Technology Assessment Report No. 56A

Updated Preliminary Economic Analysis on adrenaline auto-injector (EpiPen, Anapen, Twinject and others) for first aid treatment of anaphylaxis

Previous analysis
Technology Assessment Report 56
Listing adrenaline auto-injectors in the Pharmaceutical Schedule for first-aid treatment of anaphylaxis (last updated July 2004)

Author:	[redacted]
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Subject:	Cost-utility analysis for adrenaline auto-injectors for first aid treatment of anaphylaxis

Summary of Proposal

Pharmaceutical Adrenaline auto-injector (EpiPen, Anapen, Twinject and others)
Supplier Multiple
Proposed Indication First aid treatment of food or venom related anaphylaxis
Dosing At least one injection of 0.3mg or 0.5mg (dependant on weight) following an anaphylaxis event
Pharmaceutical Price [redacted]
Current Treatment The analysis assumes no first aid treatment is currently used. However some patients may draw up a dose of adrenaline from a vial.

Executive Summary

Context
This TAR 56A supplements and updates the previous preliminary cost-utility analysis (CUA) of adrenaline auto-injectors for anaphylaxis undertaken by PHARMAC staff in 2004.

Process
PHARMAC staff considered it may be useful to revisit the cost-utility analysis for adrenaline auto-injectors. The three main reasons for this were:

- potentially lower price from generic entry;
- substantive evidence may have arisen since the last analysis in 2004; and
- possible impact of PHARMAC's revised discount rate, which given the importance of late life years saved from preventing younger deaths may have considerable impact.

Original analysis
PHARMAC staff's original analysis was documented in 'Technology Assessment Report 56: Listing adrenaline auto-injectors in the Pharmaceutical Schedule for first-aid treatment of anaphylaxis' (TAR 56)

The result of that analysis was $[redacted] per quality adjusted life year (QALY); equivalent to [redacted] QALYs per $1 million net health sector spend. Over a five year period the discounted (10%) incremental cost was $[redacted] per person with discounted incremental benefits of 1 x 10^{-5} QALYs per person from prevented mortality and 2.5 x 10^{-4} QALYs per person from reduced morbidity (total QALY gains of 2.6 x 10^{-4} per person discounted over 5 years at 10%).

Main changes to the original analysis
The main changes include:

- the combination of different sources of evidence to provide an estimation of the deaths avoided;
- a life time model is used; and
- use of a 3.5% discount rate, being PHARMAC's 2007 revised discount rate for both costs and benefits in CUAs of 3.5%

Updated results
The updated results indicate the cost per QALY of an adrenaline auto-injector, priced at [redacted] compared with no adrenaline self administration device is approximately $[redacted] QALYs gained per $1 million invested), for use in patients who have experienced a *severe/life-threatening anaphylaxis* event from food or venom.

This includes some allowance (50%) for patients who don't meet the criteria for receiving an auto-injector, and patients receiving more than one device at a time. This is further detailed in the sensitivity analysis.

The majority of the QALY benefits are due to the reduction in anaphylaxis related deaths. There are also some financial offsets from reduced hospitalisations.

This updated analysis also looks at scenario where the Special Authority would be less restrictive, i.e. patients have experienced an anaphylaxis event (not necessarily severe). Under this scenario adrenaline auto-injectors are less cost-effective.

Discussion

The main difference between the updated model and the original PHARMAC model is the approach taken to estimate the rate of anaphylaxis deaths in the treated population. As shown in the sensitivity analysis there is a fair amount of uncertainty, many from estimates that influence the rate of anaphylaxis related deaths and the rate in which an auto-injector is used given an anaphylaxis event. Also, it may be worth considering other adrenaline delivery devices such as pre-filled syringes.

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1. Context

An application for the funding of adrenaline auto injector for the first aid of anaphylaxis was received in 1997.

PHARMAC staff have previously undertaken a preliminary cost-utility analysis (CUA) of adrenaline auto-injectors for anaphylaxis (Technology Assessment Report 56).

The application was reviewed by the Pharmacology and Therapeutic Advisory Committee (PTAC) in May 1997, November 1997, August 2004, and November 2005. The relevant minutes of these meetings are included below.

PTAC May 1997

The Committee considered whether there was a health need addressed by this product, a task made difficult by the absence of accurate data on the incidence of severe anaphylaxis. The Committee concluded that there was potentially a valid health need addressed by such a product, though retaining some concerns that the product might not be carried by the patient and therefore not be available when the need arose. The Committee also noted the short shelf life of two years and the prospect that a substantial amount of the product could be discarded unused.

The Committee expressed other concerns about aspects of this product. Its high cost was noted, with much of this cost appearing to be associated with the delivery device. It was noted that other unlisted products might be available at lower cost. The Committee directed PHARMAC staff to investigate other products.

If such products were to be listed the Committee considered that these should be targeted specifically to patients at high risk. Otherwise, such products could be widely and inappropriately prescribed. The Committee considered patients at high risk to be those who have had previous life threatening anaphylaxis, which may include severely atopic children with food allergies. PTAC directed PHARMAC staff to seek advice from a paediatrician with experience in treating allergies and/or an immunologists as to whether or how targeting for the group of patients at high risk could be managed. The Committee considered there should be a restriction of one product per prescription.

The Committee requested that it reconsider this issue at a future meeting once PHARMAC staff had acquired the additional information requested.

PTAC November 1997

The Committee recommended that if Epipen and Epipen Jr were to be subsidised the following restriction would be suitable:

> Special Authority: Specialist physician or Paediatrician application and prescription: only prescribed to patients with previous life threatening anaphylactic reaction. No more than two devices when first prescribed then no more than one device per year, unless required as replacement (to qualify for replacement, prescribing doctor to sight used device).

The Committee considered that Epipen and Epipen Jr should be available for adults and children.

PTAC August 2004

The Committee reviewed a paper, including an economic assessment, from PHARMAC staff on the adrenaline injection EpiPen. Members noted that the nature of anaphylaxis means that there are no randomised controlled trials in this area, and are unlikely to be any in the future. Therefore the efficacy data available for adrenaline are based largely on theory and anecdotal evidence supported by animal models of anaphylaxis.

The Committee noted that the economic assessment by PHARMAC staff was based on improvements in compliance, and considered that this was the first time, in their experience, that compliance had been used in such an explicit manner. However, members also noted that this was a requirement of the product under consideration – the purported benefit of the auto-injector is to improve utilisation through ease of use.

Members noted that proper use of vials and syringes is very difficult, and that the paper by Simons (2001) demonstrated the wide variation in dosing. As adrenaline has a narrow therapeutic index, this is problematic, although the issue does not appear to be entirely remedied by the use of auto-injectors – neither EpiPen nor EpiPen Jr. are ideal for patients between 15 and 30 kg. They also noted, however, that other methods of administration are not yet in widespread use, with delivery by MDI impractical (due to the large number of doses needed) and sublingual adrenaline still in development.

The Committee considered that auto-injectors are infrequently used when needed, and when they are used there is also a risk of administration by an inappropriate route, such as intravenous injection. However, there was some evidence that proper use of the devices did reduce the need for a subsequent hospitalisation. Members considered that a lack of education was most likely a primary reason for low rates of use, both in ignorance of the proper use of the devices (by clinicians, parents and patients) and a general lack of knowledge of anaphylaxis itself. They noted that many clinicians will not have had first-hand experience with an anaphylactic reaction, and that a paper by Gold & Sainsbury (2000) indicated that a majority of parents studied were unable to identify an anaphylactic reaction accurately. Members also noted a paper by Oude Elberink (2002) that indicated that the auto-injectors do not appear to reduce the anxiety surrounding anaphylaxis.

Members considered that it is possible that the highest benefit from auto-injectors could be in adult patients who are required to self-administer adrenaline, rather than children where a parent would usually be administering the dose. They also considered that patients in rural and other remote areas would also be likely to gain particular benefit from the devices.

The Committee noted that the risk of death in food-allergic pre-school children is very low, with a paper by Kemp (2003) placing it at as one death in 2.2 million patient-years.

Members considered that if listed, auto-injectors should only be made available to patients where adequate education and training has been provided.

The Committee recommended that adrenaline auto-injectors be listed in the Pharmaceutical Schedule, subject to Special Authority, with a medium priority.

The Committee considered that the particularly relevant decision criteria to their recommendation are (i) the health needs of all eligible people within New Zealand as patients in rural areas are less able to be reached by emergency services in an adequate timeframe following onset of an anaphylactic reaction; (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things: as adrenaline in syringe/vial form is impractical for parents and patients to use; (iv) the clinical benefits and risks of the pharmaceuticals vi) the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule as the total cost of listing auto-injectors is likely to be relatively low; and (vii) the direct cost to health service users: as the device cost is significant for individual patients to self-fund.

