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REVIEW

# Pharmacokinetic and pharmacodynamic evidence of adrenaline administered via auto-injector for anaphylactic reactions: A review of literature

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Anaphylaxis is a severe allergic reaction that can lead to death if not treated quickly. Adrenaline (epinephrine) is the first-line treatment for anaphylaxis and its prompt administration is vital to reduce mortality. Following a number of high-profile cases, serious concerns have been raised, both about the optimal dose of intramuscular adrenaline via an auto-injector and the correct needle length to ensure maximal penetration every time.

To date, the public data are sparse on the pharmacokinetics–pharmacodynamics of adrenaline administered via an auto-injector. The limited available literature showed a huge variation in the plasma concentrations of adrenaline administered through an auto-injector, as well as variations in the auto-injector needle length. Hence, delivering an effective dose during an anaphylaxis remains a challenge for both patients and healthcare professionals. Collaborative work between pharmacokinetics–pharmacodynamics experts, clinical triallists and licence holders is imperative to address this gap in evidence so that we can improve outcomes of anaphylaxis. In addition, we advise inclusion of expertise of human factors in usability studies given the necessity of carer or self-administration in the uniquely stressful nature of anaphylaxis.

**KEYWORDS**

adrenaline auto-injector, adrenaline; epinephrine, anaphylaxis, auto-injector, epinephrine auto-injector, pharmacodynamics, pharmacokinetic

## 1 | INTRODUCTION

Anaphylaxis is a life-threatening reaction that may be induced by allergens.[1] Prompt administration of an adrenaline injection as a first-line treatment is critical for relieving the symptoms of anaphylaxis and preventing fatalities.[1] People who are at risk of severe allergic reactions are often prescribed adrenaline auto-injectors to be used as emergency first aid in serious hypersensitivity reactions until medical help arrives.[2]

Adrenaline auto-injectors (AAIs) have been designed to administer adrenaline intramuscularly (IM) into the lateral thigh by patients, relatives or their carers, to obtain a rapid response in anaphylaxis.[3] Several commercially available AAIs have been approved by health regulators worldwide. For example, in Europe, 4 AAI products are authorised and marketed for use in adults and children: Anapen, Emerade, EpiPen and Jext.[4] Several factors may affect the delivery of adrenaline to reach the muscle layer, such as needle length and skin-

to-muscle depth (STMD).[5,6] Another variable between the devices is their delivery mechanism. Some AAIs are cartridge injection systems, whereas others are syringe-based systems. The main difference being that in a cartridge-based system the needle is not attached to the glass body in which the drug is contained. Both types contain a firing mechanism but this can vary even within devices with the same delivery mechanism.[7] Following some high-profile fatalities after use of AAIs and concerns of potential underdosing, uncertainties have been identified about the accuracy and safety of adrenaline delivery using an AAI. In 2010, a 19-year-old girl died following exposure to peanuts, despite injecting herself twice with adrenaline via an autoinjector device. A pathologist's report suggested the needles had failed to penetrate the muscle, and instead had been injected subcutaneously. Some of the points highlighted by the coroner were concerns about the needle length of AAIs and to which site of the body adrenaline should be administered.[8] In 2015, a review of all the AAIs marketed in Europe was conducted by the Committee for Medicinal Products for Human Use (CHMP) to explore the concerns that the available AAIs did not adequately deliver adrenaline intramuscularly due to needle length.[9] One of the key recommendations from the CHMP review was that AAI manufacturers should conduct pharmacokinetic–pharmacodynamic (PKPD) studies with adrenaline administered using their AAIs to help understand how adrenaline penetrates body tissues when given with different auto-injectors.[9] Unfortunately, another case in 2016 was highlighted in the news where a 15-year-old girl died of an anaphylaxis reaction after eating a pre-prepared baguette that contained sesame to which she was allergic.[10] Even though adrenaline was administered twice using an AAI (EpiPen), the girl died later in the hospital. The coroner reported that the needle of the EpiPen device used was 16 mm and the dose given was 300 μg stating that the EpiPen's "inadequate dose of adrenaline for anaphylaxis and an inadequate length needle" raised serious concerns.[11] According to the UK Resuscitation Council, a needle length of 25 mm is optimal for adrenaline injection to access muscle for all ages, and the recommended emergency dose of adrenaline is 500 μg for adults and children older than 12 years.[12] None of the 3 currently licensed autoinjectors in the UK (Emerade, EpiPen, Jext) meet the optimal needle length, the longest being 23 mm. In addition, only 1 of the 3 autoinjectors is available as a 500-μg dose, with the other 2 being limited to 300 μg as the maximum dose available in each device.[13–15]

