The relationship between trends in long-acting beta-agonist (LABA) use and asthma hospitalisations in New Zealand

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Key points

- Associations between long-acting beta-agonist (LABA) use and asthma hospitalisation rates are heavily confounded.
- More reliable RCT-based data from overseas suggest 10-30% reductions in exacerbation rates, but hospitalisation -specific data are lacking.
- LABA uptake until recently has been low in New Zealand, so that LABAs might be expected to reduce hospitalisations by 2% at best.
- Asthma hospitalisations in New Zealand have reduced markedly since before the advent of LABAs, and are lower than Australia's hospitalisation rates. New Zealand's decline in hospitalisation rates has been greater than Australia's. These features are despite Australia's greater rates of LABA use.

Context

At its December 2003 meeting, the Board noted that analysis in the Asthma Strategy board paper was limited from a DHB perspective, particularly with regard to hospitalisation data.

This paper attempts to redress this stated deficiency, by explaining why routinely-available hospitalisation data as such cannot elucidate the effects of long-acting beta-agonists (LABAs) on hospitalisation rates; then, with this caveat in mind, describing hospitalisation rates for asthma and relating these to LABA/ICS use.

Why routinely collected asthma hospitalisation data do not necessarily relate to LABA and ICS use

In short, there are no New Zealand data available able to reliably relate LABA and ICS inhaler prescriptions to changes in other health costs, such as admissions to hospitals. Although it is possible to retrospectively examine trends in hospital rates and relate these to pharmaceutical usage, the data would be heavily confounded by other factors. This makes interpretation difficult, for a number of reasons described below.

1. Such information cannot be reliably extracted from routine data sources such as separate hospitalisation and pharmaceutical utilisation databases (such as PharmHouse and NMDS data held by NZHIS). As with many other instances of health sector analysis, analysis has been hampered by the inability (until very recently) to link patients' and populations' drug utilisation with outcomes such as death and hospitalisations (although deaths over time are so few as to be

statistically meaningless anyway). This means analyses at best can only be 'ecological analyses', which cannot reliably connect usage with outcomes. Linking (through NHI numbers being written on scripts) has only started to become available over the last year or so. PHARMAC has yet to examine these data, which anyway would cover too short a time to detect meaningful trends.

2. Any such links between pharmaceutical dispensings and hospitalisation outcomes will be subject to heavy confounding from other factors:

- New Zealand and international research has demonstrated there are multiple factors leading to hospital admissions, for reasons beyond the simple availability of pharmaceuticals. These include socio-economic and behavioural factors, adherence to prescribed courses of medicines, to name but a few.

- Hospitalisation rates will be further confounded by supply issues. This is where thresholds to admission are determined only in part by the severity of asthma ('demand'). Supply factors include bed availability, which can vary by season, region and year according to funding levels; alternative service provision (outpatient services, short-term 'holding'/assessment wards in Emergency Departments); clinical protocols; and the extent of competing illnesses (e.g. the winter surge in cardiorespiratory admissions placing pressure on bed availability).

- There are also issues of diagnostic shift and miscoding. This is where in past years in NZ there has been up to 30% discordance in level-1 ICD-9 diagnoses recorded in hospital administrative databases.[1] In other words, what may be coded as "asthma" may be something else, and vice versa. We do not have any data to show the degree to which diagnostic discordance has changed over recent years.

- Double counting of readmissions and of inter-hospital transfers as “new” admissions further biases the data. Again we do not know how these underlying patterns have varied over recent years.

This degree of confounding demonstrates the limitations of any simple comparison of pharmaceutical uptake with hospitalisation rates. If the intention is to demonstrate changes in hospital utilisation with pharmaceuticals, then to be valid, data should really be gathered as part of a properly constituted clinical trial – prospective, controlled, randomised, double blinded, analysing by intention-to-treat. These features are the best ways to guard against various well-known biases, such as

- overstating the impact of treatment (hence the need for controls, blinding, and inclusion of dropouts (intention-to-treat analysis)),
- comparison groups being different (hence need for randomisation with concealed allocation), and
- confounding from both known and hitherto-unidentified variables (hence need for randomisation).

None of these features can be adequately controlled for by simple comparisons of overall rates of hospital use with overall rates of pharmaceutical use.

[1] Smith MW. Hospital discharge diagnoses: how accurate are they and their international classification of diseases (ICD) codes? NZ Med J 1989 Sep 27;102(876):507-8.