PTAC November 2005

The Committee considered the application from CSL for the listing of EpiPen adrenaline auto-injectors on the Pharmaceutical Schedule. Members noted that the Committee had considered this product previously.

The Committee considered that the application was of poor quality, and did not include copies of any of the studies that were referenced in the application. Members noted that the application did not provide any new evidence in support of EpiPen, and that all references were from 2002 and earlier.

The Committee noted one study supplied by PHARMAC staff by Song et al (2005) examining the appropriateness of the EpiPen needle length. Members noted that the results of this study indicate that the EpiPen needle may not be sufficiently long enough to provide an intramuscular injection in some patients.

The Committee noted the cost-utility analysis supplied by CSL. Members noted that the proposed price for EpiPen was significantly higher than previous offers from the company. Members noted that CSL had assumed in the CUA that only one device would be prescribed to each patient; however, patients frequently have more than one device at a time.

The Committee noted that CSL had presumed an 80% rate of use in anaphylactic episodes, and did not provide a rationale for this figure. Members noted that this was significantly different from the 29% rate of use found by Gold and Sainsbury (2000). Members noted that CSL had referenced the Gold and Sainsbury paper several times throughout its analysis, but omitted to use this statistic in this instance. The Committee considered that the low rate of use found by Gold and Sainsbury is supported by Colver et al (2005). Members also noted that the Colver paper indicated that, from a study of 222 cases of food-allergic reactions, perhaps 6% might have had a more severe reaction if EpiPen was not available.

The Committee noted that CSL had estimated an annual death rate from anaphylaxis of 1 per 8000 patient-years, and noted that this was significantly higher than that estimated by Kemp (2003) of 1 per 2,000,000 patient-years and by Colver (2005) of 1.16 per 10,000,000 patient-years. Members considered that this over-estimation of the mortality rate would have resulted in an over-estimation of the cost-effectiveness of EpiPen.

The Committee **recommended** that, on the basis of no new evidence in support of the proposal, the Committee's previous recommendation to list with a medium priority should stand.

2. Review of the literature

Given that the original PHARMAC CUA was completed in July 2004 an updated search of the evidence was undertaken.

Various literature searches where conducted, primarily on Medline and to a lesser extent using the TRIP database. Search terms included ‘epipen’, ‘adrenaline’, ‘epinephrine’, ‘anaphylaxis’ and ‘anaphylactic shock’. Publications were restricted to those after 01/01/2004 in order to focus on the new evidence. See Appendix 1 for further details.

No new evidence for the efficacy of auto-injectable adrenaline was identified. The 2008 Cochrane review sums up the status of the evidence with the following, “We concluded that the use of adrenaline in anaphylaxis is based on tradition and on evidence from fatality series in which most individuals dying from anaphylaxis had not received prompt adrenaline treatment. Adrenaline appears to be life saving when injected promptly; however, there is no evidence from randomized controlled trials for or against the use of adrenaline in the emergency treatment of anaphylaxis.”

The only international cost-utility analysis identified was the one used in the Australian PBS’s decision to fund EpiPen in November 2003. There was little detail given about the analysis and no information about the approach taken or the evidence used. It was reported the CUA result was high and uncertain (See appendix 2 for further details).

After conducting a rapid literature search (see appendix 3) and comparing the results with the evidence used in the PHARMAC CUA, there doesn’t seem to be any relevant evidence omitted from the analysis.

3. Review of the Modeling

A review of the previous PHARMAC model revealed three key factors:

- Cost of the auto-injector
- Impact of Morbidity
- Impact on Mortality

Cost of auto-injector
This has the least uncertainty of the three variables. The amount that a patient receives is a little uncertain as patients may be given two at a time instead of one.

Impact on Morbidity
Estimated as a 0.68 quality-adjusted life *day* decrement (over 1.2 days) per hospitalisation avoided, i.e. 0.00186 QALYs. It was assumed a 3% absolute reduction in hospitalisations. This was based on an estimate that patients who use an auto-injector having a 15% probability of hospitalisation, compared with a 47% for those who did not use an auto-injector; and that an auto-injector was used 29% of the time.

The average QALY gain per patient was 0.00025, discounted at 10% over 5 years

Impact on Mortality
The original analysis assumed a population rate of anaphylaxis related death of 0.0015 per million per year (this estimate was confined to food related anaphylaxis in children). The treatment population was estimated to be children aged under 5 with food allergies; the prevalence of food allergies in that age-group was estimated to be 5%. The resulting rate of anaphylaxis death in the treatment population was estimated to be 1 per 2.2 million per year

Given the use of auto-injectors when people have them is estimated to be 29%; the deaths avoided were estimated to be 1 per 7.6 million per year.

It was estimated patients had a life expectancy of 50 years. Using a discount rate of 10% (the discount rate used by PHARMAC at the time the analysis was undertaken); the QALY gain per avoided death was 10.91.

The average discounted QALY gain per patient was estimated to be 0.00001, over 5 years of treatments.

4. Updated approach to the Evidence and Modeling

The key updates to the modelling are the combination of different sources of evidence to provide an estimation of the deaths avoided and a life time model is used.

In order to remodel the cost-effectiveness of adrenaline auto-injector the evidence previously used and some additional evidence is discussed and summarised below. It is broken in to the following sections:

- Incidence of anaphylaxis related death
- Correlation between death and previous events
- Correlation between dispensing and use of an Auto-injector
- Frequency of anaphylaxis deaths
- Hospitalisation rates
- Estimated treatment population
- Modelled treatment population

The key studies identified in the following section have been summarised in the table below. Two are retrospective observational studies[1,2] that provide estimates of incidence of anaphylaxis deaths. Another study[3] that provides information relating to the use of adrenaline auto-injectors in the case of recurrent anaphylaxis events and frequency of events in patients who have already had an event.

Table 1: Summary of Key Studies

	Pumphrey et al[1]	**Low and Stables[2]**	**Gold et al[3]**
Study Design	*Retrospective Observations*	*Retrospective Observations*	*Retrospective survey*
Level of Evidence	*3*	*3*	*3*
Disease category	*Anaphylaxis deaths*	*Anaphylaxis deaths*	*Anaphylaxis*
Patient group	UK population 1992-1998	Greater Auckland area (~30% of NZ) 1985-2005	Children, previous anaphylaxis resulting in respiratory tract or cardiovascular, Australia
Intervention (n)	*NA*	*NA*	*Included being prescribed an adrenaline auto-injector (Epipen) (68)*
Comparator (n)	*NA*	*NA*	*NA*
Median follow-up	NA	NA	20 months (mean)
Primary Endpoint	NA	NA	Knowledge and practice of first aid anaphylaxis management.
Key Results	164 anaphylaxis deaths recorded,74 where food or venom related	18 anaphylaxis deaths recorded, Up to eight were food and venom related[i]. Age range was 33-76.	Epipen only used in 29% of recurrent anaphylactic reactions. Average rate of 0.98 allergic reactions per patient year. 37% of these where anaphylactic.

[1] In two cases the cause was undetermined

4.1 Incidence of anaphylaxis related death

The incidence of food and venom related anaphylaxis related death used by this updated analysis extrapolates to 1.18 per 4.4 million (i.e. the number of deaths expected each year in New Zealand). This is taken from a range of 0.83 – 1.53 per 4.4 million person-years. This range is based on the incidence rates reported by Pumphrey et al[1] for the United Kingdom and Low and Stables[2] for the Auckland region. These reports were selected because the first was based on a larger population and is more likely to provide a good estimate of future events. The second was based on a New Zealand population so is more generalizable to the New Zealand setting. Both of these studies were not limited to specific populations such as children.

The ranges of food and venom related anaphylaxis deaths extrapolated from the literature range from 0.27 and 4.68 per 4.4 million person-years. The lower range of 0.27, as used in TAR56

(sourced via Kemp, AS[5]) was not used in this Updated analysis because the patient population was restricted to children (age <16) and only measured food allergy-related deaths. The higher rates reported where 4.02 and 4.68 per 4.4 million person-years. The estimate of 4.02 per 4.4 million patient years[7] was not used as this was based on 1 death and may not represent the average incidence observed in the wider population. The higher estimate was not used as it was uncertain if this was related to food and venom.

Table 2 below has further details of the studies identified that report on the incidence of anaphylaxis death.