The aim of this review is to summarise the evidence base underlying dosing recommendations for administration of adrenaline using auto-injectors for anaphylactic reactions based on the published PKPD literature.

## 2 | METHODS

### 2.1 | Study selection

A systematic literature search was conducted using the PubMed and EMBASE databases (from inception up to 13th March 2019) for relevant studies using combinations of keywords: Adrenaline OR Epinephrine, AND Auto-injector* OR Auto injector* OR Automatic injector* OR Pen* OR self-injectable OR (equipment AND supplies), AND Intramuscular OR IM OR Injection* OR 'Intramuscular absorption', AND Pharmacokinetics OR PK OR Pharmacodynamics OR PD OR Pharmacology OR Drug-Related side effects OR adverse reactions OR Drug Monitoring OR Pharmacovigilance OR Adverse drug reaction OR monitoring, physiologic OR TDM OR therapeutic drug monitoring, AND Anaphylaxis OR Anaphylactic.

Studies were included if they reported original research involving the use of adrenaline intramuscularly for the treatment of anaphylaxis; detailed the injection method or device; and specified the needle length. Exclusion criteria were as follows: nonhuman studies; adrenaline given by other routes; not given for anaphylaxis; review articles, letters, editorials, conference abstracts and opinion articles; and those not published in the English language.

### 2.2 | Data abstraction and synthesis

A systematic approach was applied for data abstraction and synthesis as detailed in the protocol [PROSPERO registration number (CRD42019119926)].[16] The primary outcome of interest was studies reporting effective treatment or treatment failure of anaphylaxis using adrenaline delivered via AAIs. Secondary outcomes were reported needle lengths associated with treatment failures and adverse events.

The databases were searched using the above search terms by 1 reviewer (J.M.) and a list of potential eligible articles was generated based on titles and abstracts screening. Full text review was conducted independently by 2 reviewers (J.M., A.N.R.) using the inclusion and exclusion criteria. Any disagreement was resolved by a third reviewer (Y.J.). For included studies, the following data were extracted: patient age, weight or body mass index (BMI; if documented), device used to administer the adrenaline, dose administered, needle length, effective treatment of anaphylaxis, any adverse events and any PKPD parameters reported.

## 3 | RESULTS

In total, 173 articles were identified using the search criteria, with 166 remaining following the removal of duplicates. Although 18 of the 166 were identified for full text review, none of these fully met our inclusion criteria (Figure 1). Review of the title and abstracts ($n$ = 166) identified 10 studies that provided data for our outcomes of interest: those reporting PK data following administration of adrenaline in a controlled environment (3 studies); and those using radiological imaging to measure STMD and skin-to-bone depth (STBD) to determine the appropriate needle length to deliver adrenaline intramuscularly into the lateral thigh (7 studies). Additional articles were found from the referenced list of the included articles. These included a further 2 PK studies and 4 imaging studies, producing a total of 16 studies for our assessment.