Patient-based cohort and RCT evidence linking asthma hospitalisations to LABA and ICS use

Hence more reliable data should really be obtained from the large international body of evidence, rather than incomplete local data. What is lost with relevance (not NZ) is gained with reliability and validity (because ecological comparisons are poor). Use of such descriptive data could be argued to be facile – i.e. relevant to local needs, but fatally unreliable.

Unfortunately there are few if any international data directly relating LABA use to hospital utilisation. As has already been presented previously to the Board (LABA TAR tabled December 2003), LABAs have been shown in RCTs to reduce asthma exacerbations by 10 to 30% (the MIASMA[2] meta-analysis of salmeterol vs. doubling the dose of ICS, and FACET[3] RCT adding formoterol to low or high dose ICS). Unfortunately these data do not clearly differentiate between hospital-requiring exacerbations and less severe exacerbations.

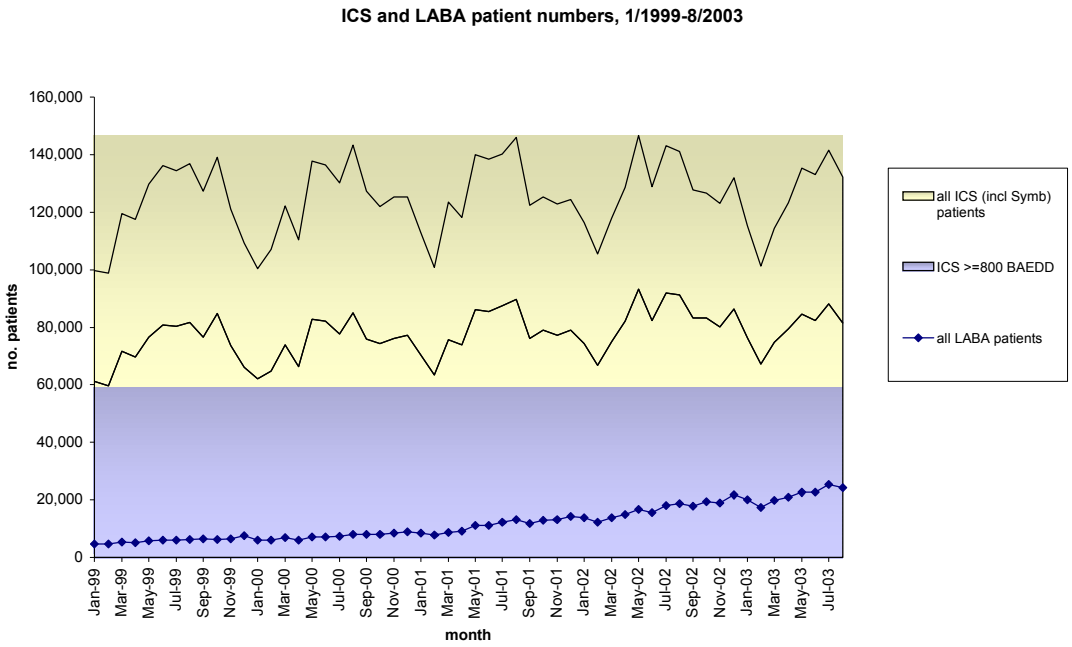
Other reasons why it is impossible to show LABA use materially affecting hospitalisation rates, specific to New Zealand

1. In New Zealand, comparisons between pharmaceutical use and hospitalisations are limited by narrow timeframes. Pharmaceutical utilisation data for inhaled medications in New Zealand are only available since the beginning of 1999; coding changes make data before this time unreliable. Likewise, routinely available hospitalisation data are available only up to the calendar year 2002. This means there are too few years' data to comfortably examine trends – just four years.

2. Uptake of LABAs in New Zealand has been low, and certainly too low until recently to have any appreciable effect on asthma hospitalisations. As described in the December 2003 board paper, the uptake of LABAs overall has increased to 30% of all eligible patients, being some 24,000 patients (of 81,000 patients using ICS $\geq$ 750 mcg BAEDD). Uptake in previous years (August actual) had been 8%, 9%, 15% and 20% – 6,000 to 11,000 patients. This compares with 140,000 patients using ICSs, and roughly 500,000 patients with asthma (see graph below).

[2] Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ. 2000 May 20;320(7246):1368-73.

[3] Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med. 1997 Nov 13;337(20):1405-11.