Table 2: Incidence of anaphylaxis related deaths

Data source	Population	Time period	Patient years observed	Notes	No. all anaphylaxis-related deaths per 4.4 million*	No. food and venom anaphylaxis-related deaths per 4.4 million
Pumphrey et al[1]	UK population	1992-1998	~400m	Adrenaline used pre-arrest in 14% of fatal cases	1.85	0.83
Low and Stables[2]	Greater Auckland area (~30% of NZ)	1985-2005	~23m		4.02	1.53
Macdougall et al[4]	Under 16 population UK	1990-2000	~130m	One death due to overdose of adrenaline following a mild food allergic reaction	NA	0.27 (Restricted to food related events)
Kemp AS[5]	Based on Macdougall et al, extrapolated to the Australian population					
Bock et al[6]	Uncertain	1994-1999	Uncertain	32 food related fatalities were observed	NA	NA
Sorensen et al [7]	Patients presenting at Thisted Hospital, Denmark	1973-1985	~0.6m		4.02	4.02 (Only one death event observed in study, due to bee sting)
Helbling et al[8]	Canton Bern, Switzerland	1996-1998	~3m		4.68	0 - 1.56 (One death had an unknown cause)
Moneret-Vautrin et al[9]	Based on Helbling et al					

* includes reactions to drugs and media contrast

4.2 Correlation between death and previous events

It was found that not all causes of anaphylaxis death were preceded by the patient having an anaphylaxis event, and in some cases the patient had not had an allergic reaction. This section looks at the correlation between death and previous anaphylaxis events.

Anaphylaxis events
Pumphrey et al[1] found that in 19% (14/72) of food and venom related deaths, patients had a previous severe reaction[1]. It is assumed these severe reactions could be classified as anaphylaxis events. This is the rate used in the anaphylaxis model.

Severe Anaphylaxis events
This analysis looks at 2 groups of patients, those who have experienced an anaphylaxis event and those who have experienced a severe anaphylaxis event (i.e. life threatening). No information was found on the difference in the risk of death between the two, but it seems reasonable that the risk of death would be higher if the previous anaphylaxis event was life threatening. For this analysis it is assumed the risk of death is twice the rate if the patient has had a previous life threatening events.

Given about a third of anaphylaxis events are assumed to be severe/life-threatening, it is assumed that in 9.5% (half of the anaphylaxis events) the patient has previously had a severe/life-threatening anaphylaxis event.

Other evidence
One other study[2] reported on anaphylaxis prior to death; the result reported was that, in 1 of 2 cases of food related anaphylaxis deaths there was previous severe anaphylaxis. However given the small numbers the results from Pumphery et al[1] as discussed above provided a more reliable estimate.

Other studies report of previous reactions (allergic) but do not provide information on anaphylaxis. It seems that in most cases, prior to death patients had an allergic reaction.

Table 3 below has further details of the studies indentified that report on correlation between death and previous events.

Table 3: Correlation between death and previous events

Data source	Population	Time period	Correlation
Pumphrey et al[1]	UK population	1992-1998	19% (14/72) of patients who died (food and venom) had previous severe reaction. A further 46% (33/72) had previous reactions. All food related deaths had a previous reaction.
Low and Stables[2]	Greater Auckland area (~30% of NZ)	1985-2005	1 of 2 food related deaths previously had multiple anaphylaxis events. Both had previous history of seafood allergy
Macdougall et al[4]	Under 16 population UK	1998-2000[i] (2 years)	3 fatal events from food reported[i], previous reactions, 33% (1/3) hospitalised and 66% (2/3) mild/moderate reaction.
Bock SA[6]	Uncertain	1994-1999	28/32[ii] food related deaths had prior history
Sampson et al[10]	13 cases identified by investigators, all in children	uncertain	6/6 fatal events (all from food), patients had a previous allergy

[i] Only the anaphylaxis events between 1998 and 2000 had information regarding previous reactions.
[ii] Two patients had no prior history, for another two it was unknown.

4.3 Correlation between dispensing and use of an Auto-injector

Use of Auto-injector in the case of anaphylaxis event
Gold et al[3] reported that 29% of patients (13/45) who had been dispensed an EpiPen device used it when having an anaphylactic event; these were patients who had a previous reaction. This is the rate used in this analysis. This rate was also used in TAR 56.

The Gold et al study was conducted in children so is unlikely to represent the population treated in New Zealand and is based on relatively small patient numbers. To capture some of this uncertainty the rate is varied down to half and up to double in the sensitivity analysis.

One other study was identified that reported 4/9 patients who died of anaphylaxis used their adrenaline self-treatment kit[1].

Preparedness of patients
Sicherer et al reported 32% of parents of paediatric patients could correctly use the auto-injector. Also 71% had an auto injector on them at the time of the interview; of which 71% of these where unexpired[11]. Another study also indentified that 16/45 (35%) children prescribed adrenaline auto-injectors knew when and how to use them[12].

Effectiveness of adrenaline
Two studies[4,6] identified report the use of adrenaline (close to the onset of anaphylaxis) in those who had died from anaphylaxis. This shows that some patients die despite the early use of adrenaline. Based on these two studies it is assumed that at least 17% of patients will still die despite using an adrenaline auto-injector.

It is uncertain if the patients who did not receive adrenaline early would have lived if they had. No data was identified that provided an estimate of the reduction in deaths from the use of early adrenaline.

Due to lack of data the estimate of the reduction in death's from using adrenaline early in the updated model is 83%, based on 17% of patients dying despite early use of adrenaline.

Table 4: Correlation of being dispensing and use of an Auto-injector

Data source	Population	Time period	Correlation
Gold et al[3]	Children, previous anaphylaxis resulting in respiratory tract or cardiovascular involvement attending paediatric allergy service, Woman's and Children's Hospital, Adelaide, Australia	1996-1998 (2.5 years)	13/45 (29%) of patients who had had an anaphylaxis event used their EpiPen. No deaths reported
Sicherer et al[11]	101 families of food allergic paediatric patients	N/A	At interview 71% had auto-injector on them, 71% of these were unexpired 32% could correctly use device
Hayman et al[12]	14 parents of patients and 46 children prescribed an auto-injector	N/A	2/14 (14%) parents and 16/45 (35%) of children knew when and how to use an auto-injector.
Pumphrey et al[1]	Fatalities from food and venom, UK population	1992-1998	4/9 (44%) patients who had self treatment kits used them. Adrenaline used pre-arrest in 8/69 food and venom related of fatal cases[i]
Macdougall et al[4]	Under 16 population UK	1998-2000	2/3 children died despite receiving early adrenaline.
Bock SA[6]	Uncertain	1994-1999	4/32 patients died despite receiving early adrenaline.

[i] Not included as early use, i.e. before an ambulance could arrive

4.4 Frequency of anaphylaxis events

Rate of Anaphylaxis

Gold et al[3] reported a rate of anaphylaxis events of 0.36 per year. The study population had a median age of 4 at presentation. Of the studies identified, this study gave the most representative study population of the intended NZ population. However applying this rate over a lifetime gives a lifetime frequency of 26[i] anaphylaxis events; this seems higher than would be expected.

There is some reason to believe that the average rate of anaphylaxis over a patients life may be less because, as stated by Kemp, "food-induced immediate hypersensitivity reactions occur most commonly in preschool children to milk, egg and peanuts; frequently, in the case of egg and milk, and less commonly with peanut they resolve by 5 years of age."[5] However is it important to consider that this analysis also looks at venom related events and that egg and milk reactions only accounted for 14% of allergic reaction in the Gold et al[3] study.

Given this information, the rate of anaphylaxis used in the updated model is 0.18 per year (i.e. 1 per 5.5 years). This results in an average of 13[i] anaphylaxis events of a patient's life time.

Other evidence

Vander leek et al[14] reported a rate of 0.33 adverse reactions per patient year from accidental peanut exposure. However it was not stated what proportion of these were anaphylactic reactions. Also the patient population was less representative of the New Zealand population compared to the Gold et al study.

Table 5: Frequency of anaphylaxis events

Data source	Population	Time period	Patient years observed	Anaphylaxis events
Gold et al [3]	Children, previous anaphylaxis resulting in respiratory tract or cardiovascular involvement attending paediatric allergy service, Woman's and Children's Hospital, Adelaide, Australia	1996-1998 (2.5 years)	123[i]	0.36 anaphylaxis events per patient year
Yocum et al [13]	Those identified by medical records as having anaphylaxis in Olmsted County, USA	1983-1987	~0.7m	133 patients had 154 anaphylaxis events over a five year period
Vander Leek et al[14]	Children with adverse reactions to peanuts, diagnosed before the age of 4	5 years (pre 2000)	~200[i]	0.33 adverse reactions per patient year from accidental peanut exposure The chance of a reaction being potentially life threatening is, 44% if previous reaction was non-life threatening, 71% if previous reaction was potentially life threatening

[i] Only patients who had previously had an adverse reaction were observed, as opposed to the general population.