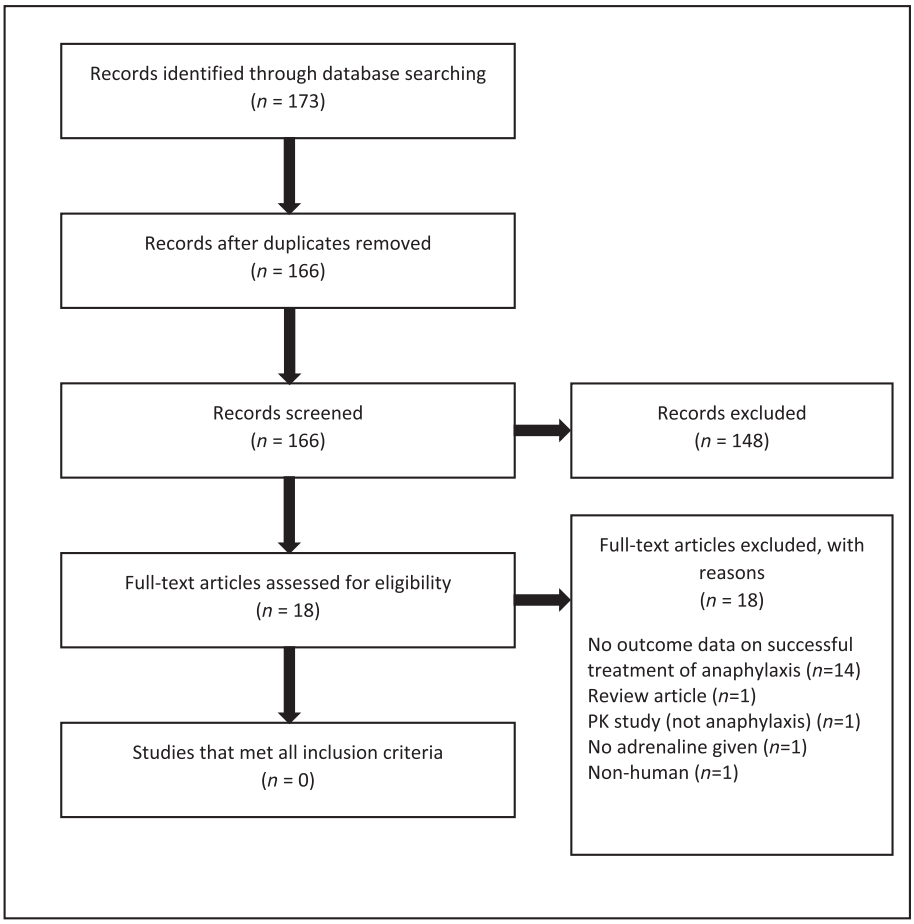


**FIGURE 1** PRISMA flow diagram for systematic review. Sixteen studies that provided information about our outcomes of interest were analysed

We report the findings from the sixteen studies that provided data for outcomes of interest using 2 main approaches: PK studies and ultrasound studies.

## 3.1 | PK studies

Five PK studies were identified, with variable peak plasma concentrations of adrenaline reported depending on route and time after administration (Table 1). The reported PK parameters: peak plasma concentrations ($C_{max}$), time of maximum concentration ($T_{max}$) and area under the curve (AUC) are presented in Table 1. All the studies reported $C_{max}$; however, due to the inconsistency between study cohorts and variation in adrenaline plasma concentrations between studies, it was not possible to pool results for further statistical analysis and inform the dosing of adrenaline in anaphylaxis situation.

Duvauchelle et al.[17] demonstrated no difference in $C_{max}$, $T_{max}$ or AUC between IM and subcutaneous (SC) administration (although intended to be IM, ultrasound scans demonstrated adrenaline was administered SC in 10 of 12 women, all of whom were overweight, with a mean BMI of 29.7 kg/m$^2$), whereas Simons et al.[20] showed peak plasma concentrations to be much lower following SC compared to IM administration with the same 0.3 mg dose (2877 *vs* 12 222 pg/mL). However, this same study also showed that IM injection of 0.3 mg of adrenaline via the *needle and syringe* method into the deltoid achieved an even lower peak plasma concentration (1821 pg/mL).