If:

- between 8% and 30% of eligible patients used LABAs (1999 and 2002 data), and
- eligible patients (high-dose ICS users) account for one half of hospitalisations[4], and
- LABA use reduces exacerbation rates by 10-30%,

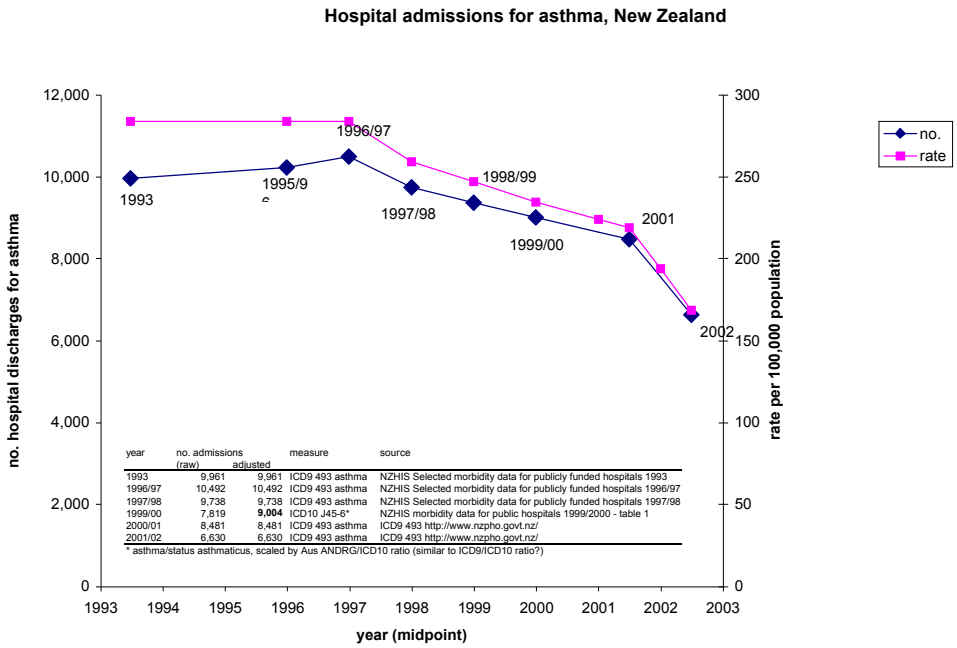
then hospitalisations might be expected to have decreased by 1% in 1999[5] and 3% in 2002[6] at best – that is, a difference of 2% over the four years. This would mean negligible effects on overall hospitalisation rates. Higher LABA uptake might have had the potential to impact on hospitalisations.

Hospitalisations for asthma in New Zealand and Australia, relating to LABA and ICS use

Bearing in mind the above caveats – that descriptive correlations between overall pharmaceutical use and overall asthma hospitalisation rates are meaningless; that there are few years to compare; and that LABA uptake in New Zealand has been too low to have any theoretical effect – associations between pharmaceutical use and hospitalisations in Australasia are unclear.

Hospitalisation rates for asthma have been falling in New Zealand since 1997 (before the advent of LABAs). Between 1996/97 and 2002, hospitalisations rates for asthma decreased by 41% (see graph).

[4] Pethica BD, Penrose A, MacKenzie D, Hall J, Beasley R, Tilyard M. Comparison of potency of inhaled beclomethasone and budesonide in New Zealand: retrospective study of computerised general practice records. BMJ 1998;317:986-990
[5] 1999: 8% uptake * ½ hospitalisations s attributable to high-dose ICS users * 10-30% RRR
[6] 2002: 30% uptake * ½ hospitalisations s attributable to high-dose ICS users * 10-30% RRR



Asthma hospitalisation rates in New Zealand in 2002 were highest in parts of the east of the North Island and Northland (see graph and figure):