[i] Based on a 5 year old

4.5 Hospitalisation rates

Differences in Hospitalisation rates
There are conflicting on views on the degree on reduction in hospitalisations when an auto-injector is use.

Gold et al[3] reported differences in hospitalisation rates for those who used an auto-injector and those who did not. The results were 15% and 47% for that those using an auto-injector and those not using an auto-injector respectively. This equates to a 68% reduction in hospitalisation.

The Australasian society of clinical immunology and allergy[15] recommend that after an adrenaline auto-injector is used, an ambulance should be called and the patient should receive medical observation in hospital for at least 4 hours. This suggests there will be no reduction in the number of hospitalisations.

In order to balance these views a reduction rate 34% (i.e. half of that reported by Gold et al) was used. This can viewed as either a reduction in the number of hospitalisations or the length of stay in hospital.

Hospitalisation rates following an anaphylaxis event
Gold et al[3] reported a 47% rate of admission to hospital for patients who did not use an adrenaline auto-injector.

The rate of hospitalisation following anaphylaxis reported by Yocum et al[17] was 7% (it is assumed these patients did not have access to an adrenaline auto-injector). This is considerably lower than the rate reported by Gold et al[3]. The possible reasons for this difference include differences in age, allergen and previous events. In the NZ treatment population patients would have had a previous event and it would be food or venom related (so more like the Gold et al study population). However a significant proportion of the patient population will not be children (so more like the Yocum et al study population).

New Zealand's hospitalisations for anaphylaxis (food related and unspecified[ii]) in 2009 numbered 470[16]. Using the number of anaphylaxis events reported by Yocum et al[17] the estimated number of food and venom related anaphylaxis event in the NZ population is 997 per year (see section 4.6), the hospitalisation rate would be 47%.

The average length of hospital stays reported were 2.1 days, Yocum et al[17]; 0.7, New Zealand[16]; and it was not reported by Gold et al[3].

In the updated model the rate of hospitalisation rate of 47% was used; This is based on both the results from Gold et al[3] and the inferred rate in NZ as estimated above.

[ii] It is assumed that venom related would be classified unspecified as there is no other appropriate ICD10 code.

Table 6: Hospitalisation rates

Data source	Population	Time period	Patient years observed	Hospitalised
Gold et al [3]	Children, previous anaphylaxis resulting in respiratory tract or cardiovascular involvement attending paediatric allergy service, Woman's and Children's Hospital, Adelaide, Australia	1996-1998 (2.5 years)	123[I]	15% (2/13) EpiPen users, 47% (15/32) non EpiPen users.
Yocum et al [17]	Those identified by medical records as having anaphylaxis in Olmsted County, USA	1983-1987	~0.7m	7% of anaphylaxis events hospitalised

[I] Only patients who had previously had an adverse reaction where observed, as opposed to the general population.

4.6 Estimated *targeted* treatment population

The assumption around the treatment population effects all the probabilities listed in the previous sections as they were based on certain populations that may differ than the population receiving treatment in the NZ setting. For example, it is assumed that the more patients treated the more anaphylaxis deaths are prevented. However this relationship is unlikely to be linear, i.e. treating 10 times more patients is unlikely to result in 10 times more deaths avoided. This is because the initial population treated are expected to be at higher risk of death.

In November 1997 PTAC recommended the following special authority

> *"Special Authority: Specialist physician or Paediatrician application and prescription: only prescribed to patients with previous life threatening anaphylactic reaction. No more than two devices when first prescribed then no more than one device per year, unless required as replacement (to qualify for replacement, prescribing doctor to sight used device)"*

Severe Anaphylaxis events as a proxy for treatment population
The best identified estimate of this population is based on the Helbling et al[8] report. This reported a rate of severe anaphylaxis events equivalent to 271 per 4.4 million patient years. Using the above figure of anaphylaxis events per year of 0.18, the estimated cumulative population is 1,500.

Anaphylaxis events as a proxy for a treatment population
A rate equivalent to 997 anaphylaxis events per 4.4 million patient years was reported by Yocum et al[17]. Using the above figure of anaphylaxis events per year of 0.18, the estimated cumulative population is 5,500.

Other studies of incidence of events

Two other studies where identified that reported on rates of anaphylaxis hospitalisation and severe events. However due to the reasons given below these were not considered to be the best estimates for the patient population under assessment.

The rate of hospitalisation of severe events in a Denmark hospital was reported by Sorensen et al[7] as equivalent to 70, per 4.4 million patient years. This hospitalisation rate is the same as reported as Yocum et al[13]**Error! Bookmark not defined.**, but Yocum et al reported a much higher rate of anaphylaxis. This suggests that in the Denmark population there may have been more anaphylaxis events than reported because of those not hospitalised. Sorensen et al[7] did state they thought their estimate would be close to the population rate, but this is at odds with both the results from Yocum et at[**Error! Bookmark not defined.**] and Hebling et al[8].

The rates of severe events reported by Macdougal[4] were to 9.3 severe events per 4.4 million patient years. This is considerabley lower than reported by Yocum et al, this is probably because it is restricted children; the majority of deaths of anaphylaxis occur in adults (as shown in table 8) and it is expected that the majority of severe events also occur in adults. Another reason the rate is low is because it is restricted to food related events. Given these limitations this is not used as an estimate for the NZ population.

Australian dispensing experience as a proxy for treatment population
This PBS estimate is not used in the model because of the differences in restrictions. This is provided as additional background information.

The population adjusted (from Aus to NZ equivalent) usage of EpiPen is 10,500 – 11,500[18] dispensings per annum. This rate has been growing since first listing in November 2003; usage started out at about 5,000 dispensings per year.

The Australian restrictions allow two devices per prescription for patients aged under 17; other patients get just one. Matching information of units (supplied to us [redacted] in 2009) with dispensing volumes, there is about twice the number of units as prescriptions. This indicates that most patients are under the age of 17.

The patient population represented by these rates can be drawn from the prescriber restrictions in place in Australia, these are shown below. Access in Australia is much wider that proposed by PTAC.

Australian PBS restriction

> Initial supply for anticipated emergency treatment of acute allergic reactions with anaphylaxis in a patient who:
>
> (a) has been assessed to be at significant risk of anaphylaxis by, or in consultation with, a clinical immunologist, allergist, paediatrician or respiratory physician. The name of the specialist consulted must be provided at the time of application for initial supply; or
>
> (b) has been discharged from hospital or an emergency department after treatment with adrenaline for acute allergic reaction with anaphylaxis.
>
> Continuing supply for anticipated emergency treatment of acute allergic reactions with anaphylaxis, where the patient has previously been issued with an authority prescription for this drug.
>
> Note:
>
> The auto-injector should be provided in the framework of a comprehensive anaphylaxis prevention program and an emergency action plan including training in recognition of the symptoms of anaphylaxis and the use of the auto-injector device. (For further information see the Australasian Society of Clinical Immunology and Allergy website at www.allergy.org.au.)
>
> Note:
>
> Authorities for increased maximum quantities, up to a maximum of 2, may be authorised for children aged less than 17 years where 2 auto-injectors are necessary to ensure 1 is on hand at all times. No increased maximum quantities will be authorised for patients aged 17 years or older.
>
> No repeats will be issued.