There was also considerable variation in the peak plasma concentrations recorded after a single 0.3 mg dose of IM adrenaline ranging from 402 pg/mL in Duvauchelle et al.,[17] to 12 222 pg/mL in Simons et al.[20] Even in studies conducted by the same author (Simmons), there was a considerable variation in $C_{max}$ following IM injection with an EpiPen 0.3 mg (2136 pg/mL,[19] 12 222 pg/mL[20] and 2289 pg/mL[21]). Although the value for $T_{max}$ was not reported in most studies, graphs representing plasma concentrations showed a biphasic response to IM adrenaline. The initial spike in adrenaline concentration seemed to occur within the first 15 minutes and then a second spike 30–60 minutes later. In Duvauchelle et al.,[17] this second spike was consistently higher than the initial peak plasma concentration.

## 3.2 | Imaging studies

Eleven studies were identified involving the use of imaging, mainly ultrasound (USS) to determine the STMD (Table 2). Of these, 8 were in paediatric subjects and 6 also investigated STBD. Studies used the needle length from AAIs to gauge whether the proposed injection would lead to the adrenaline being administered within the muscle layer. If the STMD was greater than the needle length, this would lead to the adrenaline being administered within the SC tissue. If the STBD

**TABLE 1** Summary of PK studies

| Author, year | Age | Subject number | Device[a] | Administration route and dose | Mean $C_{max}$ (pg/mL)[b] | $T_{max}$ (h)[b] | AUC† (h pg/mL) | Comments |
|---|---|---|---|---|---|---|---|---|
| Duvauchelle et al., 2018[17] | Mean | 30 | Anapen | IM 0.3 mg | Male | 0.21 ± 0.12 | 69.3 ± 54.0 (0–20 min) | The PK analysis showed there was no considerable difference between $T_{max}$, $C_{max}$ and AUC. The ultrasound results for normal weight men confirmed the adrenaline injections were located IM in all cases except 1 (Anapen device). While for overweight women, in 10 cases adrenaline injections were located SC, with only 1 seen in the muscle and 1 undetermined. Adrenaline concentrations before dosing were not quantifiable (<39.06 pg/mL), confirming very low level of endogenous circulating adrenaline in resting adults. |

IM injections administered into mid anterolateral thigh unless otherwise documented. AUC = area under the curve; $C_{max}$ = maximum (peak) plasma concentration; F = female; IM = intramuscular; M = male; NR = not reported; PK = pharmacokinetic; SC = subcutaneous; $T_{max}$ = time of maximum drug concentration; SEM standard error measurement; CV = coefficient of variation.
[a]Needle lengths as documented by manufacturer: Anapen 10 mm± 1.5 mm[22]; Auvi-Q (not documented)[23]; EpiPen approx. 16 mm[14]; EpiPen Jr approx. 13 mm.[24]
[b]Values are presented with ± standard deviation, unless otherwise specified.
NA = Not appropriate to draw conclusions based on the analysis of median values alone due to the high variability.

was shorter than the needle length, then this would lead to the adrenaline being administered within the periosteal layer or bone.

The results showed that adults were disproportionately at risk of adrenaline being administered SC whereas children were more at risk of periosteal or intraosseous (IO) injection. For adults a needle length of ≥23 mm was associated with the lowest number of potential SC injections.[27] For children <30 kg, the 7.5 mm needle (Auvi-Q) was associated with no risk of periosteal/IO injection.[27] However, due to its short needle length, the risk of SC injection was as high as 69% in those weighing <15 kg.[27] In this weight category, the next available needle length (approximately 13 mm) was shown to have a high risk of periosteal/IO injection in 3 studies: 29%,[30] 32%[27] and 43%.[31] In 2 paediatric studies, allowing for variation in study design, Emerade (16 mm [150 μg] and 23 mm [300 μg]) seemed to be associated with the most favourable results with a 2% risk of SC injection and no risk of periosteal/IO injection in any weight cohort (no pressure applied when using USS to mimic device).[26,27] However, in another paediatric study where a slightly longer needle was used as the reference (25.4 mm), again with no pressure being applied during USS, the risk of periosteal/IO injection was as high as 12% in those aged 2–5 years.[32]