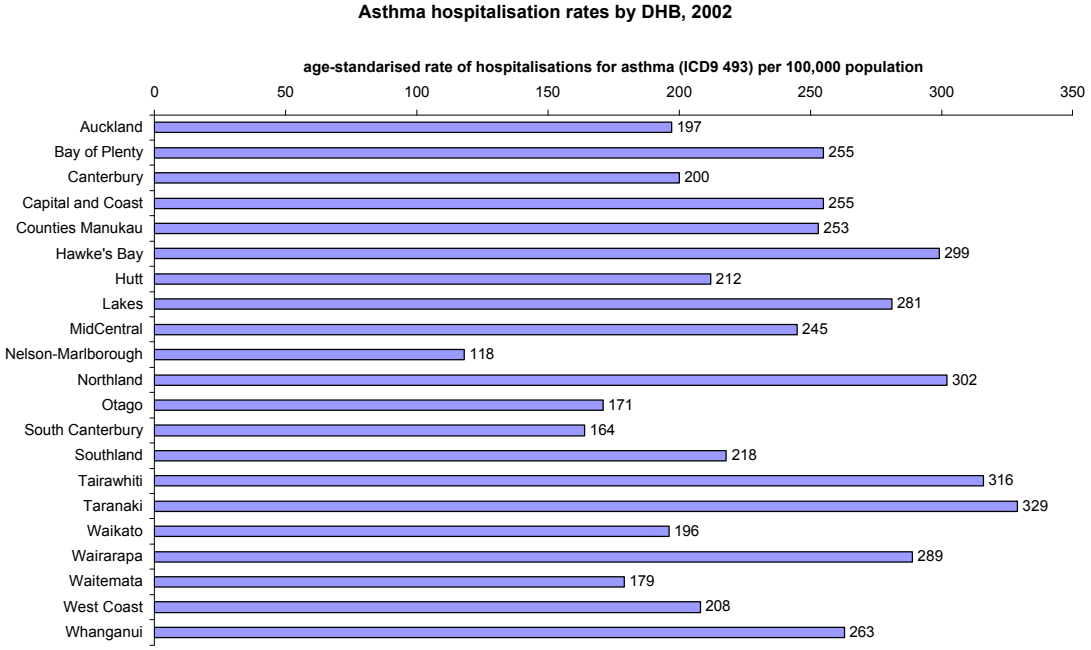
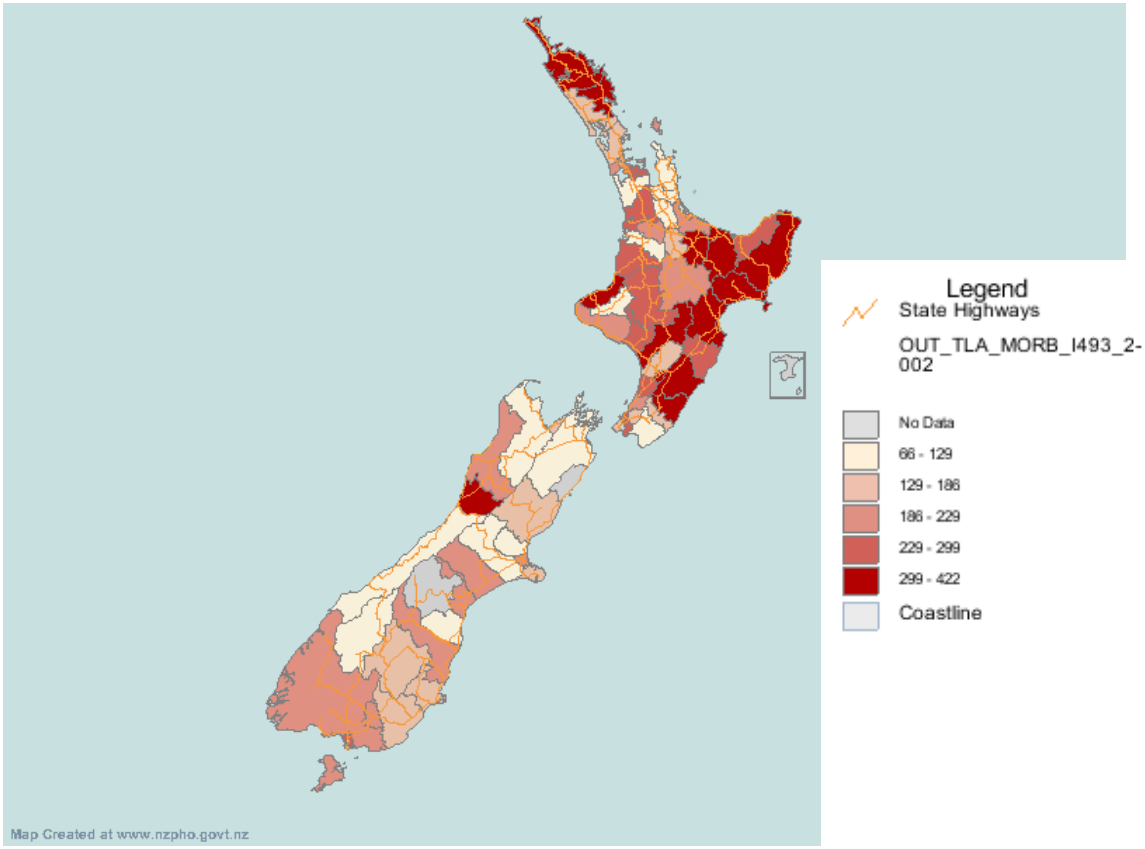