Table 7: Estimated *targeted* treatment population

Data source	Population	Time period	Patient years observed	Notes	Rates
Helbling et al[8]	Canton Bern, Switzerland	1996-1998	~3m	Restricted to food and venom	271, food and venom related, severe anaphylaxis events per 4.4 million patient years
Yocum et al[17]	Those identified by medical records as having anaphylaxis in Olmsted County, USA	1983-1987	~0.7m	Restricted to food and venom [i]	997 anaphylaxis events, 70[ii] hospitalised, per 4.4 million patient years
Sorensen et al[7]	Patients presenting at Thisted Hospital, Denmark	1973-1985	~0.6m	Restricted to food and venom	70, food and venom, hospitalised anaphylactic shocks per 4.4 million patient years
Macdougall et al[4]	Under 16 population UK	1998-2000	~33m	Restricted to food related events	9.3 severe events, 40.4 reaction per 4.4 million patient years
Australian PBS[18]	Australians receiving publically funded EpiPen (significant risk of anaphylaxis or discharged from hospital)	2007 – 2009 (2 years)	NA	[redacted] the amount of devices is twice the amount of dispensing reported here (population equivalent).	10,500 – 11,500 dispensings per 4.4 million patient years

[i] 68% of events had an indentified allergen, the food and venom events have been scaled to include the unidentified events

[ii] The allergen for the hospitalisation events was not stated, it is estimated it had the same distribution as the anaphylaxis in general

Table 8: Further information of allergen and age

	Events that are food or venom related	*food*	*venom*	median age	Age range
Death events					
Pumphrey[1]	45%	*24%*	*21%*	38	8-85[i]
Low and stables[2]	33%	*11%*	*22%*	49	35-63 [i]
Anaphylaxis events					
Helbling[8]	77%	*18%*	*59%*	39	8m-83y [ii]
Sorenson[7]	50%	*10%*	*40%*	49	19-77 [ii]

[i] Corresponds to those with food or venom related deaths

[ii] Corresponds to all events

4.7 Modelled treatment population

Given the public pressure in the past to fund an auto-injector and the current market size, there is some uncertainty to how well this product can be restricted. Therefore, the treatment population is estimated to consist of those who it is targeted to, those who partially meet the targeting criteria and those who don't. This is also expected to vary based on the targeting criteria.

Restricted to patients who have had a severe anaphylaxis event

In this model where patients have had a previous severe anaphylaxis event, it is assumed that 50% of patients who receive an adrenaline auto-injector meet the restriction of having a previous severe anaphylaxis event. Of the other patients who receive treatment it is assumed 25% will have had a non-severe anaphylaxis event and 25% will have not had an anaphylaxis event and therefore are assumed not to receive any benefit.

In order to calculate the cost effectiveness three different models are used, one for each group of patients. The model for those who have no gain is based on the other two models but assumes no benefit from being dispensed an adrenaline auto-injector.

Table 9: Modelled treatment population were patients have had a previous severe anaphylaxis event

Weight	Model	Patients
50%	Severe	1,500
25%	Anaphylaxis	750
25%	No Gain	750
		3,000

Restricted to patients who have had an anaphylaxis event

In this model where patients have had a previous anaphylaxis event, it is assumed that 50% of patients who receive an adrenaline auto-injector meet the restriction of having a previous anaphylaxis event. The other 50% will have not had an anaphylaxis event and therefore are assumed not to receive any benefit.

Table 10: Modelled treatment population were patients have had a previous anaphylaxis event

Weight	Model	Patients
50%	Anaphylaxis	7,300
50%	No Gain	7,300
		14,600

5. Updated Economic Model

Like the original PHARMAC model, this updated analysis models the effects of auto-injectable adrenaline on morbidity through reduced hospitalisations and effects on mortality through deaths avoided. The key differences are the combination of different sources of evidence to provide an estimation of the deaths avoided. In addition, a life time model and a lower discount rate are used.

Time horizon
The model has a life time horizon. The cycle length was 1 year, with patient's initial age of 5.

Key assumptions

- Patients use their auto-injector 29% of the time
- The annual rate of death changes between models
    - 70 per million, previous severe reaction
    - 40 per million, previous anaphylaxis event
- Patients who use their injector are:
    - 83% less likely to die (i.e. 0.83 RRR)
    - 34% less likely to be hospitalised (i.e. 0.34 RRR)

The inputs used in the model are shown in table 11 below.

Table 11: Summary of inputs in the model

Input	Value used when restricted to patients who have had a severe anaphylaxis event	Value used when restricted to patients who have had an anaphylaxis event
Incidence of food or venom related deaths	1.18 per 4.4 million	
Proportion of patients who die who have had a previous event	0.095 have had a previous severe anaphylaxis event	0.19 have had a previous anaphylaxis event
Annual rate of events	271 severe events per 4.4 million total population	997 anaphylaxis events per 4.4 million total population
Cumulative number of patients who have suffered an event (i.e. patient population)	1,500	5,500
Annual rate of death (without an auto-injector)	0.00007 per treatment population	0.00004 per treatment population
Probability of having an auto-injector available and then using it	0.29	
Anaphylaxis events per year	0.18	
Hospitalisation rate following anaphylaxis (without auto injector)	0.47	
Relative risk reduction in hospitalisation rate following anaphylaxis with auto injector	0.34	
Relative Risk reduction death following an anaphylaxis event, when auto-injector is used	0.83	
Cost of hospitalisation	$1,200	
Auto-injector usage	2 per 20 months	
QALY loss from being hospitalised following an anaphylaxis event	0.0019	
Age the patient is first dispensed an auto-injector	5	
Median age of anaphylaxis caused death	43[i]	
Proportion of patients dying from anaphylaxis (without an injector)	0.6%[ii]	0.3%[ii]

[i] This is an output resulting from the inputs used, and fit with the medians reported by Pumphery[1] and Low and Stables[2], see table 8 for further details.
[ii] This is an output resulting form the inputs used.

Number of Auto-injector's used

The supplier [redacted] has indicated when the patient is dispended the injector it will have 20 months until it expires. The model assumes patients are limited to one but some patients may get them more regularly, or may get multiple prescriptions. Therefore it is assumed that on average patients will have 2 devices at a time.

Costs

Hospitalisation costs are taken from ICD10 codes T78.0 and T78.2 (Anaphylactic shock due to adverse food reaction and Anaphylactic shock, unspecified). The 2009 price for these events was $1,200. This is associated with an average length of stay of 0.7 days. This is based on 40% of patients being discharged the same day while others stay longer[16].

Cost for general practice visits have not been included as it is not assumed that this will change with the use an adrenaline auto-injector.

Health related Quality of life

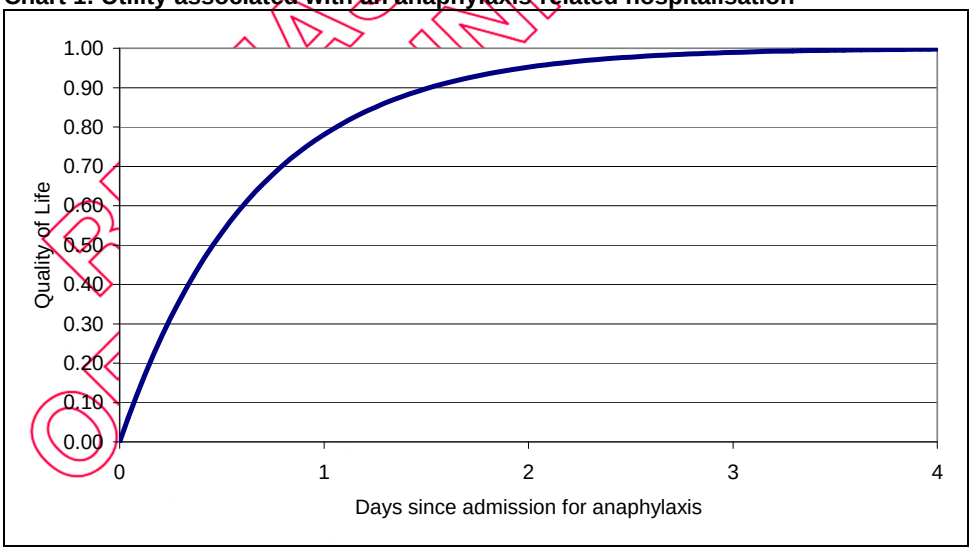
The decrease in Quality of Life (QoL) was based on the previous analysis. The QoL is estimates are the same for both models.

QoL decreases for having an anaphylaxis event have not been included as it is assumed these will not change with the use of an adrenaline auto-injector.

Hospitalisation
The only morbidity information that we have, that from Gold et al[3], reveals a decrease in anaphylaxis-related hospitalisations.