Apart from needle length, the other risk factors for adrenaline being administered SC, and not IM, were an increased BMI[6,25,26,28,29,32–34] and female sex for adults (independent of BMI).[6,29,33] Johnstone et al.[29] reported in their study that 87% of females were at risk of SC injection compared to 0% of males. In this study, the BMI range was higher for females (21.9–46 kg/m$^2$) compared to males (18–29.4 kg/m$^2$), but even in patients with a similar BMI, women were still at increased risk of SC injection, including some females who had a normal BMI. Bhalla et al.[6] and Song et al.[33] also reported similar findings (54% [females] *vs* 5% [males] and 42% [females] *vs* 2% [males], respectively). Interestingly Bewick et al.[25] also found that the anatomical site of the thigh where the AAI is injected may also have an impact on whether the adrenaline is delivered IM or SC, with the proximal thigh having the highest risk of SC injection, particularly in children >30 kg (61%).

## 4 | DISCUSSION

It is widely agreed that adrenaline is an essential life-saving medicine when used promptly and effectively in anaphylaxis. This review was prompted by the ongoing questions raised by coroner inquests into those patients who have unfortunately died in whom adrenaline autoinjectors are suspected to have been ineffective.[8,10] Product design becomes fundamental in ensuring that an adrenaline autoinjector is intuitive and easy to use thus enabling the full dose to be delivered. The critical variable features in authorised products seem to be length of needle, concentration of solution and delivery mechanism. Adrenaline itself is an old medicine and so is likely to be authorised in the EU based on well-established use supported by bibliographic evidence. Thus, we would expect the supporting evidence to be public and available for assessment justifying a systematic literature review based on recognised criteria. To our knowledge, this is the first review to use a systematic approach to summarise evidence

**TABLE 2** Summary of identified imaging studies

| Author, y | Age | USS method | Subjects n (wt.) | Needle length (mm) | % at risk of SC injection | % at risk of IO injection | Comments |
|---|---|---|---|---|---|---|---|
| Bewick et al., 2013[25] | 1–16 y | USS of lateral thigh (x3) and mid-calf | 62 (<30 kg) | 12.7 | 27% proximal thigh<br>16% mid-thigh<br>2% distal thigh<br>0% mid-calf | Not assessed<br>Not assessed<br>See comments<br>Not assessed | Weight, BMI and waist circumference were predictive of children whose STMD was greater than the AAI needle length. Assessment was also made with 'additional pressure' to mimic AAI use and the authors found that it would not have altered the proportion of children whose injection was SC rather than IM. |
| | | | 31 (>30 kg) | 15.9 | 61% proximal thigh<br>29% mid-thigh<br>13% distal thigh<br>0% mid-calf | Not assessed<br>Not assessed<br>See comments<br>Not assessed | STBD was measured in 11 children. None had a STBD less than the needle length. |
| Bhalla et al., 2013[6] | 18–55 y | USS of ALT with pressure[a] | 120 | 15.9 | 31%, (54.4% f, 5% m) | Not assessed | BMI and thigh circumference significantly associated with STMD |
| Dreborg et al., 2016[26] | <18 y | USS of ALT with pressure[a] | 102 (15–30 kg) | 12.7<br>15.7<br>16 | 1%<br>0%<br>0% | 11%<br>37%<br>0% | 16 mm and 23 mm needles represented Emerade 150 and 300 µg respectively (no additional pressure applied) |
| | | | 100 (>30 kg) | 15.2<br>15.7<br>23 | 9%<br>9%<br>2% | 3%<br>3%<br>0% | |
| Dreborg et al., 2018[27] | 0.2–72 y | USS of ALT with pressure[a] | 100 (<15 kg) | 7.5<br>13<br>16 | 69%<br>0%<br>1% | 0%<br>32%<br>0% | 16 mm and 23 mm needles represented Emerade 150 and 300 µg respectively (no additional pressure applied) |
| | | | 102 (15–30 kg) | 7.5<br>13<br>16 | 54%<br>0%<br>0% | 0%<br>10%<br>0% | |
| | | | 100 (>30 kg) | 15<br>23 | 12%<br>2% | 3%<br>0% | |
| | | | 99 (adults)[b] | 15<br>23 | 33%<br>10% | 0%<br>0% | |
| Duong et al., 2017[28] | <18 y | USS of ALT no additional pressure | 110 (7.5-25 kg)<br>77 (≥25 kg) | 13<br>16 | 0.9%<br>5% | 0%<br>0% | Patients with a higher BMI had an increased STMD and STBD |
| Johnstone et al., 2015[29] | 18–75 y | USS of ALT and anterior thigh | 28 (NR)[b] | 15 | 68% (87% f, 0% m) | Not assessed | Even in males and females with a similar BMI the risk of SC injection |

