhibitors where interaction with phenylephrine caused increases in systolic blood pressure of greater than 60 mmHg and required intervention [9, 10]. Blood pressure and heart rate changes also appear to be potentiated in patients with underlying hypertension. One study reports severe hypertensive episode requiring intervention in 10 % of study participants given 10 % topical drops as a mydriatic agent in ophthalmic surgery, all of whom had underlying hypertension; no episodes of hypertension were reported in normotensive participants [11]. Phenylephrine may also interact with cocaine (medical or recreational) potentiating the hypertensive effects of phenylephrine [12, 13].
Table 1 Cardiovascular effects following administration of phenylephrine alone or in combination with other medications—overview of literature review

| Phenylephrine dose | Population | Result | Comments | Reference |
|--------------------|------------|--------|----------|-----------|
| Oral               |            |        |          |           |
| 10—25 mg           | Normotensive participants (n=88) | ↑ HR cf. placebo doses ≥10 mg | Conflicting results | Cohen et al. [6] |
| 10 mg              | Normotensive participants with nasal congestion (n=88) | ↑ BP cf. placebo doses ≥15 mg | —20 % of participants showed ↑ BP, while 32 % showed ↓ BP 60 min after administration —30 % of participants showed ↑ HR, while 44 % showed ↓ HR 60 min after administration —Nine participants had ↑HR >10 bpm | McLaurin et al. [7] |
| 250 mg             | Normotensive volunteers (n=7) | Average ↓ in HR—21 bpm | Threshold for pressor response estimated to be 50 mg. | Keys and Violante [8] |
| 45 mg              | Normotensive volunteers (n=4), concurrent MOA inhibitors | Significant ↑ in BP | ≥67 mmHg ↑ in BP in two participants administered single 45-mg dose of phenylephrine after 7 days of MOA inhibitor therapy (tranylcypromine or phenelzine). Required intervention with phentolamine. | Elis et al. [9] |
| 10 mg              | Normotensive volunteers (n=4), concurrent MOA inhibitors with comorbidities, concurrent MOA inhibitors | Significant ↑ in BP | 20 mmHg ↑ in BP after 10 mg phenylephrine dose following 11 days on tranylcypromine | Elis et al. [9] |
| Unclear—710 mg     | 74-year-old women with comorbidities, concurrent MOA inhibitors | Significant ↑ in BP (hypertensive crisis—BP up to 230/120 mmHg) | Combination of phenylephrine from an over-the-counter preparation, terbutaline and taloxatone. | Lefebvre et al. [10] |
| Unclear—overdose   | 24-year-old otherwise healthy male | Significant ↑ in BP | Ingestion of 30–40 tablets each containing 40 mg phenylpropanolamine, 10 mg phenylephrine, 5 mg chlorpheniramine and 15 mg phenyltoloxamine | Burton et al. [46] |
| Unclear—up to 60 mg/day for 4 days | 59-year-old otherwise healthy female | ICH, SAH | Took cold and flu medications containing PE, paracetamol, dextromethorphan and chlorpheniramine for 4 days before hospitalization | Tark et al. [36] |
| Topical (eye drops, nasal packs, nasal sprays) | Cataract surgery—normotensive and hypertensive patients (n=89) | ↑ BP following both 2.5 and 10 % eye drop in both normotensive and hypertensive patients. | 4/30 patients in 10 % group and 1/29 patients in the 2.5 % group developed severe hypertension which required intravenous hypotensive agents for management—all patients who developed severe hypertension had baseline hypertension. | Chin et al. [11] |
| 2.5 or 10 % single eye drop | Cataract surgery—normotensive and hypertensive patients (n=49) | ↑ BP following both 2.5 and 10 % eye drop in both normotensive and hypertensive patients. | Severe hypertension, unstable angina and uncontrolled diabetes all exclusions. Cardiovascular endpoints measured at beginning and end of procedure—end time not defined—not continuously monitored | Kenawy et al. [47] |
| 2.5 % eye single drop | Cataract surgery—normotensive and hypertensive patients (n=217) | NC BP | Normotensive participants only—no history of cardiovascular disease | Malhotra et al. [49] |