In the absence of any empirically-derived quality-of-life scores for anaphylaxis and its aftermath, we have estimated the disutility from anaphylaxis-related hospitalisations using a simple log-linear model. On presenting to hospital with anaphylactic shock, patients are likely to have QoL of approximately 0, which rapidly improves with appropriate resuscitation and supportive measures. After discharge (average length of stay, 1.2 days) patients still have remaining anxiety from anaphylaxis. This continues to trail off over time, with little residual disutility after day three. We therefore estimate the total disutility to be 0.68 quality-adjusted life days lost per episode requiring hospitalisation. This is illustrated by the following graph:

Chart 1: Utility associated with an anaphylaxis-related hospitalisation



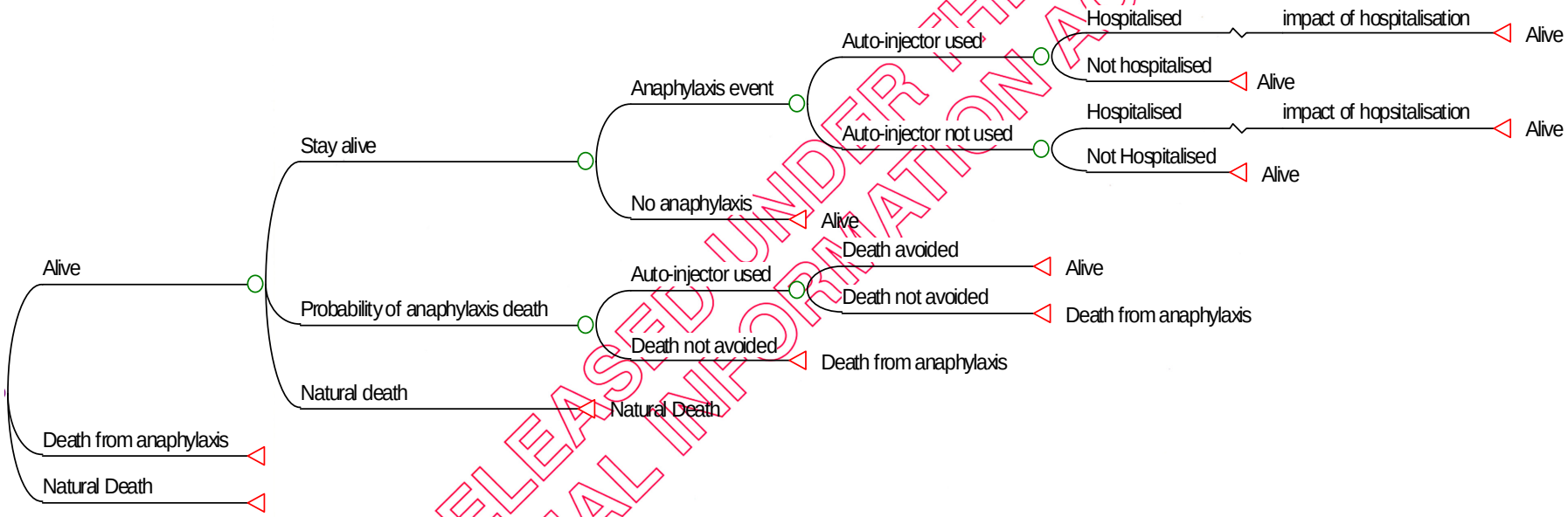
Anxiety
As the number of patients that must be prescribed an AAI for benefit to be gained is high and the cost per unit is considerable, it has been proposed that there are additional benefits from the

'peace of mind' that the devices provide. The theory is that patients prescribed AAIs would have less anxiety about accidental exposure to allergens.

We found one paper[19] that considered changes in health-related quality of life as a result of dispensing AAIs to patients with venom allergies. There was a significant decrease in patients' quality of life as a result of being dispensed an AAI – a result that contradicts previous assumptions.

We do not know by what mechanism quality of life is reduced, although we would posit the following. First, patients' anxiety regarding exposure to allergens and ensuing anaphylaxis is not reduced by the possession of AAIs. Second, anxiety is increased by (a) patients worrying about forgetting or misplacing their devices, and (b) patients worrying about accidental self-harm as a result of incorrect administration. The authors of this paper also posit that the devices may "act as an affirmation and reminder of the patient's risk and thus might negatively influence [quality of life]."

Markov model used



6. Results

6.1 Restricted to patients who have had a *severe anaphylaxis* event

The results indicate the cost per QALY of an adrenaline auto-injector, priced at [redacted] compared with no adrenaline self administration device is $[redacted] QALYs gained per $1 million invested), for use in patients who have experienced a *severe anaphylaxis* event from food or venom.

Table 12: Incremental cost and QALYs from an adrenaline auto-injector, in patients who have experienced a severe event

Weight	Model	Incr Cost	Incr Gain	Cost Per QALY	QALYs gained per $1 million invested
50%	Severe	[redacted]	0.012	[redacted]	[redacted]
25%	Anaphylaxis	[redacted]	0.006	[redacted]	[redacted]
25%	No Gain	[redacted]	0	[redacted]	[redacted]
	Average	[redacted]	**0.007**	[redacted]	[redacted]

6.2 Restricted to patients who have had an *anaphylaxis* event

The results indicate the cost per QALY of an adrenaline auto-injector, priced at [redacted] compared with no adrenaline self administration device is $[redacted] QALYs gained per $1 million invested), for use in patients who have experienced an *anaphylaxis* event from food or venom.

Table 13: Incremental cost and QALYs from an adrenaline auto-injector, in patients who have experienced a severe event

Weight	Model	Incr Cost	Incr Gain	Cost Per QALY	QALYs gained per $1 million invested
50%	Anaphylaxis	[redacted]	0.006	[redacted]	[redacted]
50%	No Gain	[redacted]	0	[redacted]	[redacted]
	Average	[redacted]	**0.003**	[redacted]	[redacted]

7. Sensitivity Analysis

7.1 One Way sensitivity analysis

A sensitivity analysis was undertaken of the Updated model for patients who have had a severe anaphylaxis event; and the cost of auto-injector used was [redacted]. The results of this are shown below in table 14.

This shows that the model is highly sensitive to the probability that the patient uses the auto-injector, the probability of anaphylaxis related death and the reduction in hospitalisations.

Probability of using Auto-injector
The probability that a patient uses their auto-injector, given they have been dispensed one, impacts both the probability of avoiding a death event and the probability of avoiding a hospitalisation. This in turn affects both source of QALY gains, reduction in deaths and hospitalisations, and also affects the costs offsets from avoiding hospitalisation.

If it is assumed that the patients use their auto-injector half as much as reported in the study (i.e. in 0.15 of cases) then the cost per QALY increases to $[redacted] QALYs gained per $1 million invested). If the auto-injector is used twice as frequently (i.e. in 0.58 of cases) the cost per QALY decreases to $[redacted] QALYs gained per $1 million invested).

Probability of death from anaphylaxis
The numerical risk of an anaphylaxis related death depends on the frequency of anaphylaxis events, the correlation between these deaths and the treatment group treated, and the size of the treatment population. The risk of death is a strong driver in the model as the majority of the QALY gains are to the avoidance of death.

When the lower rate of death is assumed (0.83 per 4.4 million per year), resulting in an annual anaphylaxis rate of death of 0.000033, the estimated cost per QALY is $[redacted] QALYs gained per $1 million invested).

When the higher rate of death is assumed (1.53 per 4.4 million per year) resulting in an annual anaphylaxis rate of death of 0.000061, the estimated cost per QALY is $[redacted] QALYs gained per $1 million invested).

Probability of being hospitalised following anaphylaxis event
Differences in hospitalisation, influenced by the base rate of hospitalisations, affect the costs and QALYs. However the affect of changing the hospitalisation is manly through the affect on costs. Because the QALY gains are mainly due to avoided deaths changes to the QALYs gained from reduced hospitalisation have relatively little effect.

If the lower reduction in hospitalisation (17%) is used the cost per QALY is [redacted] QALYs gained per $1 million invested). If the higher rate of hospitalisation (68%) is used the cost per QALY is [redacted] QALYs gained per $1 million invested).

Table 14: Sensitivity analysis, patient who have had a severe anaphylaxis

Variable	Base Case	Sensitivity analysis	Cost per QALY	QALYs per $1 million invested
Base Case			[redacted]	[redacted]
Discount Rate	3.50%	0%	[redacted]	[redacted]
		10%		
Disutility from being hospitalised following anaphylaxis	0.00186	Half	[redacted]	[redacted]
		Double		
Cost of hospitalisation	$1,200	less 20%	[redacted]	[redacted]
		Increase 20%		
Auto-injectors dispensed to patient	2 per 20 months	1 per 20 months	[redacted]	[redacted]
		2.5 per 20 months		
Reduction in hospitalisation	34%	68%	[redacted]	[redacted]
		17%		
Probability of using Auto-injector	0.29	Half	[redacted]	[redacted]
		Double		
Probability of being hospitalised following anaphylaxis event	0.400	26%	[redacted]	[redacted]
		51%		
Probability of death from anaphylaxis (without Auto injector)	0.000047	0.000033	[redacted]	[redacted]
		0.000061		
Probability of anaphylaxis event	0.18	0.135	[redacted]	[redacted]
		0.36		
Cost of an Auto-injector	[redacted]	[redacted]	[redacted]	[redacted]

7.2 Assumptions regarding targeting

Given the public pressure in the past to fund an auto-injector and the current market size (6,000 devices per year), there is some uncertainty to how well this product can be restricted. The table below shows the cost-effectiveness and patient numbers under different scenarios.

Table 15: Cost-effectiveness based on different assumptions regarding targeting

	Proportion of patients			Cost per QALY	Estimated patients
	Severe	Anaphylaxis	No Gain		
Base case	50%	25%	25%	[redacted]	3,000
Scenario A	100%	0%	0%	[redacted]	1,500
Scenario B	50%	50%	0%		3,000
Scenario C	20%	50%	30%		7,500

8. Discussion

8.1 The updated model

The base case results for the model, where patients have had a previous severe anaphylaxis event, is [redacted]. However as shown in the sensitivity analysis the result has an even greater range when some of the variables are varied over their plausible ranges. Overall it is considered that there is a similar chance that the result will be higher or lower.

The majority of the QALY benefit in this updated model is due to the deaths avoided. This is primarily affected by the size of the treatment population (relative to the deaths avoided); the age that a patient is likely to die; and how often the device is used when needed. Changes in these parameters over a plausible range created significant changes in the result, as shown in the sensitive analysis. It would be difficult to reduce the uncertainty due to the evidence available.

If the cost of an auto-injector was [redacted], the estimated lowest cost of an auto-injection device, then the cost per QALY is estimated to be [redacted]

It would be an option to supply schools with adrenaline auto-injectors, therefore reducing the cost per person. However the cost-effectiveness of this option has not been estimated. If this was done it would need to consider how many deaths are likely to be avoided given the median age of anaphylaxis death was reported to be 38 and 49 years of age, and how many anaphylaxis events happen at school. Also there would be additional costs of training school staff how to use the device.

This analysis compared an adrenaline auto-injector to no treatment was the comparator. However there other possible adrenaline delivery options that could be considered apart from an auto-injector; this includes pre-filled syringes.

8.2 Comparison against original PHARMAC model

The updated result is lower than PHARMAC's original estimate of [redacted] per QALY, as reported in TAR56 (i.e. more cost-effective). The main driver is the death rate from anaphylaxis in the treatment population; this is summarised by the first two changes in table 14 below.

The reason each of the values was used in the updated model instead of those used in the original model are further detailed in the sections 4 and 5 above.

Table 14: Summary of changes made, comparing the updated model to the original

Change made	Variable change	Updated result	Ratio of impact
Original TAR	Base Case	[redacted]	
Use death rate based on food and venom rates instead of just food, and all age groups not just children.	Death rate of 1.18 instead of 0.27 per 4.4m person years	[redacted]	0.92
Use treatment population of those who have a previous severe anaphylaxis event, instead of those with a food allergy	Treatment population of 1,500 instead of ~500,000i	[redacted]	0.03
Assume only a proportion of deaths avoidable if only given to patients with previous severe event	9.5% of deaths potentially avoidable instead of all.	[redacted]	8.65
Lower reduction rate of hospitalisations, less frequent hospitalisations (due to less frequent anaphylaxis events) updated higher cost of hospitalisation	34% instead of 68% reduction in hospitalisation when a device is used, increased cost to $1200, up from $952.	[redacted]	1.73
Other changes, lower discount rate, death occurs after about 20 years of treatment, higher price of injector price, and lifetime Markov model	Discount rate was 3.5% instead of 10%, 1.5 devices per 20m instead of 2 per 2 years, Cost of auto-injector [redacted] instead of [redacted], most other changes where to the structure of the model	[redacted]	0.88
Assume 50% of patients don't meet the restriction of having a previous severe event, 25% having a previous non-severe anaphylaxis event but still receiving some benefit, and 25% not receiving any benefit	This required an amalgamation of the results of 3 different models	[redacted]	1.61

[i] Based this on the population food allergic children under 5, But here has been scaled up for the entire population, This equates to about 10% of the population based on the number reported however Kemp[5] also stated that about 5% of the under 5 population is food allergic

These results were produced by adjusting the original analysis step by step with the updated assumptions. The second to last change was produced by changing the model type from a static model with a 5 year time horizon to a Markov model with a lifetime horizon.

Appendix 1: Refined search, looking for updated information

Summary

No New Evidence for Efficacy of epipen or any other auto-injectable adrenaline.
Common aspects reported:

- Questions about the people carrying the injector and being able to use;
- Concern about the epipen needle length being to short;
- Epinephrine solution in unsealed syringes should be replaced every few months; and
- Venom immunotherapy (VIT) is preferred by patients.

Below are the searches conducted and the key evidence identified.

Search 1 - Pubmed

Search term: 'epipen' or ' adrenaline' or 'epinephrine'
Limit(s): published after 01/01/2004
Results: 10,669

Search 2 - Pubmed

Search term: 'epipen' or ' adrenaline' or 'epinephrine'
Limit(s): Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Publication Date from 01/01/2004
Results: 1,296

Search 3 - Pubmed

Search term: epipen OR adrenaline OR epinephrine AND anaphylactic shock
epipen OR adrenaline OR epinephrine AND anaphylaxis
Limit(s) Publication Date from 01/01/2004
Results: 450

Summary of Search 3 results

Russell S, Monroe K, Losek JD. Anaphylaxis management in the paediatric emergency department: opportunities for improvement. Pediatr Emerg Care. 2010 Feb;26(2):71-6.
Extract
"…5-year period in the ED of the Children's Hospital of Alabama in Birmingham, AL, which has an annual census of 55,000……..There were 124 patient visits by 103 patients (4.5 events/10,000 ED patient visits) who met the diagnostic criteria for anaphylaxis. "

Simons FE. Anaphylaxis: Recent advances in assessment and treatment. J Allergy Clin Immunol. 2009 Oct;124(4):625-36; quiz 637-8.

Extract
"Randomized controlled trials of the pharmacologic interventions used in an acute anaphylaxis episode are needed"

Stecher D, Bulloch B, Sales J, Schaefer C, Keahey L. Epinephrine auto-injectors: is needle length adequate for delivery of epinephrine intramuscularly? Paediatrics. 2009 Jul;124(1):65-70.

Extract
"Of these, 158 children weighed less than 30 kilograms and would be prescribed the 0.15 mg epinephrine auto-injector. Nineteen of these children (12%) had a skin to muscle surface distance

of >(1/2)" and would not receive epinephrine intramuscularly from current auto-injectors. There were 98 children weighing >or=30 kilograms who would receive the 0.3 mg epinephrine auto-injector. Of these 98 children, a total of 29 (30%) had a skin to muscle surface distance of >(5/8)" and would not receive epinephrine intramuscularly. “

Rawas-Qalaji M, Simons FE, Collins D, Simons KJ. Long-term stability of epinephrine dispensed in unsealed syringes for the first-aid treatment of anaphylaxis. Ann Allergy Asthma Immunol. 2009 Jun;102(6):500-3.

Abstract:
BACKGROUND: When epinephrine auto-injectors are unavailable or unaffordable, patients at risk for anaphylaxis in the community are sometimes provided with an unsealed syringe containing a premeasured epinephrine dose for use in first-aid treatment of anaphylaxis episodes. OBJECTIVES: To study the stability of epinephrine solution in unsealed syringes under conditions of high ambient temperature, low vs high humidity, and light vs dark. METHODS: Forty unsealed syringes each containing an epinephrine dose of 0.3 mg (as a 1-mg/mL epinephrine solution) were stored at 38 degrees C for 5 months, with 10 syringes at each of 4 different standardized storage conditions: dark and light at low (15%) humidity and dark and light at high (95%) humidity. Duplicate syringes were removed monthly from each storage environment and analyzed for epinephrine content vs control syringes. RESULTS: The epinephrine dose, expressed as the percentage remaining of the mean control dose, was below compendial limits (90% to 115% of label claim) by 3 months after storage at 38 degrees C and low humidity and by 4 months after storage at 38 degrees C and high humidity. Light had no significant effect. CONCLUSION: In hot climates, if an unsealed syringe prefilled with an epinephrine dose is provided for the first-aid treatment of anaphylaxis, it should be replaced every few months on a regular basis with a new syringe containing a fresh dose of epinephrine.

Search 4 - Pubmed

Search Term: epipen OR adrenaline OR epinephrine AND anaphylactic shock
Limit(s): Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Publication Date from 01/01/2004
Results 10

Summary of Search 4 results

Oude Elberink JN, van der Heide S, Guyatt GH, Dubois AE. Analysis of the burden of treatment in patients receiving an EpiPen for yellow jacket anaphylaxis.
J Allergy Clin Immunol. 2006 Sep;118(3):699-704. Epub 2006 Jul 20.