(Continues)

**TABLE 2** (Continued)

| Author, y | Age | USS method | Subjects n (wt.) | Needle length (mm) | % at risk of SC injection | % at risk of IO injection | Comments |
|---|---|---|---|---|---|---|---|
| | | no additional pressure | | | | | in women was still higher. Key predictors for risk of SC injection were a BMI > 30 and being female. |
| Kim et al., 2014[30] | Median 17 mo | USS of ALT with pressure[a] | 100 (<15 kg) | 12.7 | 0% | 29% | Sub analysis showed those <10 kg had 60% risk of IO injection |
| Kim et al., 2017[31] | Mean 19 mo | USS of ALT with pressure[a] | 51 (7.5-15 kg) | 12.7 | 0% | 43.1% | Sub analysis showed those weighing 7.5 kg had 54.9% risk of IO injection. |
| Manuyakorn et al., 2018[32] | 1 m–18 y | USS of ALT no additional pressure | 75 1 m – 2 y[b] | 15.8 | 9.3% | 1.3% | BMI, thigh circumference and weight were correlated with STMD and STBD |
| | | | | 25.4 | 0% | 38.7% | |
| | | | | 38.1 | 0% | 100% | |
| | | | 75 (>2–5 y)[b] | 15.8 | 4% | 0% | |
| | | | | 25.4 | 0% | 12% | |
| | | | | 38.1 | 0% | 96% | |
| | | | 75 (>5–10 y)[b] | 15.8 | 16% | 0% | |
| | | | | 25.4 | 0% | 1.3% | |
| | | | | 38.1 | 0% | 53.3% | |
| | | | 75 (>10–18 y)[b] | 15.8 | 29.9% | 0% | |
| | | | | 25.4 | 5.4% | 0% | |
| | | | | 38.1 | 0% | 14.3% | |
| Song et al., 2005[33] | 20–87 y | CT scan of the thigh | 100 (NR)[b] | 14.3 | 42% f, 2% m | Not assessed | Even after controlling for BMI, women still had a greater STMD. |
| Stecher et al., 2009[34] | 1–12 y | USS of ALT no additional pressure | 158 (<30 kg) | 12.7 | 12% | Not assessed | BMI had a statistically significant impact on the probability that needle engthwas exceeded. |
| | | | 98 (>30 kg) | 15.9 | 30% | Not assessed | |

ALT = anterolateral thigh; BMI = body mass index; CT = computed tomography; f = female; IO = intraosseous injection; m = male; NR = not reported; SC = subcutaneous; STBD = skin to bone depth; STMD = skin to muscle depth; USS = ultrasound; *weight not reported; wt. = weight.

[a]Pressure applied to mimic AAI use.