Figure: age-standardised rates of hospital admissions by TLA, 2002
source: http://www.nzpho.govt.nz/

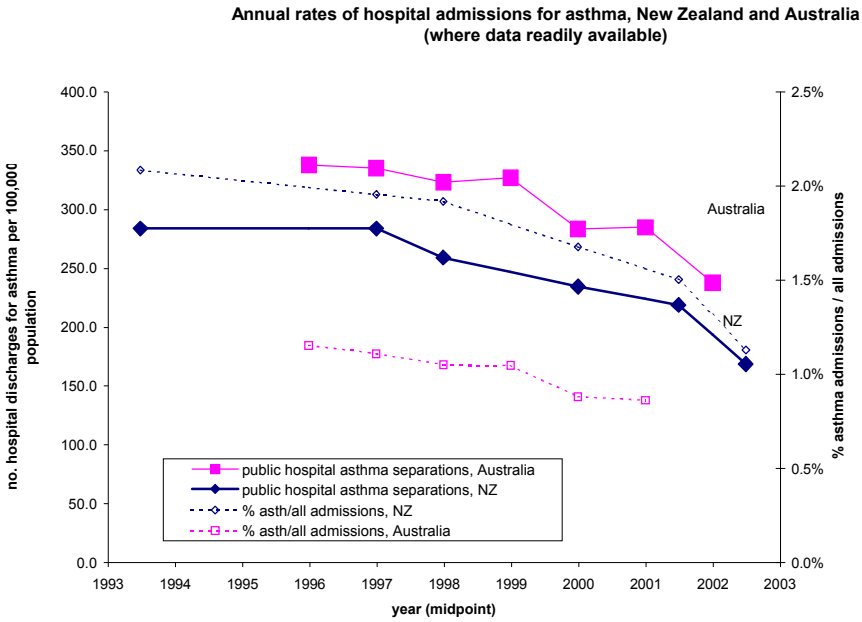


By comparison, hospitalisation rates in Australia – which has much greater usage of LABAs – have decreased also, but less markedly. Over the same time period (1997/98 to 2001/02), hospitalisations in Australia reduced by 29%.

In addition, New Zealand's asthma hospitalisation rates are lower than Australia's – 219.7 per 100,000 in NZ in 2001 and 168.7 per 100,000 in 2002, compared with 285.0 per 100,000 in Australia in 2001/02. Hence Australia's asthma hospitalisation rates are nearly 50% higher than those of NZ.

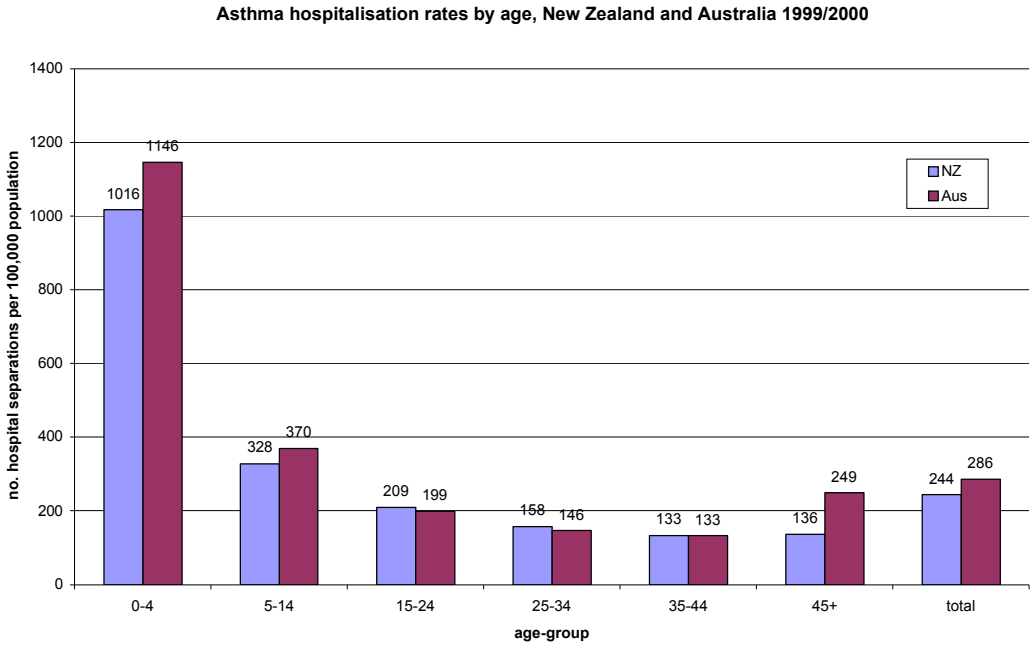
However, as a proportion of all-cause admissions, asthma causes a disproportionate burden of hospitalisations in New Zealand when compared with Australia – around 1.6% of NZ's hospitalisations are for asthma, compared with 0.9% of Australia's.