| 2.5 or 10 % single eye drop | Cataract surgery—normotensive (n=54) | NC HR | Normotensive participants only | Motta et al. [50] |
| 2.5 or 10 % single eye drop | Fundoscopy (n=29) | NC BP | Possible interaction with propranolol—not able to vasodilate to counteract pressor effect of PE | Cass et al. [40] |
| 10 % single eye drop | 49-year-old female, medically controlled hypertension | NC HR | Severe hypertension, unstable angina and uncontrolled diabetes all exclusions. Cardiovascular endpoints measured at beginning and end of procedure—end time not defined—not continuously monitored | Lam et al. [48] |
| 2.5 % single eye drop | 72-year-old female, medically controlled hypertension, diabetes mellitus | NC BP | Normotensive patients only | Weisberg et al. [41] |
| 10 % four times eye drops | 57-year-old man, no known cardiovascular disease | NC HR | Normotensive patients only | Malhotra et al. [49] |
| 500 mg via nasal pack | 30-year-old man, healthy | NC HR | Possible interaction with propranolol—not able to vasodilate to counteract pressor effect of PE | Cass et al. [40] |
| 0.25 % solution via nasal pack | 23-year-old woman, no coronary artery disease | NC HR | Severe hypertension, unstable angina and uncontrolled diabetes all exclusions. Cardiovascular endpoints measured at beginning and end of procedure—end time not defined—not continuously monitored | Lam et al. [48] |
| 0.25 % solution via nasal pack | 28-year-old man | NC HR | Normotensive patients only | Weisberg et al. [41] |
| Unclear—daily nasal spray TID | 57-year-old male | Acute hypertension (190/100 mmHg), pulmonary oedema | Possible interaction with propranolol—not able to vasodilate to counteract pressor effect of PE | Cass et al. [40] |
| Unclear—nasal spray | 30-year-old, postpartum female | ICH, SAH, occipital infarct, BP 240/110 mmHg | Patient had history of smoking cocaine | Singh et al. [12] |
| Unclear—nasal spray | 45-year-old female | SAH | Nasal spray TID for 4 months | Cantu et al. [37] |
| Injectable | 57-year-old man | Acute myocardial infarct, severe hypertension and cardiac arrhythmia | Severe hypertension, unstable angina and uncontrolled diabetes all exclusions. Cardiovascular endpoints measured at beginning and end of procedure—end time not defined—not continuously monitored | Weisberg et al. [41] |
| 2.5 or 10 % single eye drop | 57-year-old male | Acute hypertension (190/100 mmHg), pulmonary oedema | Possible interaction with propranolol—not able to vasodilate to counteract pressor effect of PE | Cass et al. [40] |
| 0.25 % solution via nasal pack | 28-year-old man | Acute hypertension (190/100 mmHg), pulmonary oedema | Patient had history of smoking cocaine | Singh et al. [12] |
| Unclear—daily nasal spray TID | 57-year-old male | ICH, SAH, occipital infarct, BP 240/110 mmHg | Nasal spray TID for 4 months | Cantu et al. [37] |
| Unclear—nasal spray | 30-year-old, postpartum female | SAH | Nasal spray daily for 1 week | Chartier et al. [38] |
| Unclear—nasal spray | 45-year-old female | SAH | Nasal spray for many weeks | Genonex et al. [39] |
Unwanted cardiovascular effects are commonly reported when phenylephrine is administered intravenously for its hypotensive effects and appear to be dose dependent [14–19]. The majority of literature relates to bradycardia and reactive hypertension when phenylephrine was used to counter the hypotensive effects of spinal anaesthesia during caesarean section [14–19]. An increase in blood pressure with associated impairment in myocardial perfusion was seen when phenylephrine was administered to patients with underlying cardiac disease (angina pectoris, old myocardial infarct or chronic coronary artery disease) [20]. Increased blood pressure [21–27], vasoconstriction resulting in worsening of orthostatic intolerance [28], atrial fibrillation after coronary artery bypass surgery [29], decreased cerebral oxygenation [30, 31], bradycardia in patients with high cervical spinal cord injury [32], cardiac arrhythmias [33], pulmonary oedema and myocardial infarction [34], and microvascular occlusion syndrome [35] have all been associated with phenylephrine use.

Cerebrovascular events have also been reported. Tark et al. report the case of an otherwise healthy 50-year-old woman who suffered intracerebral haemorrhage after oral administration of standard doses of cold medicines containing phenylephrine and paracetamol for 4 days before hospitalization [36]. Other studies have reported cerebrovascular accidents

| Phenylephrine dose | Population | Result | Comments | Reference |
|--------------------|------------|--------|----------|-----------|
| 25 μg/min         | Women scheduled for elective caesarean section (n=75) | Significant reduction (up to 20 %) in HR and CO in 100 μg/min group | | Stewart et al. [53] |
| 50 μg/min         | 31-year-old woman, emergency caesarean section | Ventricular bigeminy | | Lai et al. [54] |
| 100 μg/min intrathecal infusion | 35-year-old woman, elective caesarean section | ICH | Three 50-μg doses of PE for treatment of hypotension | Ranasinghe et al. [42] |
| 150 μg iv        | 35-year-old woman, elective caesarean section | ICH | | |

† increase, ↓ decrease, cf. compared with, NC no change, HR heart rate, BP blood pressure, PE phenylephrine, CO cardiac output, TID three times daily, QID four times daily, ICH intracerebral haemorrhage, SAH subarachnoid haemorrhage

Table 2 Standardised phenylephrine population pharmacokinetic and pharmacodynamic parameter estimates for ophthalmic PKPD analysis

| Parameter | Estimate | %BSV | 95 % CI |
|-----------|----------|------|---------|
| Pharmacokinetics | | | |
| CLstd (L h–1 70 kg–1) | 139 | 38.3 | 61.5, 235.9 |
| V1std (L 70 kg–1) | 15.3 | 106.3 | 9.5, 73.9 |
| Qstd (L h–1 70 kg–1) | 30 | 130 | 23.9, 311 |
| V2std (L 70 kg–1) | 235 | 101 | 102, 562 |
| Tabs oral (h) | 0.52 | 40 | 0.34, 0.63 |
| Lag oral (h) | 0.247 | – | 0.21, 0.26 |
| Bioavailability oral | 0.014 | | 0.008, 0.051 |
| Tabs ophthalmic 2.5 % (h) | 0.07 | 71 | 0.03, 0.11 |
| Bioavailability 2.5 % ophthalmic solution | 0.15 | | 0.077, 0.506 |
| Tabs ophthalmic 10 % (h) | 0.275 | – | 0.21, 0.34 |
| Bioavailability 10 % ophthalmic solution | 0.14 | | 0.071, 0.557 |
| Residual error Additive (μg L–1) | 0.013 | – | 0.001, 0.015 |
| Proportional (%) | 32.6 | | 25.2, 39.9 |

| Pharmacodynamics | | | |
| E0 (mmHg) | 86.3 | 4.4 | 81.6, 90.2 |
| EC50 (μg L–1) | 11.1 | 141 | 1.67, 19.9 |
| Emax (mmHg) | 51.2 | 44.8 | 20.5, 109.1 |
| Residual error Additive (μg L–1) | 9.88 | – | 7.03, 11.7 |
| Proportional (%) | 61.6 | – | 0.6, 125 |

BSV between-subject parameter variability, CI confidence interval
following phenylephrine use via topical and intravenous administration [37–42].

**PKPD relationship analysis**

The pharmacokinetic/pharmacodynamic (PKPD) analysis was based on 49 subjects (with 387 observations) who received phenylephrine ophthalmic eye drops where plasma concentrations were available for analysis. Patients had a mean age 34.3 SD 8.2 years and a mean weight 74.4 SD 3.4 kg. Pharmacokinetic and pharmacodynamic parameter estimates are reported in Table 2. The correlation of between parameter variability is shown in Table 3. PC-VPC plots, used to demonstrate goodness of fit, are shown in Fig. 1. Figure 2 demonstrates the pharmacodynamic relationship between phenylephrine concentration and MAP for a typical individual.

**Simulation**

Pharmacodynamic parameter estimates estimated from the phenylephrine ophthalmic study [3] were combined with derived pharmacokinetic estimates from a study in healthy volunteers given paracetamol and phenylephrine combination therapy [4] to simulate mean time-concentration and mean arterial blood pressure changes that might occur if patients were given oral phenylephrine with and without paracetamol. These simulations were performed using Berkeley Madonna™ modelling and analysis of dynamic systems software V 8.3.18 (Robert Macey and George Oster of the University of California, Berkeley, USA). We predict an increase in MAP of 16 mmHg after 45 mg phenylephrine; i.e., a person with a BP of 120/65 mmHg might increase to 140/80 mmHg, a systolic increase of 20 mmHg. Plots are presented in Fig. 3. The increased absorption rate of phenylephrine when combined with paracetamol results in higher peak concentrations than might be anticipated from increased bioavailability alone.

**Discussion**

Phenylephrine has now replaced pseudoephedrine in most over-the-counter (OTC) cold and influenza medications.

There are few data reporting adverse events associated with oral phenylephrine use. What little information available must be gleaned from other routes of administration where more formal studies have been conducted: phenylephrine interacts with monoamine oxidase inhibitors and possibly other drugs to potentiate its hypertensive effect; cardiovascular changes may be more pronounced in people with underlying cardiovascular disease and may lead to decreased myocardial oxygenation, cardiac arrhythmias, decreased cerebral oxygenation and exaggerated vasoconstriction and stroke.

That few adverse events following oral administration of phenylephrine are reported is not surprising, though not necessarily reflective of the actual incidence of adverse effects. Relative oral bioavailability remains poorly documented but may be as little as 0.003 [5]. Absorption is slow (Tabs 0.4 h, BSV 30.8 %), and peak concentrations will be less than that observed after rapid intravenous administration. Oral phenylephrine is generally administered in a community setting to relieve symptoms of malaise associated with colds and influenza, and as such, blood pressure changes over the short duration of phenylephrine administration are unlikely to be

| Table 3 | The correlation of parameter between-subject variability |
|---------|-----------------------------------------------|
|         | CL       | Q | V1  | V2 | Tabs |
| CL      | 1        |   | 1   |    |      |
| Q       | –0.799   | 1 |      |    |      |
| V1      | –0.817   | 0.651 | 1  |    |      |
| V2      | –0.630   | 0.093 | 0.533 | 1 |      |
| Tabs    | 0.512    | –0.463 | –0.148 | –0.239 | 1     |
recorded. The few studies examining oral phenylephrine at the recommended dose of 10 mg have shown it to be well tolerated in patients suffering from nasal congestion. However, these studies focus on phenylephrine as a single agent and not in combination with paracetamol where bioavailability is increased and peak plasma concentrations doubled [1]. Furthermore, these studies have primarily been conducted in either healthy volunteers or in otherwise healthy patients with nasal congestion.

The simulation study assumes that the administration of phenylephrine with paracetamol more than doubles the bioavailability of phenylephrine and reduces the absorption half-time by 50 % resulting in a doubling of phenylephrine plasma concentration and an approximate fourfold increase in Cmax, with large between-subject variability [4, 1]. Of concern is the possibility of increased adverse effects associated with this increase in plasma concentration, particularly in people with cardiovascular compromise or on other medications that may interact with phenylephrine. Simulation using blood pressure changes after ophthalmic administration provides an example of the magnitude of blood pressure change for a typical subject: a standard 10-mg dose of phenylephrine combined with paracetamol could result in an increase in MAP of more than 10 mmHg (Fig. 2). We report considerable between-subject variability that was unexplainable from the limited cohort investigated. The impact of age, existing hypertension and ophthalmic preparation dose accuracy are covariates that require further investigation.

An important consideration is the substantial variability in Cmax [4]: a subgroup of the population would be exposed to relatively higher phenylephrine plasma concentrations than the population mean data would suggest, leading to more serious adverse events. Indeed, one case report describes haemorrhagic stroke in an otherwise healthy female taking phenylephrine and paracetamol in combination for treatment of cold and flu symptoms [36]. It is also possible that others without underlying hypertension could also be compromised. It has been estimated that a 20-mmHg increase in blood pressure would occur with a 45-mg phenylephrine dose in normotensive patients [8], an observation consistent with our current simulation. It is possible that any given individual may experience a plasma concentration similar to that seen with a 45-mg dose when 10 mg phenylephrine is combined with paracetamol. Systemic or pulmonary hypertension is also reported in children (6 months–14 years) administered 10 % ophthalmic drops [43].

When medications are administered OTC, the burden of safety should be high—with only 40 % of consumers reading the packet label when they take a medicine for the first time and only 7 % reading safety information and warnings [44], and changing labelling to reduce the risk of adverse events is ineffective. In addition, more than one third of consumers take

![Fig. 2](image1.png) The relationship between phenylephrine concentration and MAP in patients undergoing ophthalmic surgery

![Fig. 3](image2.png) Pharmacodynamic parameter estimates from patients (mean age 34.3 years, 70 kg) undergoing ophthalmic surgery were combined with derived pharmacokinetic estimates from the current study to simulate mean time-concentration (solid lines) and mean arterial blood pressure changes (dashed lines) that might occur when given oral phenylephrine with and without paracetamol
more than the recommended dose of an OTC medication believing that it will increase the effectiveness of the medication and an additional 30 % combine different OTC medicines to treat different symptoms [44] leading to the potential for overdose of any single active ingredient and the associated adverse effects.

In 2007, the FDA determined that there was insufficient data to support increasing the dose to the higher 25 mg whilst maintaining a similar safety profile to the 10-mg dose [45]. At the same time, the committee concluded that “comparisons of the pharmacokinetics of single-ingredient products versus multiple ingredient products” and “safety evaluations of the effects of phenylephrine on blood pressure and cardiovasculature and use of phenylephrine in patients with important comorbidities such as BPH, hypertension or diabetes mellitus” be conducted [45]. Whilst there are now some data on the interaction pharmacokinetics of phenylephrine, the consequences to the population of the OTC co-administration of phenylephrine and paracetamol remain difficult to define. The literature reviewed here suggests that this increased phenylephrine exposure could be associated with many, potentially life-threatening adverse events in individuals both with underlying cardiovascular compromise and those who are otherwise healthy. Despite the FDA’s call for studies almost a decade ago, there remain no studies specifically examining the safety profile of phenylephrine in populations with underlying compromise, nor are there any studies examining the effects of chronic use of phenylephrine despite the potential safety burden.

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Author contributions H Atkinson supervised this manuscript and was assistance in reviewing and commenting on this manuscript. Changes were made.

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Author contributions H Atkinson supervised this manuscript and was involved in the design of the simulation, interpretation of the data and writing of the manuscript. A Potts reviewed the literature for the review and contributed to the design of the simulation study, interpretation and writing of the manuscript. B Anderson was involved in the design and conduct of the simulation study, interpretation and writing of the manuscript. All authors had full access to all the data.

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