Abstract:
BACKGROUND: Venom immunotherapy (VIT) is a treatment with established efficacy for the prevention of repeated anaphylactic reactions in patients with Hymenoptera allergy, which also allows patients to discontinue carrying an EpiPen. Despite their merits, both treatments can have negative aspects potentially important to patients. OBJECTIVE: We examined possible negative aspects of the EpiPen in comparison with VIT as perceived by patients. METHODS: Positive and negative aspects of both treatments were measured by using a burden of treatment questionnaire together with statements about the EpiPen. RESULTS: One hundred ninety-three patients were included, of whom 94 consented to randomization: 47 received VIT, and 47 received the EpiPen. Of the remaining 99, 75 chose VIT, and 26 chose the EpiPen. Of the patients receiving VIT, 91.5% were (extremely) positive about their treatment, and 85% would choose VIT again. Of the patients receiving the EpiPen, only 48% were positive about their treatment, and even of these patients, 68% preferred to be treated with VIT after 1 year of carrying the EpiPen. Although most patients indicated that it is reassuring to carry an EpiPen and makes them feel safe, many patients also indicated that it is inconvenient and troublesome. Especially patients who were

negative about the EpiPen indicated that they would not dare use the EpiPen if necessary and were afraid at possible side effects. CONCLUSION: In contrast to VIT, the EpiPen is perceived as burdensome by most patients with venom allergy. For most patients, an EpiPen is an unsuitable definitive treatment. CLINICAL IMPLICATIONS: As VIT enables patients with venom allergy to get rid of the EpiPen, patients should be offered VIT.

Search 5 -Trip database

Search term: epipen OR adrenaline OR epinephrine AND anaphylactic shock
Limit(s): None
Results: 2,872

Sheikh A, Shehata YA, Brown SGA, Simons FER. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD006312. DOI: 10.1002/14651858.CD006312.pub2.

Summary
Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. It is commonly triggered by a food, insect sting, medication, or natural rubber latex. The reaction occurs without warning and can be a frightening experience for those at risk and for their families and friends. Adrenaline (epinephrine) is widely advocated as the main treatment in those individuals experiencing anaphylaxis. There is no other medication with a similar effect on the many body systems that are potentially involved in anaphylaxis. The evidence base in support of the use of adrenaline is unclear. We therefore conducted a systematic review of the literature searching key databases for high quality published and unpublished material on the use of adrenaline for emergency treatment; in addition, we contacted experts in this area and the relevant pharmaceutical companies. Our searches retrieved no randomized controlled trials on this subject. We concluded that the use of adrenaline in anaphylaxis is based on tradition and on evidence from fatality series in which most individuals dying from anaphylaxis had not received prompt adrenaline treatment. Adrenaline appears to be life saving when injected promptly, however, there is no evidence from randomized controlled trials for or against the use of adrenaline in the emergency treatment of anaphylaxis. Given the infrequency of anaphylaxis, its unpredictability and the speed of onset of reactions, conducting such trials is fraught with ethical and methodological difficulties.

Abstract
Background: Anaphylaxis is a serious hypersensitivity reaction that is rapid in onset and may cause death. Adrenaline is recommended as the initial treatment of choice for anaphylaxis.
Objectives: To assess the benefits and harms of adrenaline (epinephrine) in the treatment of anaphylaxis.
Search strategy: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 1), MEDLINE (1966 to March 2007), EMBASE (1966 to March 2007), CINAHL (1982 to March 2007), BIOSIS (to March 2007), ISI Web of Knowledge (to March 2007) and LILACS (to March 2007). We also searched websites listing ongoing trials: http://clinicaltrials.gov/, http://www.controlledtrials.com and http://www.actr.org.au/; and contacted pharmaceutical companies and international experts in anaphylaxis in an attempt to locate unpublished material.
Selection criteria: Randomized and quasi-randomized controlled trials comparing adrenaline with no intervention, placebo or other adrenergic agonists were eligible for inclusion.
Data collection and analysis: Two authors independently assessed articles for inclusion.
Main results: We found no studies that satisfied the inclusion criteria.
Authors' conclusions: Based on this review, we are unable to make any new recommendations on the use of adrenaline for the treatment of anaphylaxis. Although there is a need for randomized, double-blind, placebo-controlled clinical trials of high methodological quality in order to define the true extent of benefits from the administration of adrenaline in anaphylaxis, such trials are unlikely

to be performed in individuals with anaphylaxis. Indeed, they might be unethical because prompt treatment with adrenaline is deemed to be critically important for survival in anaphylaxis. Also, such studies would be difficult to conduct because anaphylactic episodes usually occur without warning, often in a non-medical setting, and differ in severity both among individuals and from one episode to another in the same individual. Consequently, obtaining baseline measurements and frequent timed measurements might be difficult, or impossible, to obtain. In the absence of appropriate trials, we recommend, albeit on the basis of less than optimal evidence, that adrenaline administration by intramuscular (i.m.) injection should still be regarded as first-line treatment for the management of anaphylaxis.

Appendix 2: International Recommendations and Associated Cost-utility analyses

Australia: Pharmaceutical Benefits Scheme (PBS) 2003
Listing was recommended on the basis of acceptable cost-effectiveness overall, although the estimates of incremental cost-effectiveness were both high and uncertain.

UK: National Institute of Health and Clinical Evidence (NICE)
Scotland: Scottish Medicines Consortium (SMC)
Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)

No guidance found for any of these agencies.
Search terms used, 'Epipen', 'adrenaline' and 'epinephrine'.

Appendix 3: Comparison of evidence

22/02/2010 – Pubmed

Search terms Epi-pen
Results: All the results where included in the original TAR

- No evidence of epi pen vs syringe and vial
- Little evidence for efficacy of epi-pen
- Issues around people not carrying epi-pen (~50% carry) and also not knowing how to use it (~30% can use it properly)
- Expired, between 0 and 1.5 years, effectiveness reduced. That is the plasma concentrations are lower.

References

[1] Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy. 2000 Aug; 30(8):1144-50.

[2] Low I, Stables S. Anaphylactic deaths in Auckland, New Zealand: a review of coronial autopsies from 1985 to 2005. J Pathology (August 2006);38(4):328-332.

[3] Gold MS, Sainsbury R. First aid anaphylaxis management in children who were prescribed an epinephrine autoinjector device (EpiPen). J Allergy Clin Immunol. 2000 Jul; 106(1 pt 1): 171-6.

[4] Macdougal CF, Cant AJ, Clover AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. Arch Dis Child 2002; 86:236-239

[5] Kemp AS. EpiPen epidemic: suggestions for rational prescribing in childhood food allergy. J Paediatr Child Health. 2003 Jul; 39(5): 372-5.

[6] Bock SA, Munoz-Furlong A, Sampson H A. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol2001;107:191-3.

[7] Sorensen HT, Nielsen B, Ostergaard Nielsen J. Anaphylactic shock occurring outside hospitals. Allergy. 1989 May; 44(4): 288-90.

[8] Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940,000 inhabitants of the Swiss Canton Bern. Clin Exp Allergy. 2004 Feb;34(2):285-90.

[9] Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G. Epidemiology of life threatening and lethal anapylaxis a review. Allergy 2005: 60: 443–451

[10] Sampson H A, Mendekson L, Rosen J P. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. NEJM Aug 6 1992

[11] Sicherer S, Forman J, Noone A. Use Assessment of Self-Administered Epinephrine Among Food-Allergic Children and Paediatricians. Pediatrics 2000;105:359-362

[12] Hayman G, Bansal J, Bansal A. Knowledge about using auto-injectable adrenaline: review of patients' case notes and interviews with general practitioners. BMJ 2003:326:1328

[13] Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: A population-based study. J Allergy Clin Immunol. 1999 Aug;104(2 Pt 1):452-6.

[14] Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. J Pediatr. 2000 Dec; 137(6): 749-55.

[15] Australasian society of clinical immunology and allergy inc. Action plan for anaphylaxis, cited July 2010 http://www.allergy.org.au/content/view/10/3/

[16] New Zealand Ministry of Health. National Minimum Data Set (NMDS), data extracted July 2010 (ICD code used: T78.- and T78.2)

[17] Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: A population-based study. J Allergy Clin Immunol. 1999 Aug;104(2 Pt 1):452-6.

[18] Medicare Australia – Statistics. Medicare Item report, data extracted March 2010 https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml

[19] Oude Elberink JN, De Monchy JG, Van Der Heide S, et al. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. J Allergy Clin Immunol. 2002 Jul; 110(1): 174-82