[b]Weight not recorded.

about PKPD of AAIs. Although the evidence is limited, our findings highlight a wide variation in maximum plasma concentrations of adrenaline reported depending on the actual route of administration and the time after administration.[17–21] Simons et al. showed plasma concentrations of adrenaline following IM injection of normal saline, to be higher than following a dose of 0.5 mg adrenaline in another study.[17,20] There are several possible explanations for the variations seen, for example, the use of different analytical approaches, differences in PK parameters examined, heterogeneous populations and a small sample size. None of the PK studies included in this review followed the key guidelines for reporting population PK modelling recommended by the US Food and Drug Administration guidance for the industry or the European Medicines Agency guidelines on reporting results of PKPD for population PK analysis.[35,36] Thus, we were unable to conduct further pooling and analysis of the results to derive a consensus about optimal dosing of adrenaline via an auto-injector in anaphylaxis.

The variation in the AAI needle lengths across included studies is consistent with the exposed needle lengths of AAIs currently on the market, which range between 7.4 and approximately 23 mm.[13,37] Our review illustrates the challenges of delivering effective doses based on product design and usability. The lowest dose AAI intended for those <15 kg with a needle length of 7.4 mm is unlikely to hit bone but may also deliver the adrenaline SC rather than IM.[27] The next needle size of approximately 13 mm comes with around a 43% chance of hitting the bone in the same patient population.[31] At the other end of the spectrum, adults, particularly women with an increased BMI have a 87% risk of SC injection.[29] This might be because women tend to have their subcutaneous tissue distributed more around the hip and/or thigh area, while men tend to have more a central distribution of adipose tissue.[38] These findings are reflected in the product literature for some AAIs. For example, both the Jext and EpiPen summaries of product characteristics state that PK studies suggest that adrenaline absorption may be slower in in patients with a thick subcutaneous fat layer (STMD >20 mm). Jext report that adrenaline administered via the Jext device showed consistently lower exposure in the first 30 minutes following administration when compared to manual IM injection in the STMD >20 mm cohort.[15] EpiPen report that female subjects with a thick subcutaneous fat layer (>20 mm STMD under maximum compression) had slower adrenaline absorption reflected in a trend to lower plasma exposure in such subjects in the first 10 minutes following injection.[14] In contrast to Jext, overall adrenaline exposure from 0 to 30 min for all groups of subjects receiving EpiPen exceeded exposure resulting from syringe delivery.[14] However, a trend to higher adrenaline concentrations following EpiPen compared to manual IM injection in healthy subjects who have well perfused subcutaneous tissue cannot necessarily be applied to patients in established anaphylactic shock who will be peripherally shut down with diversion of blood from skin to leg muscles.[14]

UK and US recommendations on needle length for IM injection when treating an anaphylactic reaction are a 25-mm needle for most age groups, except for some adults (males weighing >118 kg and in females weighing >90 kg) who may require a longer needle of 38 mm depending on weight and preterm or very small infants who require a shorter 16 mm needle.[12,39] This advice is based on experience from IM vaccination and administration with a needle and syringe and does not consider the additional force exerted by the patient or the AAI needle delivery mechanism. The CHMP report published in 2015 highlighted several studies that showed that the contents of AAIs can be delivered to a depth greater than that of the exposed length of the needle.[9] However, none of these were conducted on human tissue. In the CHMP assessment report, there was concern that the fascia lata between the subcutaneous tissue layer and the muscle may prevent the propulsion of adrenaline into the muscle if the needle is unable to breach the fascia.[9] However, this concern is not mentioned in the corresponding summaries of product characteristics. At present there is no EU authorised AAI with a needle length of 38 mm available.

This review has several limitations. We were unable to identify studies that fully met our inclusion criteria and therefore relied on PK studies involving patients who did not have anaphylactic reactions and imaging studies to derive the outcomes of interest. Some of the studies identified in our review were sponsored by industry, and that may have a risk of publication bias. We also acknowledge that some imaging studies may have been missed as this was not related to our initial research question, which was mainly focused on the PKPD of adrenaline in a person experiencing anaphylaxis.

Any possible influence of human factors on the injection technique and use of authorised AAIs for the treatment of anaphylaxis, a stressful emergency, has to our knowledge received limited examination and is recognised in the CHMP report, which stated that "an important parameter that needs to be considered is how competent patients, or carers of patients, are in actually using AAIs".[9] Although no full PKPD studies with target identification including information on PK modelling and validation were reported at the time of publication, 2 clinical trials have been conducted. One study explored the PKPD of adrenaline administered in healthy subjects (18–54 y) with different STMDs[40] and a second trial focused on the PK of 2 different doses of adrenaline administered via auto-injectors intramuscularly to teenagers with food allergies as well as the impact of using 2 different needle lengths.[41] These studies may address some of the gaps identified in our review and add to the evidence for optimal dosing and needle length for the use of adrenaline for the management of anaphylactic reactions in older children and adults. However, these types of trial are far removed from the reality of use of AAIs.

It is worth highlighting that the coroner of the teenager death in 2016, raised a concern about the inappropriateness of the adrenaline administered dose, and the inadequate needle length of the AAI (EpiPen) used (personal communication). The adrenaline dose in EpiPen was 300 μg, and the EpiPen needle length was 16 mm, which is suitable for small or prepubertal child according to the UK Resuscitation Council.[10] The recommend dose in an emergency treatment in anaphylaxis reaction, according to the UK Resuscitation Council is 500 μg for adult and children aged >12 years, and the preferred

needle length to administer adrenaline via IM route is 25 mm.[10] Considering the data summarised in our paper, it is not possible to quantitatively demonstrate whether the dose may have been insufficient, or the exposure was too low in fatal cases. Also, because of the variability in adrenaline plasma concentrations reported in the PK studies, we were not able to determine the relationship of plasma concentrations after injection to physiological concentrations.

Given the scarcity of the evidence on adequate dosing of such widely used life-saving medication as the AAI included in this review, there is a need for an international collaboration between those with PKPD expertise and clinical trial networks to tackle this evidence gap. Currently, AAIs are authorised as a medicine and not a device. We advise that given the unique nature of AAIs and their great public health importance, regulatory assessment should combine both pharmaceutical and device usability assessment. We suggest that the World Health Organisation develop a monograph to cover quality, safety, efficacy and usability of AAIs.

## 5 | CONCLUSION

Our review identified variability in reported plasma concentrations following injection of adrenaline using recommended routes and devices licensed for the treatment of anaphylaxis in adults and children. None of these studies were performed during anaphylaxis, where patients may become hypotensive, and have vasodilatation and increased vascular permeability.[42] We therefore do not know the true absorption of adrenaline during anaphylaxis. One possible way to gather these data would be during food challenge and other allergy testing admissions. If patients develop anaphylaxis, they could administer their AAI, a cannula would be inserted as part of the management of the anaphylaxis and PK samples could be taken from this opportunistically. The severity of an allergic reaction can range from mild local symptoms to anaphylactic shock. Scoring algorithms are available and should be used in any PKPD studies during anaphylaxis to ensure consistency in the perceived severity of each reaction.[43] Further research is required using recommended PK modelling approaches. The influence of human factors on product design and having to use these drug devices under stress as an emergency also requires further study. Ultimately, international consensus reflected in a World Health Organisation monograph is required.

### COMPETING INTERESTS

Authors J.M., Y.J., B.E., S.T. and A.N.R. declare that they have no conflicts of interest that are directly related to the contents of this review.

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Conception: A.N.R. and B.E. Design and review protocol: J.M., A.N.R., Y.J. Data search, articles selection: J.M. and A.N.R. Data extraction, analysis and interpretation: J.M., A.N.R., Y.J. Manuscript draft: J.M., A.N.R., Y.J. B.E. and S.T. critically reviewed and checked the manuscript draft. All authors approved the final version of the manuscript.

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