The above comparisons over time between NZ and Australian hospitalisation rates can be seen in the following graph:

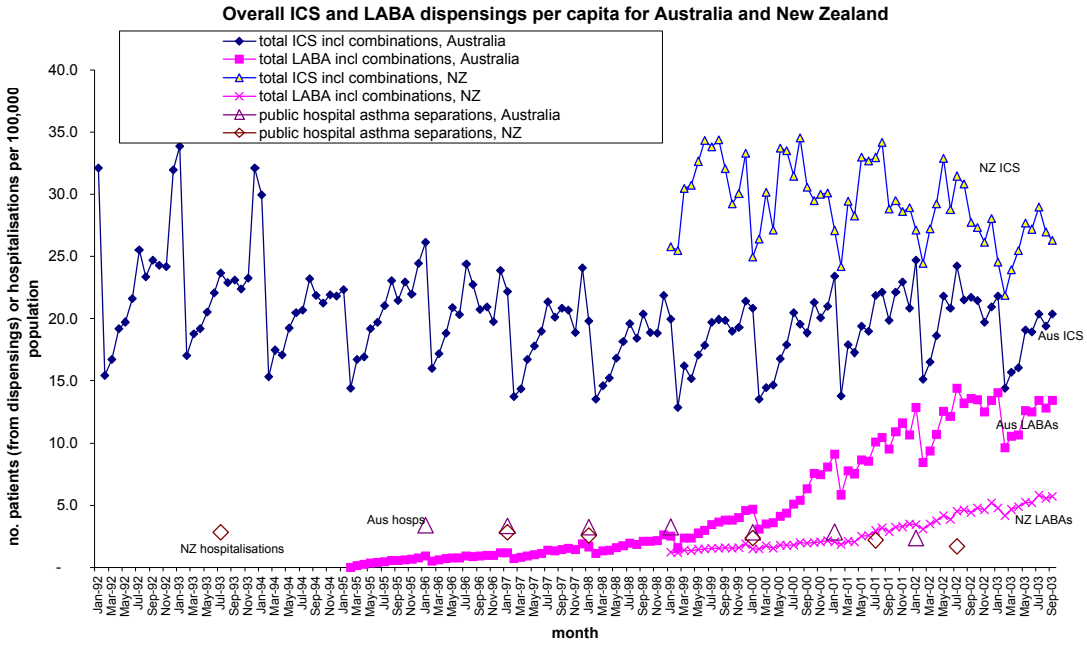


source: PHARMAC analysis of:
AIHW hospital separations data for Australia at http://www.aihw.gov.au/hospitaldata/datacubes/index.html (1993/94-1997/98 ICD9 493 asthma; 1998/99-2001/02 ANDRGs E69A-C Bronchitis and Asthma Age>49 W CC, (Age<50 W CC) or (Age>49 W/O CC), Age<50 W/O CC);
NZHIS hospital separations data for New Zealand (NZHIS Selected morbidity data for publicly funded hospitals 1997/98 ICD9 493 asthma; #72579 NZHIS morbidity data for public hospitals 1999/2000 - table 1 J45 asthma + J46 status asthmaticus, scaled by Aus ANDRG/ICD10 ratio 1999/200 (presumed equivalent to ICD9/ICD10 ratio); NZ Public Health Observatory http://www.nzpho.govt.nz/ 2001 and 2002 ICD9 493;
denominated by Australian and New Zealand census data (with intercensal interpolations and extrapolations)

Asthma hospitalisation rates are especially lower for New Zealand children compared with Australian children (see graph).



The above differences in hospitalisation rates are in the context of, despite similar prevalence rates of asthma, Australia having higher rates of LABA use than New Zealand, lower rates of ICS use (see graph), and higher rates of short-acting beta-agonist use.



However, although these comparisons and time trends are interesting, all of the above caveats to the data still apply.

Also, note there is no clear correlation between even the use of ICSs (as dispensed) and hospitalisation rates by DHB, as can bee seen in the following graphs: