An evaluation of the contribution of pharmacy sales data for purposes of public health

A thesis submitted in accordance with the conditions governing candidates for the degree of

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Presented by

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Declaration

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

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Abstract

The contribution of over-the-counter (OTC) medicines sales data from pharmacies for public health (PH) has previously attracted interest in the UK. In this study, data for several OTC medicines were utilised to explore their contribution to (a) understand the impact of medicine reclassification or increased regulation on supply and (b) the surveillance of infectious diseases in the community in Wales.

Following the reclassification of ophthalmic chloramphenicol (June 2005) an increase in primary care supply (OTC + prescription) of 54% (47,026 units) in eye drops and 29% (15,657 units) in eye ointment were observed (2004 to 2010). Despite this increase the items of eye drops prescribed were similar 12 months before and five years after the reclassification. The impact of regulatory changes concerning the non-prescription sale of opioid-containing analgesics was studied. In the 12 months following September 2009 legislative changes there was a significant fall in sales of codeine- and dihydrocodeine-containing solid oral dosage forms ($p<0.05$). Similarly, following the pack size restriction of non-prescription pseudoephedrine and ephedrine products (April 2008), significant ($p<0.05$) year-on-year reductions in the total weight of pseudoephedrine sold were observed. Sales of non-prescription ophthalmic chloramphenicol were monitored on a small area basis in two areas with known outbreaks of infective conjunctivitis. In both areas sales data did not demonstrate the required sensitivity. When monitoring seasonal influenza, significant positive correlations were observed between cough/cold/flu medicines sales and indicators of influenza activity in Wales.

In alignment with the professional standards for PH practice for pharmacy produced by the Royal Pharmaceutical Society, the work undertaken demonstrated a number of potential uses of medicines sales data for PH. Routine data collection, particularly if captured at time/point of sale, would further enhance its usefulness in detecting and tracking PH incidents.

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Key Abbreviations

ACPO	Association of Chief Police Officers
ADR	Adverse Drug Reaction
APPDMG	All-Party Parliamentary Drug Misuse Group
AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
CAS	Common Ailment Service
CASPA	Comparative Analysis System for Prescribing Audit
CDSC	Communicable Disease Surveillance Centre
CHM	Commission on Human Medicines
CI	Confidence Interval
CPPE	Centre for Pharmacy Postgraduate Education
CPW	Community Pharmacy Wales
CSM	Committee on Safety of Medicines
DH	Department of Health
DHC	Dihydrocodeine
DID	Defined daily doses per 1,000 Inhabitants per Day
DDD	Defined Daily Doses
ED	Emergency Department
GI	Gastrointestinal
GP	General Practitioner
GPhC	General Pharmaceutical Council
GSL	General Sales List
HPA	Health Protection Agency
HPT	Health Protection Team
ICD-9	International Classification of Diseases (Ninth Revision)
ILI	Influenza-Like Illness
IMS	Intercontinental Marketing Services
IQR	Interquartile Range
LHB	Local Health Board (Wales)
LSOA	Lower Super Output Area
MCA	Medicine Counter Assistant
MHRA	Medicines and Healthcare products Regulatory Agency

MP	Multi-purpose
NHS	National Health Service
NHSD	NHS Direct (England)
NHSDW	NHS Direct Wales
NI	Northern Ireland
NICE	National Institute for Health and Care Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
NTA	National Treatment Agency for Substance Misuse
OTC	Over-the-Counter
OXY	Oxymetazolin
P	Pharmacy medicine
PAGB	Proprietary Association of Great Britain
PASW	Predictive Analytics SoftWare
PCO	Primary Care Organisation
PE	Phenylephrine
PHE	Public Health England
PHW	Public Health Wales
PIL	Patient Information Leaflet
POM	Prescription Only Medicine
PSE	Pseudoephedrine
PSNC	Pharmaceutical Services Negotiating Committee
RPS	Royal Pharmaceutical Society
RPSGB	Royal Pharmaceutical Society of Great Britain
RSA	Regional Sales Analysis
SHA	Strategic Health Authority (England)
SPC	Summery of Product Characteristics
UK	United Kingdom
URTI	Upper Respiratory Tract Infection
US	United States
WHO	World Health Organization
WIMD	Welsh Index of Multiple Deprivation
XYL	Xylometazolin

Chapter 1:

General Introduction

General Introduction

1.1 Public health

A more recent definition of public health was adapted from Donald Acheson's early definition in the Acheson report (Acheson 1988) and it defines public health as:

"The science and art of promoting and protecting health and wellbeing, preventing ill health and prolonging life through the organised effort and informed choices of society, organisation, public and private, communities and individuals." (Wanless 2004)

As with other recently cited definitions of public health (Armstrong 2007; Department of Health [DH] 2010; Faculty of Public Health 2010), the revised definition by Derek Wanless recognises that many factors contribute to the health and wellbeing of the population whether physically, psychologically, socially or environmentally. Furthermore, there is an emphasis on collaboration between, and input from, different government agencies, healthcare professionals and public health organisations. In the United Kingdom (UK), improving public health is an issue of significant importance and each country has committed to meet the various public health needs of its population through national public health strategies (DH 2010; Department of Health, Social Services and Public Safety 2010; NHS Scotland 2012; Welsh Government 2009a).

The practice of public health can be broadly divided into three domains: health improvement, health protection and health services (Griffiths et al. 2005). The first domain, health improvement, includes key aspects that aim to reduce both inequalities in health and the wider social influences of health such as housing and employment. The second domain, health protection, includes prevention and control of infectious diseases, environmental hazards and emergency preparedness. The final domain, health services, emphasises on service delivery, promoting evidence-based public health practice and support

appropriate research, audit and evaluation of public health interventions. Other variations of the above model exist, such as a four-domain model that has been developed in England to create a new public health outcomes framework (Public Health England [PHE] 2013a). This new system encompasses additional health and well-being indicators that are used to support the development and practice of public health (PHE 2013a).

In the UK, the National Health Service (NHS) supports many public health activities under each domain through its various health service contractors. By way of example, general medical practitioners (GPs) provide vaccine and immunisation services to NHS patients under the general medical services contract (DH 2013). Such would be considered an activity under the health protection domain. Similarly, community pharmacies contracted by the NHS to provide pharmaceutical services also engage in a variety of public health activities on a regular basis as per the contractual agreement (NHS Wales 2006).

1.2 Role of community pharmacy

Community pharmacies in England and Wales deliver a variety of NHS funded services (NHS Wales 2006). The NHS services provided are divided into three categories, namely essential, advanced and enhanced services (NHS Business Services Authority and NHS Prescription Services 2012). As their name implies, essential services are services that must be provided by all pharmacy contractors as they are commissioned nationally, such as dispensing a NHS prescription and disposal of medicine waste. Advanced services are those that not compulsory but could be provided once the pharmacists and the pharmacy premises have met the required criteria. Lastly, enhanced services are services that are provided locally in agreement with the responsible NHS commissioning body based on the local health needs (NHS Wales 2009). In Wales, certain NHS services provided under the pharmacy contract are different to those provided in England as responsibility over the NHS in Wales was transferred to the devolved Welsh Government on 1 July 1999 (National Audit Office 2001). ‘Discharge Medicines Review’, as an example, is an advanced service provided by Welsh community pharmacy although a similar

provision in England (New Medicines Service) exists (Community Pharmacy Wales [CPW] 2011; Pharmaceutical Services Negotiating Committee [PSNC] 2013).

Under the specifications of essential services, a number of activities undertaken in community pharmacy are related to public health, namely disposal of unwanted medicines, promotion of healthy lifestyles, signposting patients to other NHS services and provision of support for self-care (CPW 2011). All of these provisions take advantage of the distribution of community pharmacies and make use of the medicine- and health-related knowledge that pharmacists and pharmacy staff possess. Of these four provisions, promotion of healthy lifestyles and support for self-care consist of many activities that are relevant to public health. The former ranges from providing opportunistic advice on healthy living and public health topics to participating in national or local public health campaigns. Support for self-care includes providing advice on self-management of minor and long-term conditions and recommending appropriate over-the-counter (OTC) medicines. These advice-giving and health supporting roles have long been fulfilled by community pharmacists, even before they were incorporated into the current pharmacy contract in 2005 (Anderson 2007).

Other public health roles of community pharmacy, many of which are enabled by locally agreed enhanced services arrangements, have been reported. Examples include provision of emergency hormone contraception (O'Brien 2009), influenza vaccination (Warner et al. 2013), smoking cessation services (West et al. 2005), infection control and prevention (Watson et al. 2003), screening of cardiovascular and major diseases (Horgan et al. 2010; Ayorinde et al. 2013), and prevention and management of drug abuse, misuse and addiction (Britton and Scott 2006). Recently in Wales, vaccination for influenza was delivered for the first time by selected community pharmacies under the enhanced services arrangements (Public Health Wales [PHW] 2012). This gave community pharmacy the opportunity to contribute to public health protection by increasing the uptake of vaccination in high-risk patient groups. The extension of the public health role for community pharmacy in the

prevention of influenza had been welcomed by pharmacy organisations (Patel 2012).

The intention for community pharmacy to have a greater public health role has been presented in several government plans and policies for England, Scotland and Wales (DH 2005, 2010; Public Health Institute of Scotland 2003; Welsh Government 2009a). In accordance with the aims of these national strategies, a range of pharmacy-based health services, each tackling a unique public health issue, has been developed and promoted during the last decade (Agomo 2011; Anderson et al. 2008). However, one aspect of pharmacy practice that has considerable public health potential, but has not been fully exploited in the UK, is the knowledge and data community pharmacy businesses have on the sales of OTC medicines. These data have been suggested to hold potential value for pharmaceutical health surveillance, which could provide useful information on population health needs, disease pattern and inform health-related policy decisions (Jones 2009; Public Health Institute of Scotland 2003; Royal Pharmaceutical Society [RPS] 2013; Walker 2000). It is the public health potential of this data which is the subject of the current research.

1.3 Reclassification of medicines

In the UK, the Human Medicines Regulations (2012) classify human medicines into three legal categories, namely: Prescription-only medicines (POMs), Pharmacy (P) medicines and General Sales List (GSL) medicines. POMs can usually only be supplied direct to a patient in accordance with a valid prescription issued by a practitioner who possesses the authority to prescribe. An exemption to this requirement is in an emergency and under certain conditions where a pharmacist can make an emergency supply of a POM to a patient without first obtaining a prescription (RPS 2011a). Medicines that are considered reasonably safe to be used without any form of healthcare supervision are classified as GSL medicines and can be purchased from most retail outlets (Pitchford 2012). In contrast, P medicines can only be sold from a pharmacy under the supervision of a pharmacist (RPS 2011a).

The term OTC medicine refers to both P and GSL medicines, and they are also known as 'non-prescription' or 'behind-the-counter' medicines (RPS 2011a). The legal status of a human medicine is a part of the marketing authorisation that a product must receive before it can be sold in the UK. The Medicines and Healthcare products Regulatory Agency (MHRA) make licensing and classification decisions based on evidence of safety, quality and efficacy relating to a medicinal product (MHRA 2008a). The goal of conferring a legal status on a medicine is to govern the sale, supply and promotion of the product in a way that is proportionate to its safety, which, in turn, determines the ease of access by the general public.

1.3.1 Reclassification

According to European Union Directive on Medicinal Products for Human Use (2001/83/EC), a medicine shall be subject to prescription control if it meets the following criteria:

- dangerous when not used under medical supervision; or
- it is frequently and to a very wide extent used incorrectly, or
- further investigation of activity and/or side-effects is required; or
- are normally prescribed by a doctor to be administered parentally

There is an underlying assumption that medicines that do not meet these criteria could be available without a prescription (MHRA 2012a). For a medicine that contains a new chemical entity it is normally first available as a POM. However, if accumulated experience over time provides sufficient evidence that use is safe without medical supervision, it may be possible to change (or switch) the medicine from POM to P status. Likewise, should it be further shown that professional advice, such as that provided by a pharmacist, is not required for the safe and effective use of the P medicine it may be granted GSL status. This process of altering the legal status of a medicine is known as reclassification (MHRA 2012a).

The drivers behind the decision to reclassify a medicine from POM to P status are multifactorial. For patients, it has been suggested that OTC availability will

widen patient choice, increase their access to treatment, increase patient autonomy and create potential financial savings for those who are not exempt from NHS prescription charge (Blenkinsopp and Bradley 1996; Brass 2001; Brass et al. 2009; Cohen et al. 2005; MHRA 2012a; Prayle and Brazier 1998). For pharmacists, it enables them to offer a wider range of treatment to their patients (Bellingham 2002), become more involved in patients' care and make better utilisation of pharmacists' skills and knowledge (Brass et al. 2009). The government is also supportive of the reclassification policy in the hope that it will reduce its drug expenditure by shifting drug acquisition cost from the state to patients themselves (Blenkinsopp and Bradley 1996; Bond and Hannaford 2003; Brass et al. 2009). Lastly, pharmaceutical companies are driven by their commercial interest to maximise profit and are actively seeking for opportunities to expand on the range of products that could be sold directly to consumers (Bond 2001; Blenkinsopp 2004).

In the last ten years, there had been more than ten successful POM to P switches in the UK (Proprietary Association of Great Britain [PAGB] 2012). In supporting this trend, the UK pharmacy regulator, the General Pharmaceutical Council (GPhC), has also been considering making P medicines self-selectable on open display in pharmacies. The purposes of this proposed change were to further increase the accessibility and enhance patient selection of medicines without a prescription (GPhC 2012).

Converse to the deregulation of a medicine, re-introduction of prescription requirement for an OTC product is also possible. This could be prompted by emergence of safety concerns which no longer justify a medicine's OTC availability for self-medication (Figure 1.1).

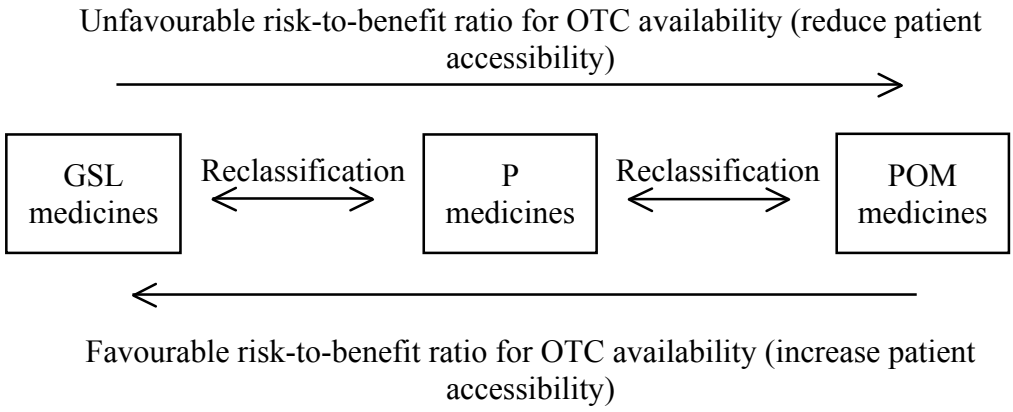


Figure 1.1 Relationship between risk-to-benefit ratio and over-the-counter (OTC) availability of a medicine (modified from Blenkinsopp and Bond 2005)

Such reclassification could be related to the identification of previously unknown side effects, drug interactions or increased likelihood of misuse and/or abuse (Blenkinsopp and Bond 2005; Brass 2001). As an example, terfenadine was a non-prescription antihistamine available as a P medicine in the UK but was subsequently reclassified to POM status due to cardiac side effects (Wise 1997). Another strategy employed by medicine regulators to reduce the potential harm of an OTC medicine is by amending the licensing details of a medicine, through limiting the pack size, concentration and/or dose that a pharmacist can supply without a prescription (Blenkinsopp and Bond 2005). This approach to restoring the balance between benefits and risks is exemplified with the reclassification of larger packs of paracetamol and aspirin in 1998 because of increase numbers of death caused by deliberate self-poisoning (Committee on Safety of Medicines [CSM] 1997). At the time, non-effervescent products containing paracetamol and salicylates that are of a pack size greater than 32 tablets/capsules were reclassified from P to POM status. The reduced non-prescription access to large packets of paracetamol had been suggested to have lowered the numbers of related deaths and thus protected the public's health (Hawton et al. 2013).

In the UK, a spontaneous adverse drug reaction (ADR) reporting system called the Yellow Card Scheme has been in operation for over 40 years to detect unknown side effects of medicines (MHRA 2013a). Initially the scheme was restricted to only receive reports from doctors but it has since been extended to

all healthcare professionals as well as the general public. Currently, suspected ADRs associated with prescription and non-prescription medicines can both be reported via the Yellow Card Scheme. A notable example of the contribution of the scheme to OTC medicine safety was the identification of the possible link between aspirin and Reye's Syndrome in children under 16 years (MHRA 2013b). Whilst the Yellow Card Scheme has an important role in ensuring the safety of non-prescription medicines following their reclassification, the numbers of reports of ADRs associated with OTC medicines have been low (Avery et al. 2011) and could be due to under-reporting by healthcare professionals and consumers (Blenkinsopp and Bond 2005; Bond et al. 2003).

1.3.2 Impact of reclassification of medicines

The impact of medicine reclassification on patient and the wider healthcare environment is clearly of interest to medicine regulators who imposed the changes. As mentioned earlier, the increased access to medicines is linked to a number of potential safety risks to the public's health (Blenkinsopp and Bond 2005; Brass 2001). In circumstances where the reclassification decision was made to address a safety concern related to a medicine, evaluation of the impact of the reclassification policy is of even greater importance. There is a need of a way to assess whether a reclassification policy has indeed had an influence on patients' access to medicines. How this access should be monitored is unclear but it has been suggested that sales volume can be used as a surrogate to estimate patients' access (Brass 2001). The growing focus on the public health agenda for pharmacy has prompted calls for medicine sales data to be better gathered, utilised and shared (Armstrong 2007; Jones 2009; Walker 2000). Nonetheless, there are few studies utilising medicines sales data to investigate the impact of medicines reclassification or regulatory changes related to a medicine.

1.3.3 Review of relevant literature

Using the multi-purpose (MP) search function (Ovid 2012), English language articles were identified in Medline and Embase database searches (via Ovid) between January 1996 and July 2013 using the following search terms ($ indicate truncation):

* over-the-counter or non-prescription or behind-the-counter or OTC
  Total hits: 17,574

* sale$ or wholesale$ or suppl$ or retail$
  Total hits: 553,683

* restrict$ or policy or regulat$ or law or reclass$ or switch or deregulat$
  Total hits: 3,164,870

Several search fields were searched by the MP search function, including: title, abstract, medical subject heading, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword and name of substance word.

Boolean operator ('and') was used to combine the searches and produced 505 matching articles. After screening the titles, abstracts and/or full texts, 10 articles that utilised OTC medicine sales data to examine the impact of medicine reclassification policy or regulatory changes related to medicines are selected for review and are presented in Table 1.1.

Table 1.1 Studies utilising medicines sales data to examine the impact of medicine reclassification or regulatory changes related to medicines

Source	Study design	Sample	Country	Medicine studied	Outcome measure	Outcome
Wirtz et al. 2013	4 years before and 4 years after legal prohibition of non-prescription sale of antibiotics (interval depends on the country studied)	National sample of between 46% to 86% of all private sector retail pharmacies in ambulatory care in the four Latin American countries	Chile, Colombia, Venezuela, Mexico	Penicillins, sulphonamides, trimethoprime, macrolides, quinolones, cephalosporins (1999 - 2006)	Defined daily doses per 1,000 inhabitants per day (DID)	Immediately after policy implementation, antibiotic consumptions reduced significantly in Chile (-5.56 DID; $p<0.05$) and Colombia (-1.0 DID; $p=0.001$). No significant change in DID was observed in both Venezuela and Mexico ($p>0.05$)
Deslandes et al. 2011	2 years after reclassification to non-prescription availability	National sample of community pharmacies (unspecified data coverage) in Wales, Scotland, Northern Ireland (NI) and two regions of England (North East and South Central Strategic Health Authority [SHA])	UK	Azithromycin (2008)	Unit pack sold per 10,000 population	Between 2008 and 2010, a reduction in OTC sales was observed in all countries studied (packs per 10,000 population). In Wales, from 1.64 packs to 0.44, respectively. In Scotland, from 1.32 to 0.48 packs. In NI, sales reduced from 0.35 to 0.16. In England, from 1.14 to 0.35 for North East SHA and from 1.14 to 0.35 packs for South Central SHA

Table 1.1 (continued) Studies utilising medicines sales data to examine the impact of medicine reclassification or regulatory changes related to medicines

Source	Study design	Sample	Country	Medicine studied	Outcome measure	Outcome
Walker and Hinchliffe 2010	18 months before and 40 months after reclassification to non-prescription availability	National sample of 89% and 87% of all community pharmacies in England and Wales, respectively	UK	Ophthalmic chloramphen-icol (2005)	Unit pack sold per 1,000 population; number of dispensed prescription per 1,000 population	A marked increase in sales of OTC ophthalmic chloramphenicol was observed following the reclassification. Between 2007 and 2008, sales of eye drops were equivalent to 67% and 52% of their corresponding volume supplied on prescriptions in England and Wales, respectively. Year-on-year prescribing of ophthalmic chloramphenicol was unaffected in either country during the entire four years study period ($p>0.05$)
Dhippayom and Walker 2006	24 months before and 12 months after reclassification to non-prescription availability	National sample of pharmacies (unspecified data coverage) in Wales	UK	Omeprazole (2004)	Unit pack sold per 1,000 population; number of dispensed prescription per 1,000 population	During the 12 months following the reclassification, a total of 5,758 packs of OTC omeprazole were sold across Wales. Over the same period, an 8.6% decline in sales of OTC histamine$_2$ (H_2) antagonist was observed. The availability of OTC omeprazole had no impact ($p>0.05$) on the primary care prescribing of ulcer-healing drugs between 2002 and 2005

Table 1.1 (continued) Studies utilising medicines sales data to examine the impact of medicine reclassification or regulatory changes related to medicines

Source	Study design	Sample	Country	Medicine studied	Outcome measure
Hawton et al. 2004	2 years before and 4 years after implementation of legal restrictions on OTC pack sizes	UK sample of pharmacies and general retail outlets (unspecified data coverage)	UK	Aspirin (1997) and paracetamol (1998)	Mean pack size; number of unit pack sold; number of tablets sold; number of death by suicidal overdose; number of patients admitted to liver unit, listed for liver transplant and undergoing transplantation for paracetamol-related poisoning; number of non-fatal poisoning related to analgesics; number of tablets taken
Outcome					
In the one-year period after legislation was introduced, mean pack size for OTC paracetamol and aspirin containing products reduced from 35 to 24 tablets per pack and from 65 to 25 tablets per pack, respectively. Cumulative total of non-prescription paracetamol tablets sold remained steady from 520 million in 1996/97 to 580 million in 2001/02. The 12-month total packs of aspirin sold OTC also remained steady from 11 million packs in 1996/97 to 12 million packs in 2001/02; the numbers of tablets sold have however halved. In the 12 months after the change in legislation, there was a 22% reduction in suicidal deaths from paracetamol and salicylates ($p<0.001$). Overall, liver unit admittance, liver transplants and actual transplantation from paracetamol-induced hepatotoxicity reduced by approximately 30% between 1998 and 2002 (all $p<0.05$). Non-fatal poisoning with paracetamol reduced by 15% in the first year following OTC pack size restriction ($p<0.001$). Mean numbers of tablet taken in paracetamol and salicylates overdose reduced up to 31% in the three years after the change in legislation (all $p<0.05$).					

Table 1.1 (continued) Studies utilising medicines sales data to examine the impact of medicine reclassification or regulatory changes related to medicines

Source	Study design	Sample	Country	Medicine studied	Outcome measure	Outcome
Furler et al. 2002	At least 2 years before and 1 year after reclassification to non-prescription availability (interval depends on the country studied)	National sample of 97% of community pharmacies in Canada and unspecified data coverage in the US and the UK	Canada, US, UK	H_2-receptor antagonist (1994 for UK, 1995 for US, 1996 for Canada)	Per capita sales in US dollar; number of dispensed prescription per capita	Non-prescription sales of H_2-antagonist increased from 1994 to a peak of $2.05 per capita in 1996 in the US. A small increase in sales of H_2-antagonist ($0.12) was observed in the UK in the 12 months after reclassification. Sales of H_2-antagonist in Canada could not be determined. A decline in prescription supply of H_2-antagonist was observed in the US only, from 0.14 in 1995 to 0.12 prescription per capita in 1997
Sheen et al. 2002	2 years after implementation of legal restrictions on OTC pack size	National sample of pharmacies and general retail outlets with 97% data coverage	UK	Paracetamol (1998)	Number of packs sold; weight of drug sold in grams	The weight of paracetamol sold OTC fell by 60% (242,597,912g/409,054,172g) during the two years after reclassification whilst the number of packs sold remained unchanged. These observations were accompanied by a 73% (45,929,400g/26,453,320g) increase and a 76% reduction (510,17,070g/66,465,780g) in weight of ibuprofen and aspirin sold OTC over the same period, respectively

Table 1.1 (continued) Studies utilising medicines sales data to examine the impact of medicine reclassification or regulatory changes related to medicines

Source	Study design	Sample	Country	Medicine studied	Outcome measure
Hawton et al. 2001	2 years before and 1 year after implementation of legal restrictions on OTC pack size	National sample of pharmacies and general retail outlets with 97% data coverage	UK	Aspirin (1997) and paracetamol (1998)	Mean pack size; number of packs sold; number of tablets sold; number of death from paracetamol or salicylate overdose; number of patients referred to liver units, listed for liver transplant and undergoing transplantation; number of overdoses and tablets taken; blood concentrations of the drugs; prothrombin time
Outcome					
Mean pack size reduced significantly for all paracetamol and aspirin related medicines 12 months after the legal changes ($p=0.01$). An increase in packs of paracetamol sold OTC was observed ($p=0.003$) but the total number of tablets sold remained unchanged ($p>0.05$). A significant reduction ($p<0.05$) in number of tablets sold for paracetamol compounds, salicylates and salicylate compounds was observed. In the 12 months after the change in legislation, number of deaths from paracetamol and salicylates poisoning fell by 21% ($p=0.01$) and 48% ($p=0.01$), respectively. The rate of liver transplant decreased by 66% ($p<0.0001$). The number of non-fatal self-poisoning with paracetamol of any formulation decreased significantly by 11% ($p<0.0001$). The average number of tablets taken in paracetamol overdoses reduced by 7% ($p=0.04$). The mean blood concentrations of salicylates after overdose decreased (-17%), as did prothrombin time (-2%).					

Table 1.1 (continued) Studies utilising medicines sales data to examine the impact of medicine reclassification or regulatory changes related to medicines

Source	Study design	Sample	Country	Medicine studied	Outcome measure	Outcome
Lundberg and Isacson 1999	1 year before and 6 years after reclassification to non-prescription availability	Two community pharmacies in Tierp, Sweden	Sweden	Nasal drops and nasal sprays containing oxymetazoline or xylometazoline (1989)	Number of packs sold and dispensed prescription per 1,000 inhabitants; physician visits for rhinitis; cost of physician visits for rhinitis	From 1988 to 1995, OTC sales of nasal drops decreased from 208 to 30 packs per 1,000 inhabitants, respectively. Sales of nasal spray increased from 152 to 669 packs per 1,000 inhabitants, respectively. Supplies on prescription decreased from 143 packs in 1988 to 37 packs per 1,000 inhabitants in 1992. Physician visit for rhinitis decreased from 10% in 1988 to 8% in 1994 ($p<0.05$), which was equivalent a reduction of public expenditure from 2.1 to 1.6 million Swedish crowns
Carlsten et al. 1996	2 years before to 4 years after reclassification to non-prescription availability	Estimated national sales of medicines to the general public (unspecified data coverage)	Sweden	16 drugs* (1980 – 1992)	Number of defined daily doses (DDD) for prescription sales and for OTC sales	An increase in OTC sale was observed in the 2 years post-reclassification for all medicines studied except for oxymetazoline and sodium cromoglycate. The increase in sales ranged between 12% and 307%. There was a 26% reduction in prescription sales for 12 out 16 medicines studied compared to their corresponding volume sold 2 years prior to reclassification

*Oxymetazolin (1981), hydrocortisone (1983), clotrimazole (1983), econazole (1983), miconazole (1983), lignocaine (1987), ibuprofen (1988), oxymetazolin (1989), xylometazolin (1989), loperamide (1989), nicotine (1990), sodium fluoride (1991), oestriol (1991), hydrocortisone-miconazole (1992), loratadine (1992), sodium cromoglycate (1992)

Medicines sales data for different therapeutic classes of drugs were utilised to examine the impact of medicine reclassification and medicines regulations in different countries. Of the seven studies relevant to the UK, three investigated the legal restriction on the sales of OTC paracetamol and salicylates in 1998. The study by Sheen et al. (2002) assessed the impact of legislation on sales of medicines only. It was found that while mass of aspirin and paracetamol sold fell, that of ibuprofen has increased during the two years following pack size restriction. The authors suggested the increase use of ibuprofen posed an additional risk for gastrointestinal (GI) adverse events and this could burden the healthcare services.

By contrast, the two studies conducted by Hawton et al. (2001, 2004) assessed the sales of medicines in conjunction with other data related to paracetamol, salicylate and ibuprofen poisoning. The additional information aided the interpretation of medicine sales statistics. The results revealed there was reduction in sales of some but not all of the OTC paracetamol and salicylate preparations. The results of the 2001 study indicated a decline in both paracetamol and salicylates sold OTC but the 2004 study indicated the sales of OTC paracetamol have reverted back to its pre-legislative change level. Thus there may be differences in the short-term and long-term impact of pack size restriction on sales of OTC medicines.

The other four UK-related studies investigated the impact of switching a medicine from POM to P status. Two of the studies (Deslandes et al. 2011; Walker and Hinchliffe 2010) examined the reclassification of an antibiotic. Deslandes et al. (2011) found there was a low level of sales for oral azithromycin following its availability OTC but noted that sales data from one pharmacy multiple in all areas studied were missing. Similarly, sales figures for OTC ophthalmic chloramphenicol reported in a study by Walker and Hinchliffe (2010) was thought to be an underestimate of the actual supply picture due to missing sales data. However, unlike OTC azithromycin, a substantial increase in OTC supply of ophthalmic chloramphenicol was reported following its reclassification.

The impact of the reclassification of omeprazole on the prescribing and sale of ulcer healing drugs was examined in a study by Dhippayom and Walker (2006). Although it was shown the reclassification of omeprazole probably had an impact on OTC sales of H_2 antagonist, sales of OTC omeprazole were only monitored for 12 months post-reclassification. This length of follow-up may not have been long enough for the full impact of reclassification to be observed and assessed. Furler et al. (2002) examined the impact of switching H_2 antagonist to non-prescription status in the US, UK and Canada. Although the study successfully demonstrated a variation in prescription and non-prescription drug utilisation between the three countries, changes in sales were reported in US dollar spent per capita and such was difficult to be compared with findings of other studies.

Lundberg et al. (1999) utilised the sales data for OTC nasal sprays and investigated the impact of their reclassification to non-prescription status on the prescribing of nasal decongestants and physician visits. Against the backdrop of reductions in prescribing and physician visit for rhinitis and sinusitis over the study period, increase in OTC sales of nasal sprays indicated an extended use of OTC medicines following reclassification. A large number of medicines reclassified in Sweden were studied by Carlsten et al. (1996). Overall there was an increase in OTC sales following medicine reclassification. However, the OTC medicines sales data utilised in this study were derived from hospital and prescription sales of medicines, of which the prescription sales were calculated based on an inconsistent sampling ratio of prescription data over the study period. As a result, the reported sales statistics for OTC medicines may have been unreliable.

Wirtz et al. (2013) studied the impact of prohibiting OTC sales of antibiotics in four Latin American countries. Using medicine sales data, the study successfully quantified the sales of selected antibiotics and found the policy interventions had an impact on overall antibiotic consumption in some but not all of the countries studied. However, in countries where there had been a reduction in antibiotic use, it was not known whether this was due to a fall in antibiotics dispensed on legitimate prescriptions or due to a fall in those that

were illegally purchased OTC. The authors recommended complementing the analysis with a qualitative study of the policy interventions to better understand the potential causes of differential effects.

1.3.3.1 Summary of relevant literature

In summary, OTC medicines sales data have been utilised to examine the impact of POM to P reclassification. Of those that were relevant to the UK, only one study has collected data for more than three years and examined the long-term impact of POM to P switch of a reclassified medicine (Walker and Hinchliffe 2010). In the present study, the long-term impact of POM to P reclassification for ophthalmic chloramphenicol will be investigated.

There were fewer studies that examined the effect of increased regulation on medicine utilisation. Of those that were reviewed, three out of four studies were related to the pack size restriction of non-prescription paracetamol and aspirin. Other therapeutic classes of OTC medicine that have recently undergone legal restriction changes in the UK have not been studied. This will be another focus of the current study which will investigate the impact of increased OTC medicine regulation on the OTC sales and prescribing of selected medicines.

1.4 Disease surveillance

There are a number of infectious diseases of interest to public health and which have the potential to be linked to the sale of OTC medicines. Some examples include: diarrhoea caused by norovirus and cryptosporidium (both linked to the sale of anti-diarrhoeal and rehydration products), headlice (linked to sales of insecticides), upper respiratory tract infections caused by influenza (linked to sales of cough and cold remedies) and infective conjunctivitis (linked to sales of ophthalmic anti-infectives). It has been suggested, therefore, monitoring the sales of these medicines may be of potential value to the surveillance of diseases and their outbreaks in the community (Health Protection Agency [HPA] 2010a).

On occasions community pharmacists may be the first healthcare professional to be aware of an emerging, local, public health issue. Their close contact with the local community and involvement in the sales of selected OTC medicines puts them in this unique position. They are, however, rarely in a position to capitalise on this because they may be unaware of what is happening in the surrounding areas and the public health implications of a shift in sales. It is by aggregating data from a number of pharmacies and working with a public health resource that the full public health implications may become apparent.

The utilisations of medicines sales data for disease surveillance and outbreak detection have been advocated in the UK (Jones 2009; Public Health Institute of Scotland 2003; HPA 2010a; Walker 2000). However, the role of community pharmacy in this area of public health protection appears to be minimal in the UK (Agomo 2011). In the next section, the utilisation of medicines sales data in infectious disease surveillance and outbreak detection will be reviewed.

1.4.1 Review of relevant literature

English language articles were identified in Medline and Embase searches (via Ovid) between January 1996 and July 2013 using the following search terms ($ indicate truncation):

* behind-the-counter or over-the-counter or OTC or non-prescription
  Total hits: 17,574

* infect$ or outbreak$ or pandemic$ or epidemic$ or disease$ or illness$
  Total hits: 6,834,717

* biosurveillance or surveillance or monitor$ or detect$ or syndromic
  Total hits: 3,055,984

* sale$ or wholesale$ or suppl$ or retail$
  Total hits: 553,683

The search terms were searched in the following search fields: title, abstract, medical subject heading, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword and name of substance word. Boolean operator ('and') was used to combine the search results and revealed a total of 131 articles.

After screening each article by title and/or abstract, 22 articles were identified as relevant to OTC medicines sales data and infectious disease or outbreak surveillance. The full texts of the 22 articles were examined to identify those with a similar study design and aim to the present study.

Of the 22 articles identified, 6 articles focused on the description, design, implementation and experience of disease surveillance system that involved OTC medicines sales data. Another 6 articles were methodological papers that examined the statistical and analytical procedures relating to OTC medicines sales data and disease surveillance. The remaining 10 articles that utilised OTC medicines sales data for the monitoring of infectious diseases or detection of disease outbreaks in the community were included in the review (Table 1.2).

Table 1.2 Studies utilising medicines sales data to monitor or detect outbreaks of infectious diseases in the community

Source	Study duration	Sample	Setting	Medicine monitored	Comparison disease indicator	Outcome
Liu et al. 2013	13 months (July 2010-2011)	Retail outlets enlisted in the National Retail Data Monitor database cover 33% of total OTC product sales nationwide	Pittsburgh, US	Anti-fever, cough and cold, chest rubs, electrolyte paediatric, throat lozenges	Number of patients with influenza-like illness* (ILI) presenting at an urgent care centre	Over the entire study period, cough and cold medicines (r^2=0.39) and chest rubs (r^2=0.37) sales were most strongly associated with ILI patient volume (all $p<0.0001$). Results from timer series modelling suggest changes in the sales of cough medicines preceded the changes in patient volume by two day during the flu season and showed the strongest positive correlation out of all of the medicines studied (cross-correlation=0.41, $p<0.05$)
Sočan et al. 2012	3 years (December 2006-2009)	Medicines supplied by a pharmaceutical company (Gorenjske lekarne) to 13 municipalities in northern Slovenia	Slovenia	Nasal decongestants, medicines for sore throat, antitussives, mucolytics	Incident rate of ILI (clinical symptoms: malaise, headache, myalgia, sore throat, cough, shortness of breath)	Curve for the sales of mycolytics and antitussive best matched with the curve of ILI incidents. Poisson regression model created based on i) total sales of all four medicines and ii) weighted combination of sore throat, nasal decongestants and mycolytics sales predicted the increase in ILI incident rate during the 12 months testing period (week 49/2006-week 39/2007)

*Pharyngitis, upper respiratory infections, laryngitis; sinusitis, cough, viral syndrome, pneumonia, otitis media, conjunctivitis, bronchitis and flu as defined by ICD-9 disease code

Table 1.2 (continued) Studies utilising medicines sales data to monitor or detect outbreaks of infectious diseases in the community

Source	Study duration	Sample	Setting	Medicine monitored	Comparison disease indicator	Outcome
Kirian et al. 2010	4 years (July 2003-2007)	Retail outlets enlisted in the NRDM database covering 47% of retail outlets during 2005-2007	San Francisco Bay area, US	Diarrhoeal remedies (bismuth, attapulgite, subsalicylates, loperamide)	Number of gastrointestinal (GI) cases, number of diarrhoeal outbreaks (all-cause and *Norovirus* outbreak); number of outbreak-related cases	No significant correlation was found between non-prescription sale of the selected anti-diarrhoeal remedies and diarrhoeal cases (none exceeded 95% confidence interval), nor was the sales association with numbers of diarrhoeal-related outbreaks or number of outbreak-related cases per week (for both all-cause outbreaks and *Norovirus* cause outbreaks)
Edge et al. 2006	3 years (April 2001-2004)	19 pharmacies, representing 53% of the provincial population and 12% of all pharmacies in the study area	Unknown province, Canada	Antinauseant and antidiarrhoeal products	Number of GI cases due to bacteria (*Samonella*, *Campylobacter*, *E. Coli*, *Shigella*, *Yersinia*), parasites (*Cryptosporidium*, *Entamoeba*, *Giardia*) and viruses (*Norovirus*, *Rotavirus*)	Over the entire study period, the highest correlation was observed between sales of antinauseant and antidiarrhoeal and counts of *Norovirus* cases (r^2=0.44) but sales data provided no earlier detection. Significant increases in the sales of medicines coincided with significant increase in cases of *Norovirus* infections in the winter of 2002/03 and 2003/04 (all $p<0.05$)

Table 1.2 (continued) Studies utilising medicines sales data to monitor or detect outbreaks of infectious diseases in the community

Source	Study duration	Sample	Setting	Medicine monitored	Comparison disease indicator	Outcome
Das et al. 2005	2 years and 7 months (August 2002-March 2005)	One large pharmacy chain (unspecified data coverage)	New York City, US	ILI medicines (products with text strings of 'flu' or 'tussin' in product name); antidiarrhoeal medicines	Ratio of fever/influenza-like syndrome to other syndrome visits to emergency department (ED); ratio of diarrhoea syndrome to other syndrome visits to ED	Non-prescription sales of ILI medicines positively correlated with ED visits of fever/influenza-like syndrome (r^2=0.60, p<0.001). During the 2003/04 influenza season, sales of ILI medicines exceeded above 95% confidence limit 2 to 3 weeks before the increase in ED fever/influenza like visits. A weaker positive correlation was observed between sales of antidiarrhoeal medicines and diarrhoeal related ED visits (r^2=0.24, p<0.005)
Ohkusa et al. 2005	6 months (November 2003-April 2004)	A nationwide sample of 1,100 pharmacies representing 2% of all pharmacies in Japan	Japan	Common cold medicines (antipyretics, antitussives, expectorants, exogenous enzyme, bronchodilator, antihistamines, vitamins, herbal products)	Number of influenza outpatients from national surveillance scheme; ILI cases from selected medical institutions; number of influenza diagnosis by a volunteer sample of paediatricians	Pattern for the sale of OTC common cold medicines was dissimilar to that of influenza and ILI activity reported by all three surveillance systems between December and January. A sales peak was observed in early February and the onset preceded the peak ILI activity recorded by selected medical institutions by 1-2 weeks, and coincided peak ILI activity reported by the national surveillance scheme and volunteer sample of paediatricians

Table 1.2 (continued) Studies utilising medicines sales data to monitor or detect outbreaks of infectious diseases in the community

Source	Study duration	Sample	Setting	Medicine monitored	Comparison disease indicator	Outcome
Magruder et al. 2004	1 years and 5 months (September 2001-January 2003)	300 drug stores in the study areas (unspecified data coverage)	Maryland, Washington DC, Virginia, US	Influenza remedies	Number of physician diagnosis of acute respiratory disease	After correcting for annual cycle and day-of-the-week effect associated with both medicine sales and physician diagnostic data, a positive correlation between OTC sales of influenza remedies and physician diagnoses of acute respiratory diseases was observed in all regions studied (r value ranged from 0.25 to 0.75). Changes in the sales of influenza remedies preceded changes in physician diagnoses in 2 out of 6 regions studied (up to 3 days). No early detection or a delayed detection of acute respiratory disease was observed in 4 other study regions (up to 8 days)
Hogan et al. 2003	4 years (1998-2001)	Sample of pharmacies and general retail outlets with over 90% market share	Harrisburg, Indianapolis, Philadelphia, Pittsburgh, Salt Lake City and Scranton, US	Electrolyte products	Hospital discharge diagnosis of respiratory and diarrhoeal diseases* in children (<5 years old)	A strong correlation between electrolyte sales and hospital diagnoses of respiratory and diarrhoeal disease (r=0.90, 95% CI, 0.87-0.93) was observed for the 18 outbreaks in the study period. On average, changes in the sales of medicine preceded changes in number of hospital diagnosis by 1.7 to 2.5 weeks

*Pneumonia, influenza, bronchiolitis caused by respiratory syncytial virus and other causes, rotavirus gastroenteritis, and all-cause paediatric gastroenteritis

Table 1.2 (continued) Studies utilising medicines sales data to monitor or detect outbreaks of infectious diseases in the community

Source	Study duration	Sample	Setting	Medicine monitored	Comparison disease indicator	Outcomes
Edge et al. 2003	4 months for Battfords outbreak (February-May 2002); 24 months for Walkerton (January 1999-Decemember 2000)	1 out of 3 pharmacy in Battlefords; 1 out of 6 pharmacies in Walkterton	Battlefords, Saskatchewan, Canada; Walkerton, Ontario, Canada	Antinauseant and antidiarrhoeal products	Number of acute gastrointestinal (GI)-related visits to ED; Number of GI-illness; Number of vomiting/diarrhoea visits to ED; number of outbreak-related cases	Increase in OTC medicine sales coincided with a rise in ED visits and outbreak-related cases during both of the outbreaks. The quantity of selected OTC medicines sold exceeded above 3 standard deviations upper limit 13 days after onset of the diarrhoeal outbreak in Walkerton
Goldenberg et al. 2002	6 months (August 1999-January 2001)	A major retailer chain (unspecified data coverage)	Allegheny County, Pennsylvania, US	Cough medicines	Not applicable (the outbreak tested was simulated based on the mortality data of a historical anthrax outbreak which was used to estimate the change in OTC sales)	Cough medicines sales data was unable to detect the anthrax outbreak within 3 days of onset but may be possible if more people were involved the outbreak. Sales data was also unable to detect onset of local influenza epidemic during the study period in Allegheny County

The majority of the studies reviewed were conducted in the US population and notably no study was conducted in the UK. Respiratory and GI-related infections have emerged as the two most extensively studied areas in terms of disease surveillance involving OTC medicines sales data. There were five papers on the monitoring of respiratory infections, four papers on GI-related infections and one paper on the detection of anthrax outbreak.

1.4.1.1 Respiratory infections

OTC medicines monitored in the studies reviewed were predominantly indicated for the symptoms of upper respiratory tract infections (URTI). A wide range of OTC products were implicated, including anti-fever, nasal decongestion, sore throat lozenges, cough medicines and chest rubs. In one particular study, sales data for herbal products, vitamins and enzyme supplements were also utilised (Ohkusa et al. 2005). Another study utilised the sales of OTC electrolyte products to monitor the combined incidence of respiratory as wells diarrhoeal diseases in children (Hogen et al. 2003). For some of the studies reviewed, the source and completeness of the medicines sales data in relation to the study population were not described (Das et al. 2005; Magruder et al. 2004).

Sales of OTC medicines were compared with a variety of reference data for which were used as indicators for disease or outbreak activity. For example, volumes of patient with influenza-like illness (ILI) presenting at secondary care (Liu et al. 2013) or emergency care services (Das et al. 2005) have been used. Magruder et al. (2004) utilised the number of physician diagnoses of acute respiratory diseases. Ohkusa et al. (2005) and Sočan et al. (2012) made use of numbers of influenza and ILI cases in the study population that were recorded by routine influenza surveillance schemes.

The results from most of the studies suggest sales of common OTC cough, cold and flu medicines positively correlated with the indicators of ILI and influenza activity (Das et al. 2005; Liu et al. 2013; Magruder et al. 2004). This association potentially allows non-prescription medicines sales data to serve as an additional tool for respiratory disease surveillance. In one study, however,

sales data for medicines supplied both on prescriptions and sold OTC were aggregated to monitor ILI activity (Sočan et al. 2012). A time-dependent relationship between sales of medicines and ILI activity has been reported. This was found in a study by Liu et al. (2013) as the strength of the correlation between medicine sales and ILI activity varied with the time point of the flu season (pre-, during or post-flu season). Similarly, in another study, Ohkusa et al. (2005) observed a persistent mismatch between OTC sales of cold remedies and influenza activity as reported by three influenza surveillance systems during the early influenza season. The variation in association between sales of OTC medicine and disease indicators between the various studies may be attributed to the differences in OTC medicines monitored, disease indicators used, circumstance of the outbreak and/or the modelling methods used.

Several studies also investigated the whether OTC medicines sales data were capable of providing an earlier warning for indicators of respiratory diseases. The results from the studies suggest there was a lack of consistency in the early detection capability of medicines sales data for ILI. For example, a study by Liu et al. (2013) found a change in the sales of cough and cold medicines preceded changes in ILI patient volume by 2 days during flu season but such was not observed in the post-flu season. Das et al. (2005) found increase in sales of selected cold medicines began 2-3 weeks earlier than fever/influenza-like visits to emergency department but this was only observed for one out of the three winter seasons studied. In a study by Magruder et al. (2004), the early signal generated from the sales of influenza medicines for an increase in physician diagnosis of acute respiratory diseases was only demonstrated in one out of the six regions studied. The absence of a consistent pattern indicates the early detection value of OTC medicines sales data for ILI and/or influenza may not be universal.

1.4.1.2 Gastrointestinal-related infections

The monitoring of GI-related infectious diseases and detection of outbreaks have been studied using the sales data of a range of OTC anti-diarrhoeal, anti-nauseant and electrolyte products. However, of the four studies reviewed (Edge 2006, 2003; Hogan et al. 2003; Kirian et al. 2010) only the study by Kirian et

al. (2010) specified the products that constituted antidiarrhoeal remedies. Multiple disease indicators have been used, including numbers of hospital discharge diagnoses of respiratory and diarrhoea diseases (Hogan et al. 2003), volume of GI-related visits to emergency department (Edge et al. 2003) and GI-related disease case data obtained from public health departments (Edge et al. 2006; Kirian et al. 2010). Three of the studies utilised medicines sales data to detect the occurrence of known outbreaks (Edge et al. 2003; Hogan et al. 2003; Kirian et al. 2010) and one study correlated sales with reportable GI-related infections (Edge et al. 2006).

The results from the studies reviewed indicated mixed results for the use of OTC medicine sales data in surveillance of GI-related diseases. A study by Hogan et al. (2003) found that the sales of OTC electrolyte products positively correlated with the number of hospital diagnoses of combined respiratory and diarrhoeal diseases in children. In the same study, sales of medicines indicated an early detection potential by preceding the disease signal generated by the hospital diagnoses by 1.7 to 2.5 weeks. However, the relationship between sales of electrolyte products and respiratory/diarrhoeal diseases in children was based on authors' unpublished work. Whether this relationship would hold for other populations is not clear.

In another study that involved two waterborne outbreaks (Edge et al. 2003), increases in sales of OTC anti-nauseant and anti-diarrhoeal products coincided with an increase in number of outbreak-related GI cases. For one outbreak the increase in sales exceeded the upper statistical threshold two weeks after the start of the outbreak. However, the relationship between medicine sales and the disease indicators (number of GI-related cases and ED visits) was only presented with descriptive figures and no statistical analysis was undertaken.

The study by Kirian et al. (2010) did not find a significant correlation between sales of anti-diarrhoeal medicines and diarrhoea illness case counts, outbreak counts, or the number of outbreak-associated cases. In this study, the authors concluded the findings did not support the implementation of a GI outbreak surveillance system with the medicines sales data that were utilised.

Edge et al. (2006) investigated the relationship between sales of OTC anti-diarrhoeal and anti-nauseant medicines and number of GI-related cases due to bacteria, parasites and viruses. It was found sales significantly and positively correlated with cases of *Norovirus* infections but not with either case of bacterial or parasitical infections. The finding suggests that medicine sales data may serve to be a supplemental tool for the virological surveillance of *Norovirus*es in the community. However, the relationship observed between sales of OTC anti-diarrhoeal and anti-nauseant medicines and *Norovirus* cases may be limited only to the population studied.

Overall, there is conflicting evidence for and against the use of OTC medicines sales data in monitoring GI-related disease and/or outbreaks. Given each of the studies was unique, in terms of the disease indicators used, products monitored, outbreak setting and analytical method used, the generalizability of the findings of each of the studies were limited.

1.4.1.3 Anthrax outbreak

One early study investigated the potential of OTC cough medicines sales data in identifying a hypothetical anthrax outbreak (Goldenberg et al. 1999). The products monitored and the completeness of the medicines sales data were both undefined. Unlike the other studies mentioned previously, no comparison disease indicator data was used. Instead, changes in the sales of OTC cough medicines were statistically simulated based on data obtained from a previous anthrax outbreak, which occurred in an area different from where the cough medicines sales data was collected. The hypothetical nature of the study limited the generalizability of the results although it showed sales of OTC cough medicines may be sensitive to a large scale outbreak of anthrax.

1.4.1.4 Summary of relevant literature

In summary, the potential of medicines sales data for the surveillance of ILI and GI-related diseases has been demonstrated. However, many elements of the study design and the study settings varied from study to study. This reflected the difference in availability of surveillance information in different

countries and the pattern of medicines utilisation in different populations. These variabilities limited the generalizability of any findings.

Two notable points were gathered from the studies reviewed. Firstly, no study has yet utilised medicines sales data to monitor the occurrence of eye infections in the community despite ophthalmic anti-infective preparations having been available OTC for many years. Secondly, the experience and use of OTC medicines sales data for the monitoring either GI-related or respiratory infections have not been reported for the UK population. These will form the basis of the present study which will focus on utilising OTC medicines sales data to identify outbreak of a common eye infection in the community and also for the surveillance of seasonal influenza in a UK population.

1.5 Study aims

The aims of the present study were to explore the application of OTC medicine sales data in (a) evaluating the impact of increased regulation and medicine reclassification on the volume of selected medicines prescribed in primary care and their sales OTC from community pharmacy, and (b) in the detection of infective conjunctivitis outbreaks and surveillance of seasonal influenza in Wales.

Chapter 2:

Impact of regulatory changes on supply of codeine and dihydrocodeine analgesics

Impact of regulatory changes on supply of codeine and dihydrocodeine analgesics

2.1 Introduction

2.1.1 Analgesics containing codeine and dihydrocodeine

Adult oral analgesics have the largest total market value of over-the-counter (OTC) medicines sold in the United Kingdom (UK) and is estimated to be worth over £370 million in 2009 (Proprietary Association of Great Britain [PAGB] 2011a). Studies have found they are the most commonly used OTC medicines among the UK population (Hanna and Hughes 2011; Porteous et al. 2005; Urquhart et al. 2004) and many people keep home supplies of non-prescription analgesics to self-manage pain (Wazaify et al. 2005). The high levels of non-prescription analgesic use reflect the findings that pain is one of the most common symptoms experienced in the UK adult population (McAteer et al. 2011).

A wide range of non-prescription oral analgesics are available for OTC purchase in the UK and they can be sold either as General Sales List (GSL) medicines or Pharmacy (P) medicines. Analgesics sold as GSL medicines consist predominantly of three active ingredients, namely paracetamol, aspirin and ibuprofen. These GSL products are widely available from any retail outlets in small pack sizes typically less than 16 tablets per pack (Royal Pharmaceutical Society [RPS] 2011a). In contrast, oral analgesics that fall under the P medicine category are only obtainable from pharmacies. These products could contain the same active ingredient as analgesics in the GSL category but are available in larger pack sizes, or they could contain a drug that used to be a prescription-only medicine (POM) that was subsequently reclassified to a P medicine. Compound analgesics containing multiple active ingredients with a weak opioid are also classified as P medicines and are widely available from pharmacies.

Codeine phosphate and dihydrocodeine (DHC) tartrate are both classified as weak opioids (World Heath Organization [WHO] 1996) and they can be found

in many OTC oral analgesics sold in the UK (Chemist and Druggist 2008). Whereas codeine can be found in a number of non-prescription medicines indicated for diarrhoea and coughs, the only indication of DHC is for pain (British National Formulary [BNF] 2013; Chemist and Druggist 2008). Under the Misuse of Drugs Act 1971, both codeine and DHC are classified as a class B controlled drug but they are permitted to be sold without a prescription in doses up to 25.6mg for codeine and 14.92mg for DHC (Medicines and Healthcare product Regulatory Agency [MHRA] 2009a). At the time of writing, OTC products containing codeine or DHC are only available as P medicines and not as GSL medicines. Therefore, although the term 'OTC medicine' has been used to refer to medicines under both the GSL and the P category (RPS 2011a); in the current study it is used to refer to the P medicine category which all non-prescription codeine and DHC containing preparations fall under.

Codeine and DHC are commonly used as painkillers and their conversions to morphine and dihydromorphine in the liver are believed to be responsible for their analgesic effects in humans (Sweetman 2007). Codeine and DHC are both frequently prescribed on prescriptions in the UK (National Treatment Agency for Substance Misuse [NTA] 2011) and are either used alone or in conjunction with a non-opioid analgesic, such as paracetamol or ibuprofen (Knaggs and Hobbs 2012). According to the BNF (2013), codeine is indicated for mild to moderate pain taken orally at a dose of 30 to 60mg every 4 hours as required and DHC is indicated for moderate to severe pain taken orally at a dose of 30mg every 4 to 6 hours when required. The WHO recommends codeine and DHC to be used in step two of the WHO analgesics ladder, which is the intermediate stage between a non-opioid analgesic, such as a non-steroidal anti-inflammatory drug (NSAID), and a strong opioid, such as morphine sulphate (WHO 1996).

In the UK, codeine and DHC containing analgesics are not available for sale OTC as a single ingredient product. Instead, they are only sold in multi-ingredient formulations combined with a non-opioid analgesic, namely paracetamol, ibuprofen or aspirin (Chemist and Druggist 2008). As of 2009,

there were 42 non-prescription analgesics available OTC containing codeine and four products containing DHC (MHRA 2009a). Of the 42 codeine containing products, 36 were combined with paracetamol, two were combined with ibuprofen and four were combined with aspirin. The four DHC containing products were all combined with paracetamol (MHRA 2009a). Prior to a change in relevant legislations in 2009 (discussed in Section 2.1.3), these combined multi-ingredient painkillers had been marketed in the UK for a variety of mild to moderate pain, including headache, migraine, toothache, period pains and also for the relief of rheumatic pain, muscular aches and joint pains (Chemist and Druggist 2008).

Compound oral analgesics sold OTC contain a lower amount of codeine and DHC compared to some of those available on a prescription. For example, a total quantity of 8mg to 12.8mg of codeine phosphate can be found per tablet in an OTC preparation, whereas between 8mg and 30mg can be found in a POM. The amount of DHC tartrate in an OTC preparation is usually 7.46mg per tablet, whereas in a POM between 10mg and 30mg can be found. Tablets containing even higher quantities of codeine or DHC up to 60mg as a single ingredient preparation can also be obtained on a prescription (BNF 2013). The efficacy of low dose codeine and DHC found in OTC products has been questioned in the past (Dickman 2008) and the BNF (2013) states that at these low doses (8mg codeine per compound tablet) they may not provide significant additional pain relief in comparison to using paracetamol or ibuprofen alone. A recent review of the literature also found there was little evidence to support the use of low dose compound analgesics containing opioids over non-opioid analgesics (Moore et al. 2010).

Despite the low content of codeine and DHC found in OTC compound analgesics, the opioid component of these preparations are known to cause a number of side effects that are not normally associated with a non-opioid analgesic (BNF 2013). The side effects include nausea, vomiting, constipation and drowsiness. Furthermore, one particular concern associated with the use of OTC opioid analgesics is the risk of developing dependence after prolonged consumption (NTA 2011; Reed et al. 2011). In the next section, various aspects

relating to the inappropriate use of OTC analgesics containing codeine or DHC will be discussed.

2.1.2 Misuse and abuse of Over-the-Counter medicines

The term misuse and abuse are often used interchangeably in relation to a medicine but a clear distinction between them should be made. Misuse has been defined as "*the use of drugs for medical purposes but in an incorrect manner*" and abuse has been defined as "*the use of drugs for non-medical purposes*" (Hughes et al. 1999). The definition of misuse refers to scenarios such as a medicine not suited for long term use being taken for a extended period of time or outside the recommended dosage; such can apply to all medicinal products. Reasons cited for non-compliance of instruction for taking an OTC medicine include: attempt to enhance the medicinal effect (Blenkinsopp and Bond 2005), not read the package labels, medicine did not work within the expected period of time (Wazaify et al. 2005) and perceived fewer and less serious consequences associated with non-compliance for an OTC medicine (Bower et al. 2012). In contrast, the definition of abuse has been used to describe situations where a medicine is deliberately used outside its licensed indication to exploit the pharmacological effect of a drug, often for non-medical reasons. Certain OTC medicines have been found to be associated with a greater risk of abuse than others (Blenkinsopp and Bond 2005).

In the UK, non-prescription medicines containing laxatives, sedative antihistamines, sympathomimetics and opioids are often implicated in problems associated with medicine misuse and/or abuse (Cooper 2011, 2013a, 2013b). In particular, community pharmacists cited compound analgesics containing weak opioids to be the category of OTC medicines most commonly misused and/or abused by the general public (Hughes et al. 1999; MacFadyen et al. 2001; Matheson et al. 2002; Pates et al. 2002; Wazaify et al. 2006). Concerns regarding the misuse and/or abuse of OTC opioids have also been raised by the medical profession in the UK (Ford and Good 2007a, 2007b; Ferner and Beard 2008; Royal College of General Practitioners 2013). These concerns were prompted by adverse patient reports that involved chronic, excessive ingestion of non-opioid analgesics, often caused by ibuprofen taken

together at the same time in a compound analgesic containing codeine or DHC. Serious morbidities resulting from chronic overdose of these products, such as gastric ulcers and renal toxicity, have been documented in the medical literature (Dutch 2008; Frei et al. 2010; McDonough 2011; Medani et al. 2010; Ng et al. 2011; Robinson et al. 2010). In addition to the concerns raised by healthcare professionals, individual case reports of fatality and adverse patient outcomes due to inappropriate use of OTC compound analgesics containing opioids also appeared in the general media and attracted wide spread attention from the public (Anon. 2012a; Bunyan 2007; Martin 2007; Morton and Wighton 2009).

A number of studies and government inquiries have been conducted in the UK to investigate the problem associated with the misuse and/or abuse of OTC medicines containing codeine and DHC. However, the prevalence of misuse and/or abuse of these preparations among the UK population remain unknown (All-Party Parliamentary Drug Misuse Group [APPDMG] 2009; Cooper 2011, 2013a; MHRA 2006; NTA 2011). One estimated figure was provided by a UK-based, online support group, Over-Count, which estimated 16,000 people were dependent on an OTC medicine (APPDMG 2009); a survey of the support group users revealed 95% of respondents reported having problems with OTC analgesics containing either codeine or DHC (Grieve 2009).

An alternative data source that might indicate the scale of the problem is the substance misuse treatment data collected by drug treatment services. Such data indicate that in England there has been a year-on-year increase in the number of people seeking treatment for addiction to OTC opioids between 2005 and 2010 (NTA 2011). The data for Wales over the same period also show there had been a steady number of treatment referrals each year (92 to 135 referrals per year) for individuals suffering from addiction to weak opioids (Welsh Government, personal communication).

Whilst these treatment data suggest a problem relating to misuse and/or abuse of OTC opioids potentially exists in the UK, affected individuals commented that these specialist treatment services are not suited to their needs and may be

under utilised (Cooper 2011, 2013c). Consequently, such data may only provide a partial assessment of prevalence. Furthermore, the covert nature associated with OTC medicines misuse and/or abuse, the lack of patient support and clearly defined treatment pathway for those who are affected (APPDMG 2009; Cooper 2011; 2013b, 2013c; NTA 2011) further add to the difficulty in identifying and monitoring the scale of the problem.

2.1.3 Sales of Over-The-Counter codeine and dihydrocodeine containing analgesics

To address the concern relating to opioid containing analgesics and their risks of dependence, various legislative and non-legislative regulatory changes affecting the non-prescription availability of these products were introduced in the UK.

The MHRA is the government agency responsible for regulating the effectiveness and safety of human medicines and medical devices in the UK. In 2005, the MHRA considered the issues surrounding the non-prescription availability of codeine and DHC containing analgesics in light of reports of dependence through regular consumption (Anon. 2004; MHRA 2006). At the time, evidences obtained during the inquiry indicated there was a low rate of adverse events against a backdrop of large numbers of OTC sales (MHRA 2006). Consequently, the inquiry concluded the problem associated with misuse and or/abuse of codeine and DHC containing analgesics was not extensive among the UK population and considered their continued availability to be appropriate. Nonetheless, several non-legislative changes regarding OTC sales of analgesics containing opioids were introduced in 2005 via a voluntary agreement between the MHRA and the medicine manufacturers (MHRA 2005a, 2006):

- Warnings about the risks of codeine and DHC addiction and medicine overuse headaches were to be added to the Summery of Product Characteristics (SPC) and Patient Information Leaflet (PIL)

- All codeine and DHC containing OTC products to be limited to a maximum pack size of 32 tablets by voluntary agreement with the manufacturers
- Where large pack of these products is justifiable, such as for dispensing purposes, it is labelled and used for this purpose only
- Sales promotion of these products to be handled with care and manufacturers should adopt a responsible approach to the sales of these products

At the time of announcement of these measures, only large packs of analgesic containing codeine and paracetamol in the effervescent form (56, 60, 84, 90, 100 tablets pack sizes) was affected by the pack size restriction. However, since there was no change in legislation these large packs continued to be available and were still being sold as a P medicine despite being labelled as for dispensing use only (MHRA 2009b). In addition to the aforementioned changes, the then professional regulator of pharmacists in the UK, the Royal Pharmaceutical Society of Great Britain (RPSGB), also published a professional guidance for pharmacists in supporting these measures. In this document it urged pharmacists that no more than one pack of opioid containing product, regardless of pack size, should be sold per transaction for non-prescription use (RPSGB 2007).

In early 2009, a report by the APPDMG (2009) was published following a two-year inquiry into the problem relating to misuse and abuse of prescription and OTC medicines. In relation to OTC medicines, evidence and views submitted by individuals, professional groups and treatment services on the subject were examined as part of the inquiry. The report concluded that, among other recommendations, there was a need for a better awareness about the addiction potentials of codeine and DHC in OTC preparations. Furthermore, it was considered that a tougher restriction on pack size, promotion and stronger warning were warranted. As a consequence, mandatory measures via legislative changes were introduced in September 2009 and affected the sales of all non-prescription analgesics containing codeine and DHC (MHRA 2009a).

These measures include:

- Prominent labels displayed on the front of the pack stating codeine and DHC can cause addiction and these medicines are for three days use only
- Prominent labels displayed on the back of the pack warning against use longer than three days that may cause medicine overuse headaches
- Removal of indications relating to colds, influenza, cough, sore throats and reference to minor pain conditions from the SPC
- Explicitly state in the PIL the indication, duration of treatment, risks of addiction and medicines overuse headaches related to these medicines
- A dedicated section in the PIL to warn about the signs and symptoms of addiction and the need to seek medical intervention
- All pack sizes greater than 32 tablets of codeine or DHC containing OTC medicines in solid dose form, including effervescent formulations, will no longer be available as P medicines but as POMs
- The advertising and promotion code of practice for these products updated to reflect new indications and warnings against addiction and prolonged use

At the time of announcement of these measures in September 2009, changes such as wording on the packaging and enclosed PIL could not be implemented immediately due to the time required to deplete the then available stock. However, measures such as restricting the sales of all codeine and DHC containing products to a maximum pack size of 32 tablets (including the effervescent formulations) were implemented immediately (Anon. 2009a).

2.1.4 Recent findings

The intentions behind the legislative changes implemented in 2009 were to (a) raise awareness about the misuse and abuse potentials of codeine and DHC containing products among the general public and healthcare professionals, and (b) reduce the likelihood of users inadvertently becoming addicted to these medicines by restricting their OTC pack size to prevent prolonged self-medication. However, whether or not MHRA's regulatory effort has had an

impact on the sale of OTC analgesics containing codeine or DHC was not known.

In a recent study, experience reported by users who are dependent to OTC codeine and DHC containing products indicate obtaining supplies from community pharmacies have been unproblematic despite an increase in regulation (Cooper 2011). Strategies employed by individuals to prevent suspicion of misuse and/or abuse included making purchases from multiple pharmacies, rehearsing responses to questions asked by pharmacy staff or selectively visit pharmacies where they are less likely to be challenged (Cooper 2011, 2013c). Consequently, the successfulness of 2005 and 2009 regulatory changes relating to OTC sales of codeine and DHC containing analgesics in preventing deliberate inappropriate use has been questioned (Cooper 2013b, 2013c).

Lastly, a number of unintended but possible outcomes of the regulatory changes on the sales of OTC codeine and DHC containing analgesics have not been explored. For instance, individuals could have simply shifted from buying large packs of these products to making more frequent purchases of smaller packs to compensate for the reduced number of tablets contained in a pack. Alternatively, individuals could have chosen or been referred by pharmacists to obtain supplies of opioid analgesics on a prescription instead. Whether or not any of these scenarios has been the case in Wales or in any other part of the UK is unclear and could mitigate the regulatory measures implemented by the MHRA.

2.1.5 Aims

The aim of the current study was to determine the impact of the voluntary (2005) and legislative (2009) regulatory changes on the OTC sales and prescribing of codeine and DHC containing analgesics in Wales. In addition, the present study also examined whether deprivation has any influence on the non-prescription sales of opioid containing analgesics.

2.2 Method

2.2.1 Study design

The study had an ecological design (Schoenbach and Rosamond 2000) and involved the retrospective analyses of primary care prescription data and pharmacy wholesale data for Wales between September 2004 and August 2010. The deprivation data used for each of the 22 primary care organisations in Wales, known as Local Health Boards (LHBs), were derived from the Welsh Index of Multiple Deprivation (WIMD) 2008. There were two parts to the present study and they are briefly outlined below:

2.1.1.1: The impact of voluntary and legislative regulatory changes

The quantities of codeine and DHC containing analgesics sold OTC from community pharmacies and those dispensed on primary care prescriptions were determined. Any changes in the quantities supplied before and after the implementation of the regulatory changes were determined.

2.1.1.2: Deprivation and Over-the-Counter sales of opioid analgesics

The relationship between deprivation and sales of OTC codeine and DHC containing analgesics were examined. The deprivation levels for each of the 22 LHBs in Wales were determined by calculating the percentages of Lower Layer Super Output Areas (LSOAs) that fell into the most deprived 20% quintile in Wales for the following deprivation domains: income, employment, health, education and overall deprivation (i.e. the WIMD). Quantities of codeine and DHC containing analgesics sold in the three most deprived were also compared with those sold in the three least deprived LHBs. In addition, the association between percentage of LSOAs that fell in the most deprived 20% quintile and the mean quantity of codeine and DHC containing analgesics sold in the 22 LHBs were assessed using correlation.

2.2.2 Data

2.2.2.1 Primary care prescription data

Prescription data were extracted from CASPA.net (Comparative Analysis System for Prescribing Audit), a data store that permits NHS Wales primary care prescription data to be interrogated. The database, which was maintained by NHS Wales Informatics Service, contained prescribing data derived from all prescriptions issued by primary care prescribers and dispensed by NHS-contracted community pharmacies, dispensing doctors and appliance contractors in Wales.

Medicines in the prescription database were arranged following the same format as in the BNF under the corresponding chapter, section and subsection numbers (BNF 2013). The quantity of prescribed medicines could be extracted in a number of different output measures as the: number of items prescribed, quantities prescribed, average price per item prescribed or in defined daily doses. The prescription data could be extracted in either a quarterly or a monthly format.

In the present study, the prescription data were extracted as the number of items prescribed and as the quantity of tablets or capsules (dosage unit) prescribed by general practitioners (GPs) for each of 22 LHBs in Wales. Data were extracted in a monthly format for a total of 72 months from September 2004 to August 2010.

2.2.2.2 Pharmacy wholesale data

Under an agreement with IMS Health and the Welsh Government, pharmacy wholesale data were obtained from the Regional Sales Analysis (RSA) database using IMS Dataview; a computer software for analysing and extracting pharmaceutical sales data stored within the RSA database.

The RSA database was a voluntary-based datastore and contained pharmaceutical sales data for medicines sold from medicine manufacturers, wholesalers and parallel importers to 614/708 (87%) NHS-contracted,

community pharmacies in Wales. The range of medicines in the RSA database for which data were made available to the Welsh Government by IMS Health was negotiated and agreed at the time of the data request, which had included both prescription-only and non-prescription medicines. As this process had taken place prior to the conception of the present study, it was not possible to access the complete set of medicines sales data that was held by IMS Health.

The wholesale transactions between medicine suppliers and establishments such as drug stores, industrial medical centres, hospital and clinics, dispensing practices and prison and military facilities were not included in the RSA database utilised in the present study. Wholesale dealings between pharmacies and third party purchasers or inter-wholesale distributions were also excluded. In other words, the wholesale data used represented the quantity of medicines purchased by pharmacies for dispensing prescriptions as well as for the purpose of OTC sale to the general public at a later date. Herein, the pharmacy wholesale data as a surrogate for actual pharmacy-to-patient sales are referred to as pharmacy or OTC medicines sales data.

The pharmacy sales data in the RSA database were available for extraction as the number of packs sold in a monthly format by Primary Care Organisation (PCO) geography. In Wales, there were 22 PCOs at the outset of the study, known as LHBs, but these had subsequently amalgamated in October 2009 to seven new LHBs as part of NHS Wales reorganisation (Welsh Government 2009b, Appendix 1 and 2). These changes were reflected in the RSA database and the OTC sales figures after October 2009 were available in the seven new LHB format. Other additional information recorded in the RSA database included: details about the manufacturer, product name, product pack size, brand name and the active ingredient for a particular product.

In the present study, pharmacy sales data extracted were the number of packs of selected codeine and DHC containing analgesics sold, each month, from September 2004 to August 2010 for each LHBs in Wales. Pack size information for each product was also extracted from the database to convert the quantity from number of packs sold into number of tablets or capsules sold.

The inclusion and exclusion criteria for the selection of products are described in Section 2.2.3.

2.2.2.3 Deprivation data

At the time of the study, no official figure of deprivation was available for Wales at LHB level therefore they had to be derived before analysis on deprivation could be undertaken. This was achieved using the deprivation indexes published in WIMD 2008 (Welsh Government 2008), which were the official measures of deprivation for small areas in Wales. The WIMD 2008 was made up of eight separate domains (or kinds) of deprivation. Each domain draws on a range of potential indicators specific to the type of deprivation in question to calculate a score (Appendix 3). Furthermore, each domain carried a different weighting which, in turn, determined its contribution to the overall deprivation index (i.e. WIMD). The eight domains of deprivation and their respective percent weighting towards the overall deprivation index are shown below:

- Income (23.5)
- Employment (23.5)
- Education, skills and training (14)
- Health (14)
- Physical environment (10)
- Access to service (5)
- Housing (5)
- Crime and fire (5)

The indexes for overall deprivation and the four highest weighting component domains: income, employment, education (skills and training) and health were extracted from WIMD 2008 for each of the LSOA in Wales. LSOA is a geographical hierarchy developed by the Office for National Statistics as a standard way to divide up England and Wales. There were a total 1,896 LSOAs in Wales each having a minimum population of 1,000 and a mean population size close to 1,500 (Welsh Government 2011). A high deprivation score is associated with more deprivation and indicates there is a higher proportion of

deprived population living within an area than one with a lower score. Table 2.1 shows the number LSOAs in each of the LHBs in Wales.

Table 2.1 Number of Lower Layer Super Output Areas (LSOAs) in each Local Health Board (LHB) before and after NHS Wales reorganization

Prior to October 2009	After October 2009	LSOAs
Bridgend	Abertawe Bro Morgannwg University	85
NeathPort Talbot		91
Swansea		147
Blaenau Gwent	Aneurin Bevan	47
Caerphilly		110
Monmouthshire		58
Newport		94
Torfaen		60
Anglesey	Betsi Cadwaladr University	44
Conwy		71
Denbighshire		58
Flintshire		92
Gwynedd		75
Wrexham		85
Cardiff	Cardiff and Vale University	203
Vale of Glamorgan		78
Merthyr Tydfil	Cwm Taf	36
Rhondda Cynon & Taff		152
Carmarthenshire	Hywel Dda	112
Ceredigion		47
Pembrokeshire		71
Powys	Powys	80

The level of deprivation for each LHB, in terms of the four selected deprivation domains (income, employment, education and health) and overall deprivation, was determined by calculating its percentage of LSOAs in the most deprived 20% quintile in Wales. LSOAs in the most deprived 20% quintile were areas with a deprivation score ranked between 1 and 380, with rank 1 being the area with the highest deprivation score thereby the most deprived. This method of aggregating LSOAs into larger geographical areas and estimation of deprivation follows the recommendation by the Office for National Statistics (Welsh Government 2011). Assignment of deprivation

scores and ranking of LSOAs were undertaken manually in Microsoft Excel spreadsheet.

2.2.3 Medicines studied

2.2.3.1 Prescription medicines

Prescription medicines included in the analysis were single- and multi-ingredient codeine and DHC containing analgesics identified in the CASPA.net prescription database, which corresponded to codeine or DHC containing products listed in the BNF (2013) section 4.7.1 (Non-opioid analgesics), 4.7.2 (Opioid analgesics) and 4.7.4 (Anti-migraine drugs). The reason for including section 4.7.1 (non-opioid analgesics) was that preparations such as co-codamol (codeine phosphate and paracetamol) or co-dydramol (DHC and paracetamol) were classified in the BNF as 'non-opioids' although they all contained an opioid component in addition to paracetamol.

Preparations studied were those in solid oral dosage forms, namely tablet, capsule or soluble (effervescent) preparations. Other oral or non-oral dosage forms such as liquids, pastilles or suppositories, were excluded from the study. Products in the prescription database that had neither a non-proprietary title or a British Approved Name, such as paracetamol 500mg, buclizine hydrochloride 6.25mg and codeine phosphate 8mg tablets (Migraleve Pink), were manually identified in the database using *Martindale: The Complete Drug Reference* (Sweetman 2007). The identified products were subsequently included in the study if they had met the inclusion criteria. Both proprietary and non-proprietary preparations were included in the prescription analysis, including any OTC packs that were prescribed on a prescription. A list of all codeine and DHC containing analgesics extracted from the NHS prescription database is shown below in Appendix 4 and Appendix 5, respectively.

2.2.3.2 Over-the-Counter medicines

Codeine or DHC containing analgesics available for extraction in the RSA database were identified using the 'Oral analgesics' chapter of *Chemist and Druggist: Guide to OTC Medicines and Diagnostics* (September 2008 issue).

Preparations included in the analysis were proprietary, adult preparations in tablet, capsule or soluble (effervescent) oral dosage forms.

After the initial selection, a manual search of the RSA database was undertaken to identify any other eligible products in the database that were not identified by the aforementioned reference book (September 2008 issue). Manually identified products were included if they had contained either codeine or DHC as the active ingredient and were indicated for pain. The details about a preparation were verified using the PILs found on the Electronic Medicine Compendium website (Datapharm 2013). Non-proprietary products listed in the RSA database that could either be sold OTC or prescribed on a prescription, such as 32 tablets pack of co-codamol 8mg/500mg, were excluded from the OTC sales analysis (explanation see Section 2.4.2.3). A full list of codeine and DHC containing analgesics extracted from the RSA database is shown below in Appendix 6 and Appendix 7, respectively.

2.2.4: Data processing and organisation

The data utilised in the present study were obtained from multiple sources and it was necessary for them to be processed and organised into suitable formats before statistical tests could be carried out.

Prescription data and pharmacy sales data were transferred from their respective databases into Microsoft Excel spreadsheet as described in Appendix 8 and Appendix 9, respectively. The total quantities of codeine and DHC containing analgesics supplied on prescription and that sold OTC for Wales were calculated in Microsoft Excel spreadsheet by combining the supplies in the 22 LHBs. The totals were subsequently rearranged into five 12-month blocks (September to August) to allow comparisons of supplies between the different 12-month periods.

The deprivation data were obtained already in Microsoft Excel spreadsheet and the percentages of LSOAs in the most deprived 20% quintile of Wales for each of the 22 LHBs were calculated in Microsoft Excel.

All processed and reorganised data were manually screened for errors before transferring to statistic software for analysis (PASW v18).

2.2.5 Data Analysis

2.2.5.1 Impact of the legislative changes

The total quantities of codeine and DHC containing analgesics supplied on prescription and those sold OTC for Wales were reported for each 12-month period together with the corresponding median and interquartile range (IQR) for the component months. The quantities supplied were compared between two consecutive 12-month periods using Wilcoxon's signed-rank test. Separate comparisons were conducted for OTC and prescription supplies of codeine and DHC containing analgesics by formulation (soluble and non-soluble) and by output measure of the quantity (number of items/packs supplied and number of tablets/capsules supplied).

2.2.5.2 Deprivation and sales of codeine and dihydrocodeine analgesics

The total of OTC codeine and DHC containing analgesics sold in number of tablets or capsules in each 12-month period were calculated for each of the 22 LHBs in Wales. The 12-month total sales for each LHB were standardised by 10,000 population using mid-2008 population estimates (Appendix 1).

The standardised, 12-month sales in the three most deprived LHBs were compared with those in the three least deprived LHBs in Wales using Wilcoxon's Signed Rank Test in terms of the four selected components of deprivation (income, employment, education and health) and overall deprivation.

To explore the association between deprivation and sales of analgesics containing codeine and DHC, the mean of the standardised 12-month sales was calculated for each LHB. Spearman's rank correlation was used to calculate the correlation coefficient (r) between the percentages of LSOAs in the 20% most deprived quintile and their corresponding mean of the standardised 12-month sales of codeine or DHC containing analgesics for the 22 LHBs in Wales.

A p-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using PASW version 18 (PASW Inc., Chicago, IL, USA).

2.3 Results

2.3.1 Over-the-Counter supply

Figure 2.1 shows the total quantities and their respective percentages of selected codeine or DHC containing analgesics sold OTC in Wales from September 2004 to August 2010. Codeine containing products accounted for 93% of the total sales over the study period (94,523,146/101,652,158 tablets or capsules). Sales of DHC containing products were predominantly made up by sales of non-soluble products, which sold significantly more than the soluble equivalent in the 12 months to August 2010 (98% more, p=0.002).

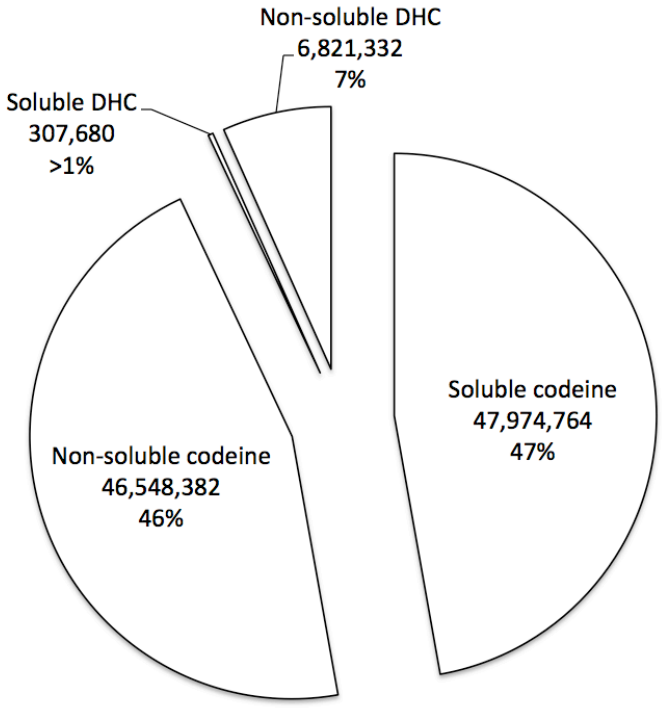


Figure 2.1 Cumulative over-the-counter sales of selected codeine and dihydrocodeine (DHC) containing analgesics in Wales from September 2004 to August 2010, expressed as the number of tablets/capsules sold and their respective percentage

2.3.1.1 Soluble codeine

The year-on-year totals of codeine containing analgesics sold OTC from community pharmacies in Wales are shown in Figure 2.2 and Table 2.2. Over the six-year study period, the sales of soluble codeine containing products in number of packs sold have remained steady whilst the number of tablets sold declined by 25% (2,272,120/9,185,640). The largest reductions in tablet sold was observed in 2006/07 and 2007/08, which saw 16% (1,546,008/9,496,356) and 10% (816,456/7,950,348) reductions, respectively, compared to the previous years. Wilcoxon's signed rank test revealed there was no significant differences ($p>0.05$) for the number of packs sold between any two consecutive 12-month periods. However, quantities of tablets sold in 2006/07 were significantly less than those sold in 2005/06 ($p=0.003$).

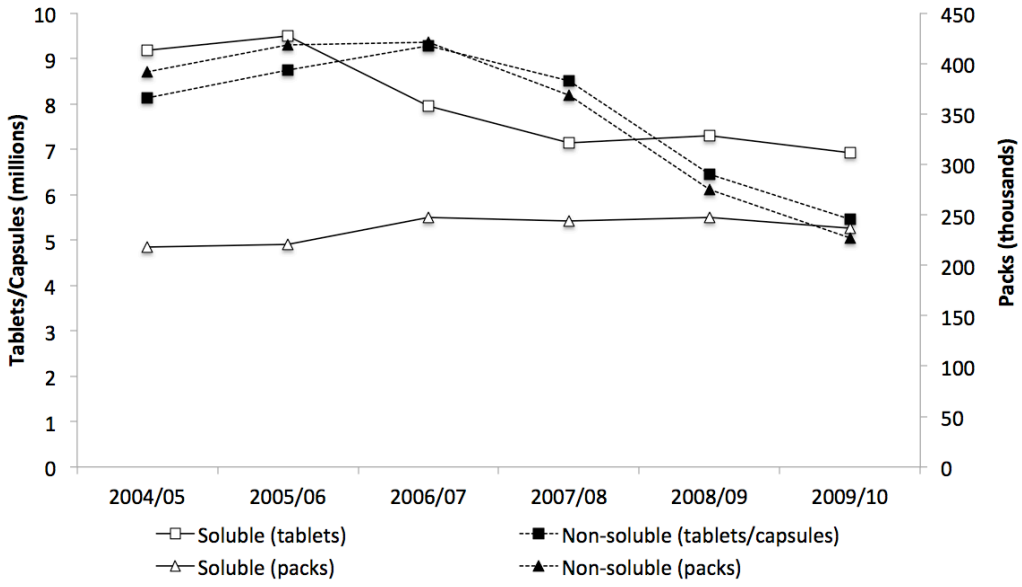


Figure 2.2 Total quantities of selected codeine containing analgesics sold over-the-counter in Wales each year (September to August)

Table 2.2 Total 12-monthly sales of over-the-counter soluble codeine containing analgesics in Wales, together with their respective median and interquartile range (IQR) for the component month. Sales in each 12-month period (September to August) were compared with the previous 12 months. A p-value < 0.05 is indicated in bold

		Total	Median	IQR	p-value
Packs	2004/05	217 967	17 844	3 746	
	2005/06	220 601	18 828	2 834	0.388
	2006/07	247 552	20 310	6 672	0.099
	2007/08	243 527	19 940	6 100	0.638
	2008/09	247 434	20 737	3 880	0.695
	2009/10	236 341	19 325	4 926	0.308
Tablets	2004/05	9 185 640	74 8170	173 037	
	2005/06	9 496 356	80 4312	142 350	0.308
	2006/07	7 950 348	69 0898	213 687	**0.003**
	2007/08	7 133 892	58 4792	183 696	0.136
	2008/09	7 295 008	61 3584	119 488	0.530
	2009/10	6 913 520	56 9040	155 144	0.239

2.3.1.2 Non-soluble codeine

Over the six-year study period, OTC sales of non-soluble codeine containing analgesics, expressed as the number of packs sold, demonstrated a similar trend pattern to the sales of the same products expressed as the number of tablet/capsules sold (Figure 2.2). Both of the measures saw a significant increase in sales (packs, tablets/capsules) compared to the previous 12 months for 2005/06 (p=0.012, p=0.005); followed by significant reductions in 2008/09 (p=0.002, p=0.002) and 2009/10 (p=0.002, p=0.002). A significant increase in the number of tablets/capsules sold was observed in 2006/07 (p=0.015) but there was no significant change in the number of packs sold. In 2007/08, a significant reduction in number of packs sold was observed (p=0.006) but not in the number of tablets/capsules sold (Table 2.3).

Table 2.3 Total 12-monthly sales of over-the-counter non-soluble codeine containing analgesics in Wales, together with their respective median and interquartile range (IQR) for the component month. Sales in each 12-month period (September to August) were compared with the previous 12 months. A p-value < 0.05 is indicated in bold

		Total	Median	IQR	p-value
Packs	2004/05	391 799	32 658	3 596	
	2005/06	418 431	35 108	1 408	**0.012**
	2006/07	421 157	35 544	4 051	0.814
	2007/08	368 234	29 568	5 659	**0.006**
	2008/09	274 962	22 518	4 756	**0.002**
	2009/10	227 011	18 502	3 522	**0.002**
Tablets / Capsules	2004/05	8 122 822	68 1645	70 115	
	2005/06	8 740 072	73 2139	34 777	**0.005**
	2006/07	9 281 248	78 0027	86 646	**0.015**
	2007/08	8 511 244	68 4635	143 199	0.071
	2008/09	6 442 784	53 4517	94 325	**0.002**
	2009/10	5 450 212	45 1686	73 606	**0.002**

2.3.1.3 Soluble dihydrocodeine

The year-on-year totals of soluble DHC containing analgesics, expressed as the number of packs and tablets sold, are shown in Figure 2.3. Sales in number of packs of soluble DHC sold declined steadily, year-on-year, from 2004/05 (5,787 packs) to 2009/10 (1,566 packs) and significant reductions were observed in 2007/08 (p=0.013) and 2009/10 (p=0.008). The equivalent number of tablets sold followed the same declining trend year-on-year and significant reductions were also observed in 2007/08 (p=0.002) and 2009/10 (p=0.008) (Table 2.4).

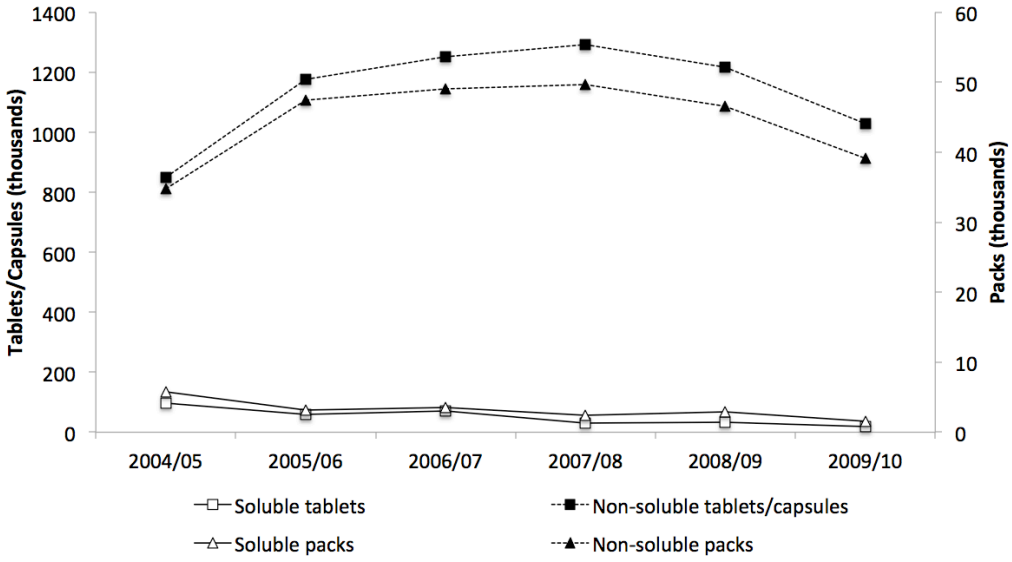


Figure 2.3 Total quantities of selected dihydrocodeine containing analgesics sold over-the-counter in Wales each year (September to August)

Table 2.4 Total 12-monthly sales of over-the-counter soluble dihydrocodeine containing analgesics in Wales, together with their respective median and interquartile range (IQR) for the component month. Sales in each 12-month period (September to August) were compared with the previous 12 months. A p-value < 0.05 is indicated in bold

		Total	Median	IQR	p-value
Packs	2004/05	5 787	22	495	
	2005/06	3 195	262	86	0.583
	2006/07	3 486	276	174	0.638
	2007/08	2 449	212	62	**0.013**
	2008/09	2 874	218	74	0.205
	2009/10	1 566	154	191	**0.008**
Tablets	2004/05	96 048	6 894	31 575	
	2005/06	59 532	4 932	1 185	0.345
	2006/07	69 432	6 804	2 619	0.239
	2007/08	29 388	2 550	942	**0.002**
	2008/09	34 488	2 616	330	0.209
	2009/10	18 792	1 848	1 617	**0.008**

2.3.1.4 Non-soluble dihydrocodeine

Quantities of non-soluble DHC containing products demonstrated a year-on-year increase in sales (packs, tablets/capsules) from 2004/05 (34767, 850276) and reached a plateau in 2007/08 (49706, 1293340). Thereafter the sales declined year-on-year up to 2009/10 (Figure 2.3). Sales in number of packs and tablet/capsules both followed the same trend pattern and a significant increase in sales for both measures was observed in 2005/06 (both p=0.002), followed by significant reductions in 2008/09 (p=0.034, 0.002, respectively) and 2009/10 (p=0.028, 0.003, respectively) compared to their respective previous 12 months (Table 2.5).

Table 2.5 Total 12-monthly sales of over-the-counter non-soluble dihydrocodeine containing analgesics in Wales, together with their respective median and interquartile range (IQR) for the component month. Sales in each 12-month period (September to August) were compared with the previous 12 months. A p-value < 0.05 is indicated in bold

		Total	Median	IQR	p-value
Packs	2004/05	34 767	2 969	554	
	2005/06	47 512	4 032	696	**0.002**
	2006/07	49 090	4 078	316	0.347
	2007/08	49 706	4 117	674	0.874
	2008/09	46 557	3 875	478	**0.034**
	2009/10	39 130	3 218	335	**0.002**
Tablets / Capsules	2004/05	850 276	73 028	13 748	
	2005/06	1 176 740	102 308	16 769	**0.002**
	2006/07	1 252 620	103 366	9 702	0.136
	2007/08	1 293 340	106 480	14 679	0.433
	2008/09	1 218 012	102 614	13 718	**0.028**
	2009/10	1 030 344	84 636	9 944	**0.003**

2.3.2 Prescription supply

The total quantities and their respective percentages of codeine or DHC containing analgesics supplied on primary care prescriptions in Wales between

September 2004 and August 2010 are shown in Figure 2.4. Non-soluble codeine containing preparations accounted for 68% of the total supplies on prescriptions (832,322,057/1,224,665,236 tablets or capsules), followed by non-soluble DHC containing preparations at 25% (307,700,571/1,224,665,236 tablets or capsules), soluble codeine at 7% (84,630,826/1,224,665,236 tablets) and DHC products at 0% (11,782/1,224,665,236 tablets).

In the final 12 months for which data were available (September 2009 to August 2010), the number of tablets/capsules sold for both non-soluble codeine and non-soluble DHC were significantly greater than their soluble equivalent (93% and 99% greater, both p=0.002).

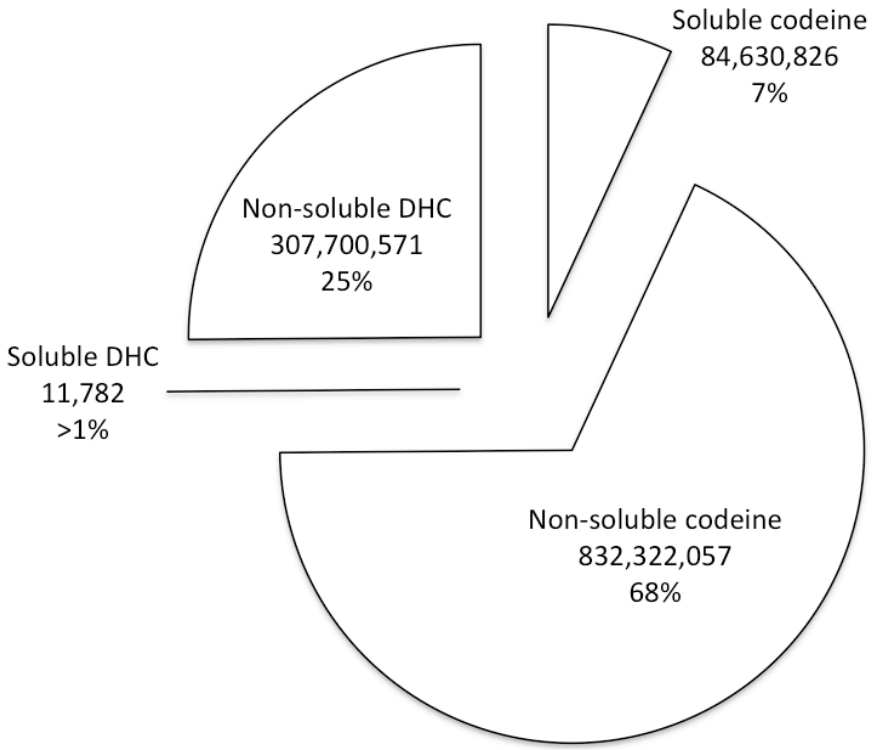


Figure 2.4 Cumulative total quantities of codeine and dihydrocodeine (DHC) containing analgesics supplied on primary care prescriptions in Wales expressed as the number of tablets/capsules sold (September 2004 to August 2010)

2.3.2.1 Soluble codeine

The year-on-year totals for codeine containing analgesics supplied on primary care prescription in Wales from 2004/05 to 2009/10 are shown Figure 2.5. There was a year-on-year reduction in both the number of items and tablets/capsules prescribed for soluble preparations from 2004/05 to 2009/10, all of which were statistically significant compared to the previous 12 months (all $p < 0.05$, Table 2.6). Overall, soluble preparations saw the number of items prescribed reduced by 34% (55,513/161,943) and the number of tablets prescribed reduced by 30% (5,089,412/16,894,235) over the six-year study period.

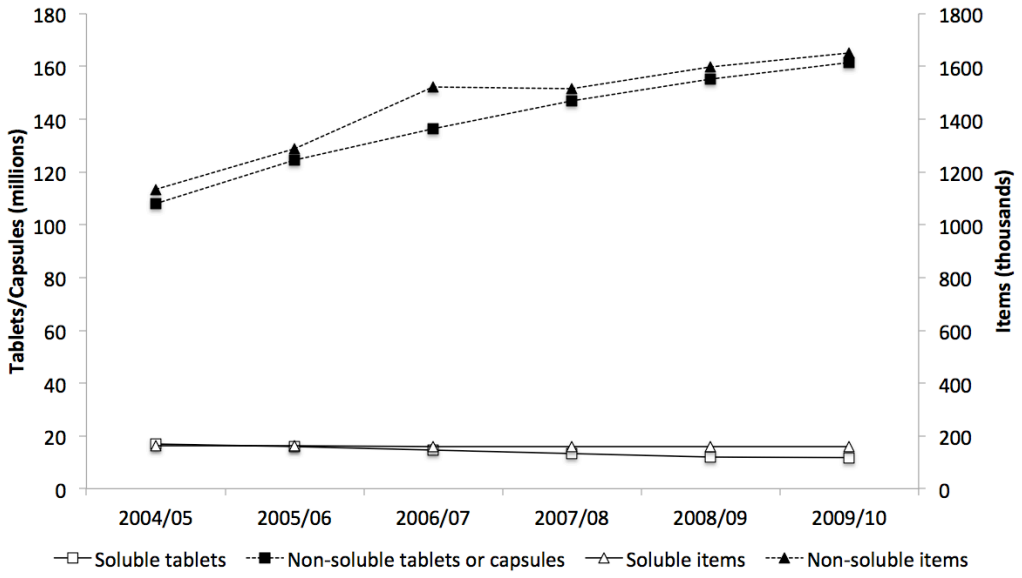


Figure 2.5 Total quantities of codeine containing analgesics supplied on primary care prescription in Wales each year (September to August)

Table 2.6 Twelve-monthly totals of soluble codeine containing preparations supplied on primary care prescriptions in Wales, together with their respective median and interquartile range (IQR) for the component month. Supplies in in each 12-month period (September to August) were compared with the previous 12 months. A p-value < 0.05 is indicated in bold

		Total	Median	IQR	p-value
Items	2004/05	161 943	13 529	536	
	2005/06	151 396	12 561	1 427	**0.002**
	2006/07	137 508	11 580	639	**0.002**
	2007/08	122 342	10 173	805	**0.002**
	2008/09	111 179	9 245	674	**0.002**
	2009/10	106 430	8 908	669	**0.006**
Tablets	2004/05	16 892 435	1 414 590	60 826	
	2005/06	15 931 444	1 315 365	153 098	**0.002**
	2006/07	14 670 289	1 240 388	62 243	**0.002**
	2007/08	13 211 488	1 104 682	77 153	**0.002**
	2008/09	12 122 147	1 007 269	73 571	**0.002**
	2009/10	11 803 023	988 941	68 364	**0.041**

2.3.2.2 Non-soluble codeine

There was a steady increase in the quantities of non-soluble codeine containing analgesics supplied on primary care prescriptions in Wales (Figure 2.5). Number of items increased year-on-year from 1,134,309 items in 2004/05 to 1,649,438 items in 2009/10, equivalent to a 45% (515,129/1,134,309) increase in overall supply over the six-year study period. Similarly, the number of tablets/capsules supplied increased constantly from 107,878,825 in 2004/05 to 161,481,832 tablets/capsules in 2009/10, equivalent to a 50% (53,603,007/161,481,832) overall increase. Both measures of quantity demonstrated a significant increase in prescription supply every year compared to their previous 12-month period (all $p<0.05$; Table 2.7).

Table 2.7 Twelve-monthly totals of non-soluble codeine containing preparations supplied on primary care prescriptions in Wales, together with their respective median and interquartile range (IQR) for the component month. Supplies in in each 12-month period (September to August) were compared with the previous 12 months. A p-value < 0.05 is indicated in bold

		Total	Median	IQR	p-value
Items	2004/05	1 134 309	95 470	13 723	
	2005/06	1 287 632	106 902	9 111	**0.002**
	2006/07	1 522 058	116 843	8 615	**0.002**
	2007/08	1 515 222	126 104	7 315	**0.003**
	2008/09	1 598 259	133 807	10 150	**0.006**
	2009/10	1 649 438	138 180	10 133	**0.012**
Tablets / Capsules	2004/05	107 878 825	9 099 895	1 378 566	
	2005/06	124 358 015	10 327 359	966 596	**0.002**
	2006/07	136 427 288	11 326 584	789 268	**0.002**
	2007/08	146 822 763	12 236 095	669 321	**0.003**
	2008/09	155 353 334	12 985 601	912 110	**0.004**
	2009/10	161 481 832	13 518 967	1 019 613	**0.004**

2.3.2.3 Soluble dihydrocodeine

Quantities of soluble and non-soluble DHC containing analgesics supplied on primary care prescription are shown in Figure 2.6. During the 2004/05 period, there was no soluble DHC containing analgesics prescribed on NHS prescriptions in Wales. Thereafter, quantities supplied on prescription between 2004 and 2010 remained low with the most prescribed in 2008/09 at a total 38 items and 3,742 tablets, respectively. The supplies on prescription during the 2008/09 period were significant greater than the 2007/08 period (p=0.013, 0.008, respectively, Table 2.8).

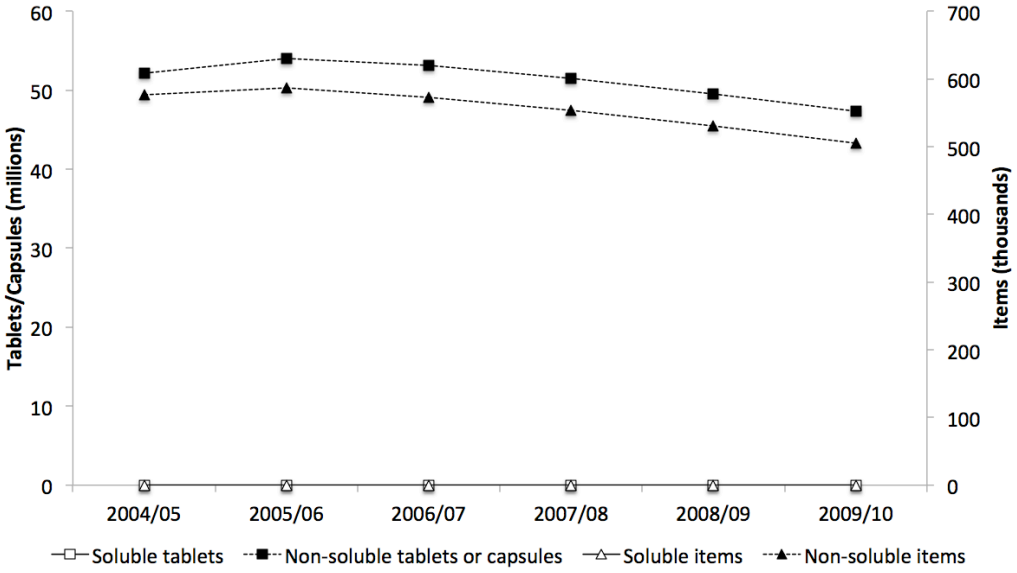


Figure 2.6 Total quantities of dihydrocodeine containing analgesics supplied on primary care prescription in Wales, between September and August, each year

Table 2.8 Twelve-monthly totals of soluble dihydrocodeine containing preparations supplied on primary care prescriptions in Wales, together with their respective median and interquartile range (IQR) for the component month. Supplies in in each 12-month period (September to August) were compared with the previous 12 months. A p-value < 0.05 is indicated in bold

		Total	Median	IQR	p-value
Packs	2004/05	0	-	-	-
	2005/06	25	1	3	-
	2006/07	28	2	3	0.653
	2007/08	22	2	3	0.503
	2008/09	38	3	2	**0.013**
	2009/10	28	2	1	0.159
Tablets	2004/05	0	-	-	-
	2005/06	1 624	80	258	-
	2006/07	1 460	116	138	0.937
	2007/08	1 884	179	115	0.433
	2008/09	3 742	310	112	**0.008**
	2009/10	3 072	262	145	0.103

2.3.2.4 Non-soluble dihydrocodeine

The total items of non-soluble DHC containing analgesics supplied on prescription saw a modest increase from 576,652 items in 2004/05 to 586,407 items in 2005/06. Thereafter, items supplied declined year-on-year from 572,161 items in 2006/07 to 504,499 in 2009/10. The prescribing of the same preparations expressed in number of tablets/capsules supplied followed a similar trend with a slight increase from 2004/05 (52,180,390 tablets or capsules) to 2005/06 (54,010,992 tablets or capsules); followed by a steady year-on-year decline up to 2009/10 (Figure 2.6). A significant reduction in both number of items and tablets/capsules supplied was observed in 2008/09 (both p=0.034) and 2009/10 (p=0.003 and 0.002, respectively) compared to the previous 12-month (Table 2.9).

Table 2.9 Twelve-monthly totals of non-soluble dihydrocodeine containing preparations supplied on primary care prescriptions in Wales, together with their respective median and interquartile range (IQR) for the component month. Supplies in in each 12-month period (September to August) were compared with the previous 12 months. A p-value < 0.05 is indicated in bold

		Total	Median	IQR	p-value
Items	2004/05	576 652	48 468	5 049	-
	2005/06	586 407	49 651	3 808	0.239
	2006/07	572 161	48 018	1 062	0.050
	2007/08	553 045	45 979	3 215	0.060
	2008/09	530 426	44 619	6 311	**0.034**
	2009/10	504 499	42 170	3 593	**0.003**
Tablets / Capsules	2004/05	52 180 390	4 402 178	495 517	
	2005/06	54 010 992	4 583 491	323 670	0.071
	2006/07	53 175 410	4 459 792	73 396	0.158
	2007/08	51 497 446	4 300 577	299 669	0.060
	2008/09	49 518 062	4 158 384	328 752	**0.034**
	2009/10	47 318 271	3 958 551	335 884	**0.002**

2.3.3 Deprivation

Each of 1,896 LSOAs in Wales were ranked from 1, most deprived, to rank 1,896, least deprived based on their corresponding deprivation score for the selected deprivation components. After assigning all 1,896 LSOAs to their respective LHB, those LSOAs that fell in the most deprived 20% quintile in Wales (rank 1 to 380) were identified. Deprivation was presented as percentages of LSOA in the most deprived 20% quintile in Wales for each of the 22 LHBs and are shown in Table 2.10.

Overall, the median percentages (IQRs) of LSOAs in the most deprived 20% quintile for Wales with respect to income, employment, education and health deprivation were 17 (17), 15 (26), 18 (21) and 14 (19), respectively. Merthyr Tydfil, Blaenau Gwent and Rhondda Cynnon & Taff were the three most deprived LHBs in term of employment, education, health and overall deprivation, whereas Merthyr Tydfil, Blaenau Gwent and Neath Port Talbot were the three most deprived LHBs for income deprivation. The three least deprived LHBs in Wales for education, health, income and overall deprivation were Ceredigion, Monmouthshire and Powys. Gwynedd, Monmouthshire and Powys were the three least deprived LHBs for employment deprivation.

Table 2.10 Percentages (n) of Lower Layer Super Output Areas (LSOAs) in 20% most deprived quintile in Wales for each 22 Local Health Boards (LHBs) based on the Welsh Index of Multiple Deprivation 2008

LHB	Income	Employ-ment	Education	Health	Overall Index
Anglesey (44)	11 (5)	9 (4)	16 (7)	11 (5)	11 (5)
Blaenau Gwent (47)	****34 (16)**	****53 (25)**	***43 (20)**	****47 (22)**	****43 (20)**
Bridgend (85)	20 (17)	33 (28)	22 (19)	32 (27)	25 (21)
Caerphilly (110)	25 (27)	34 (37)	31 (34)	31 (34)	26 (29)
Cardiff (203)	30 (61)	19 (39)	30 (60)	27 (54)	27 (54)
Carmarthenshire (112)	11 (12)	17 (19)	10 (11)	13 (14)	13 (15)
Ceredigion (47)	**†4 (2)**	4 (2)	**†0 (0)**	**†0 (0)**	**†2 (1)**
Conwy (71)	17 (12)	10 (7)	10 (7)	10 (7)	13 (9)
Denbighshire (58)	17 (10)	17 (10)	16 (9)	16 (9)	16 (9)
Flintshire (92)	12 (11)	5 (5)	17 (16)	13 (12)	11 (10)
Gwynedd (75)	7 (5)	**††3 (2)**	4 (3)	7 (5)	5 (4)
Merthyr Tydfil (36)	***36 (13)**	***56 (20)**	****39 (14)**	***58 (21)**	***50 (18)**
Monmouthshire (58)	**††5 (3)**	**†0 (0)**	**††3 (2)**	**†0 (0)**	**†2 (1)**
NeathPort Talbot (91)	*****32 (29)**	40 (36)	19 (17)	29 (26)	31 (28)
Newport (94)	29 (27)	20 (19)	27 (25)	22 (21)	29 (27)
Pembrokeshire (71)	10 (7)	7 (5)	8 (6)	8 (6)	7 (5)
Powys (80)	**††5 (4)**	**††3 (2)**	**†††4 (3)**	**††4 (3)**	**††4 (3)**
Rhondda Cynon & Taff (152)	28 (43)	*****45 (69)**	*****34 (51)**	*****36 (55)**	*****36 (55)**
Swansea (147)	28 (41)	19 (28)	24 (35)	21 (31)	24 (36)
Torfaen (60)	23 (14)	15 (9)	30 (18)	10 (6)	18 (1)
Vale of Glamorgan (78)	13 (10)	10 (8)	6 (5)	9 (7)	9 (7)
Wrexham (85)	13 (11)	7 (6)	21 (18)	18 (15)	14 (12)

*Most, **Second-most, ***Third-most deprived
†Least, ††Second-least, †††Third-least deprived

Wilcoxon's signed rank test revealed the sales of OTC non-soluble codeine in the three most deprived LHBs were significantly greater than those in three least deprived LHBs in Wales with respect to employment (p=0.001), education (p=0.043), health (p=0.043) and overall deprivation (p=0.043) but was not observed for income deprivation (p>0.05). No other significant difference between the three most and least deprived LHBs was observed for the sales of any other formulations of codeine or DHC containing analgesics (all p>0.05, Table 2.11).

Table 2.11 Mean 12-monthly sales of non-soluble codeine in the three most and three least deprived Local Health Boards (LHBs) in Wales (median [interquartile range]) per 10,000 population between September 2004 and August 2010 in number of tablets/capsules sold. Wilcoxon's sign rank test was used compare the sales and a p-values less than 0.05 is considered statistically significant

	Three most deprived LHBs	**Three least deprived LHBs**	**p-value**
Employment	30,489 (11,582)	28,041 (16,425)	0.001
Education	30,489 (11,582)	29,675 (25,481)	0.043
Health	30,489 (11,582)	29,675 (25,481)	0.043
Overall deprivation	30,489 (11,582)	29,675 (25,481)	0. 043

Spearman's rank correlation revealed no significant relationship between the sales of codeine or DHC containing analgesics and percentages of LSOAs in the most deprived 20% quintile in Wales for the four selected deprivation components and overall deprivation (all $p>0.05$). The mean 12-monthly sales of codeine and DHC analgesics in number of tablets/capsules sold are presented in Table 2.12.

Table 2.12 Mean 12-monthly sales of over-the-counter codeine and dihydrocodeine containing analgesics (number of tablets or capsules sold per 10,000 population) in each Local Health Board (LHB) in Wales between September 2004 and August 2010. The three highest quantities of sales by formulation are boxed and indicated in bold

LHB	Codeine			Dihydrocodeine			Codeine + Dihydrocodeine		
	Soluble	Non-Soluble	All	Soluble	Non-Soluble	All	Soluble	Non-Soluble	All
Anglesey	8 531	18 181	26 712	347	2 083	2 430	8 878	20 264	29 142
Blaenau Gwent	**131 623**	29 485	**161 108**	324	3 670	3 995	**131 947**	33 155	**165 103**
Bridgend	18 300	28 793	47 093	92	4 346	4 438	18 392	33 139	51 531
Caerphilly	**88 443**	**36 864**	**125 307**	325	**6 037**	**6 362**	**88 768**	**42 901**	**131 669**
Cardiff	20 415	28 210	48 625	159	3 246	3 405	20 574	31 457	52 031
Carmarthenshire	26 740	30 593	57 333	118	3 903	4 020	26 858	34 496	61 354
Ceredigion	45 628	**38 617**	84 245	**485**	4 433	4 918	46 113	**43 050**	89 163
Conwy	20 659	33 662	54 322	286	3 967	4 254	20 945	37 630	58 575
Denbighshire	10 768	19 661	30 429	**399**	3 027	3 426	11 167	22 688	33 856
Flintshire	9 096	19 134	28 230	348	3 300	3 649	9 445	22 434	31 879
Gwynedd	17 555	27 856	45 411	**413**	4 682	5 095	17 968	32 538	50 506
Merthyr Tydfil	19 180	**46 173**	65 353	132	**6 151**	**6 283**	19 311	**52 324**	71 636
Monmouthshire	**66 557**	36 290	**102 847**	249	**6 594**	**6 843**	**66 807**	42 883	**10 9690**
NeathPort Talbot	20 808	24 468	45 276	285	3 383	3 668	21 093	27 851	48 944
Newport	32 346	19 213	51 559	234	2 538	2 771	32 580	21 751	54 331
Pembrokeshire	14 813	20 506	35 319	304	3 712	4 017	15 118	24 218	39 336
Powys	12 219	14 611	26 830	139	2 103	2 242	12 358	16 714	29 072
Rhondda Cynon Taff	16 907	30 855	47 763	114	4 073	4 187	17 022	34 928	51 950
Swansea	14 114	31 791	45 905	224	5 716	5 940	14 338	37 508	51 845
Torfaen	39 176	26 120	65 296	272	3 389	3 661	39 448	29 509	68 957
Vale of Glamorgan	20 931	27 318	48 248	51	1 962	2 013	20 982	29 280	50 262
Wrexham	14 403	28 993	43 397	397	3 015	3 412	14 800	32 008	46 808

2.4 Discussion

2.4.1 Main findings

A number of regulatory measures concerning the sale and supply of OTC analgesics containing codeine and DHC were implemented in the UK between 2004 and 2010. Overall, the results indicate that there was a reduction in both the numbers of packs and tablets/capsules sold in Wales primarily due to a fall in sales of codeine-based products. The study observed changes in sales which may be explained by the various policies introduced and events occurred during the six-year study period.

Firstly, a significant fall in soluble codeine containing analgesics in number of tablets/capsules sold was observed 12 months after the voluntary restriction on pack size was introduced. However, the equivalent number of packs sold remained unaffected. These observations suggest whilst OTC soluble codeine containing analgesics continued to be sold at a frequency similar to that seen prior to the voluntary agreement, the overall quantities sold have actually reduced. This was not an unexpected outcome for the 2005 voluntary agreement given large packs of soluble codeine containing analgesics were no longer recommended for sale OTC despite they were still classed as a P medicine.

Secondly, the OTC sales for non-soluble codeine and DHC containing analgesics started to decline during the months leading up the legislative changes in 2009. Whilst the exact reasons for this could not be determined, the timing of the reductions coincided with several notable events and publications that were concerned with the misuse and/or abuse of OTC medicines. This included the launch of a high profile inquiry by the APPDMG (2009) into the addiction of OTC medicines and the publication of a professional guidance by the RPSGB (2007) advising pharmacists to limit the sales of opioid containing analgesics. Moreover, numerous articles on the subject matter also appeared in professional journals (Anon. 2007a; Colquhoun 2008; Dickman 2008; Dunkley 2007; Ford and Good 2007a, 2007b) and were reported in the general media (Bunyan 2007; Martin 2007; Morton and Wighton 2009). These may possibly

have increased the awareness and vigilance among pharmacy staff regarding the inappropriate use of non-prescription codeine and DHC analgesics; and contributed to diminishing sales even before legal measures were introduced.

Lastly, in the final 12 months of the study, during which large pack sizes of opioid containing analgesics were reclassified from P to POM status, a significant reduction in sales of non-soluble codeine containing analgesics was observed for the first time. This suggests the legislative measures introduced in 2009 were probably effective at reducing the OTC sales of these products whereas the 2005 voluntary measures appeared to have had little or no influence on OTC sales.

Over the six-year study period, the study did not find an increase in the number of packs sold OTC for either soluble or non-soluble codeine and DHC containing analgesics. This suggests that the practice of making more frequent purchases of these products to compensate for the reduced pack size was not wide spread among the pharmacy users in Wales. Concerns as to individuals switching from purchasing OTC opioid analgesics to obtaining them on a doctor's prescription were also unfounded.

For the OTC products monitored, there was no relationship between the deprivation and sales of OTC analgesics that contained codeine or DHC. This finding does not support the link between increase use of OTC medicines and socioeconomical deprivation and is in agreement with findings reported by other UK based studies (Bradley 1998; Boardman et al. 2005; Porteous et al. 2005; Urquhart et al. 2004). However, the sales of non-soluble codeine containing analgesics in the three most deprived LHBs, in terms of employment, education, health and overall deprivation, were significantly greater than those sold in the three least deprived LHBs in Wales. The reason for this could not be identified in the present study and will require further investigation.

2.4.2 Study limitations

2.4.2.1: Ecological study

The current study utilised retrospective data on a population level and, therefore, was unable to identify the factors that might have influenced patients' decisions to obtain or pharmacists' decisions to supply an OTC medicine. Similarly, it was not possible to identify the factors that were responsible for the high level of non-prescription sales in the three most deprived LHBs in Wales. A better understanding of the characteristics of those who purchased the medicines, such as demographics, socioeconomical background, health status and prescription exemption status, would be useful.

Examination of OTC medicines sales data was useful for explaining some of the changes observed in OTC sales. For example, the data demonstrated a restriction on maximum pack size resulted in a fall in the number of tablets/capsules of soluble codeine analgesics sold but had no impact on the number of packs sold. On the other hand, however, sales data were less useful for assessing the impact of other regulatory efforts, such as the impact of additional information in PIL or warning labels on the product packaging. Consequently, which of the regulatory changes, and to what extent, were responsible for the reduction in OTC sales of the products monitored could not be determined. It was likely that the impact on OTC sales of codeine and DHC containing products had been the combined effect of all of the regulatory measures that were implemented.

2.4.2.2: Pharmacy wholesale data

Pharmacy wholesale sales data were obtained from IMS Health and represented non-prescription sales of opioid analgesics from a range of pharmaceutical suppliers to community pharmacies in Wales. The coverage of the medicines wholesale data was good and included 87% (614/708) of all NHS-contracted community pharmacies in Wales. The remaining pharmacies for which data were not available belonged to a large pharmacy chain that did not contribute data to the RSA database. The pharmacy sales data obtained for this pharmacy chain as part of another study (Chapter 4) indicate its non-

prescription sale of a different OTC preparation (ophthalmic chloramphenicol) represented approximately 31% of the all non-prescription sales in Wales. Whether or not a similar proportion of opioid containing analgesics had been sold by the same company over the current study period was unknown. It is probable that the sales figures reported in the present study were an underestimate of the actual supply.

Pharmacy sales data collected by IMS Health have been utilised by a number of published studies (Cohen et al. 2010; Davis et al. 2009; Dhippayom and Walker 2006; Sheen et al. 2002) and government reports (Walker 2006) to estimate consumptions of OTC medicines in the primary care. These sales data represent stock bought by community pharmacies from their suppliers rather than actual sales to customers. Despite the difference they are considered to be a good proxy for actual sales. One reason for this is because most community pharmacy, where possible, tries to sell most if not all of its stock to generate cash flow for future stock purchases. However, one potential weakness about using pharmacy wholesale data to estimate supply is that they may be sensitive to factors unrelated to customer demand. For example, bulk order discounts or advance purchases in anticipation of peak period of sales and/or medicine shortages may skew the sales picture. However, the available sales data suggest these had not been the case for the products monitored over the study period.

In the UK and Australia, studies have reported that internet pharmacy is becoming increasingly used by as an alternative route for procuring OTC analgesics containing codeine and DHC (APPDMG 2009; Cooper 2011; Grieve 2009; NTA 2011; Nielsen et al. 2010). Although it has been speculated that the scale of internet-supplied codeine and DHC containing analgesics is probably low, how much additional consumption of these medicines were facilitated by internet pharmacies is difficult to quantify (Cooper 2011, Grieve 2009). Since the pharmacy sales data obtained from IMS Health did not include medicines that were sold by online pharmacies, whether or not there was a reduction in non-prescription supply in these settings was unknown.

2.4.2.3: Medicines studied

The current study examined the non-prescription sales of opioid containing analgesics and prescription supplies of the same class of drugs in Wales. The available data suggest there was no evidence of a switch from individuals purchasing these preparations OTC to obtaining them from their GPs on a prescription. However, since the supply for other class of OTC or prescription-only analgesics were not investigated, it remains unclear whether the demands for opioid containing analgesics were reduced or have been met by the use of another agent OTC or on prescription. One example of such would be when the maximum pack size of OTC paracetamol tablets was reduced that the non-prescription sales of ibuprofen tablets increased (Sheen et al. 2002). The reclassification of several other analgesics from POM to P status during the study, such as sumatriptan for the acute relief of migraine (2005), naproxen for period pain (2008) and diclofenac for headache and muscular pain (2008), could have confounded the sales picture of OTC opioid containing analgesics (Grieve 2009, PAGB 2011a).

During the six-year study period, Paramol was the only proprietary brand of non-prescription DHC containing analgesic sold in the UK and its sales data were complete in the RSA database. In contrast, sales data for codeine containing analgesics achieved a less than complete coverage of all products available OTC. One notable omission from the sales data was own-brand preparations sold by large pharmacy multiples (e.g. Boots brand co-codamol 8/500mg tablets). As these own-brand preparations are often retailed at a lower price compared to their proprietary equivalent, the potential cost savings may have incentivised some individuals to purchase the former over the latter. Sales statistics from market research company suggest 31% of the non-prescription adult oral analgesics market are dominated by own-brands (Chemist and Druggist 2012). Whether or not the impact of regulatory changes observed in the current study had been the same for the own-branded codeine and DHC containing analgesics was unknown and will require additional sales data to explore this further.

OTC sales data for seven proprietary brands of codeine containing analgesics (Codis 500, Nucare, Olbas, Solpadeine, Solpadeine Migraine, Uniflu, Vantage) were unavailable to the study. These seven brands have, between them, marketed 16 codeine containing preparations out of a total of 76 that were available between 2004 and 2010 (Chemist and Druggist January 2004, November 2008, August 2010 issue). Although the quantities sold for these 16 preparations could not be determined, two of the preparations (Nucare, Uniflu) came off market during early period of the study (late 2005/early 2006) while another eight products (Solpadeine) were rebranded into Solpadeine Plus for which data were available in the RSA database. Therefore, it is anticipated that the current study captured the majority of non-prescription sales and reflected the overall market trend for proprietary preparations.

Pharmacy sales data for both generic and proprietary preparations were available for study in the RSA database but only the latter were included in the analysis. The reason for adopting this method was to avoid over-estimating OTC supply, which could arise if a generic product, such as co-codamol x 32 tablets (8mg codeine phosphate and paracetamol 500mg), was treated as sold OTC when it was in fact used to dispense a prescription. Differentiating the outcome of a generic product as to whether it was sold OTC or used to dispense a prescription was not possible because such information was not recorded in the RSA database. The obvious disadvantage about this cautious approach was that some of the generic products with a P medicine licence were likely to have been sold OTC. As a result, the sales figures reported in the present study are likely to be underestimates of the actual supply in Wales.

2.4.2.4: Deprivation

The WIMD was designed specifically to measure deprivation at a small area level, namely LSOAs (Welsh Government 2011). However, pharmacy sales and primary care prescription data were both only available in LHB geography. Although calculating the percentages of LSOA in the most deprived 20% provided a way to estimate deprivation at LHB level, these were only estimates and showed how concentrated deprivation was over a large geographical area. Cautions must therefore be exercised when interpreting the findings from the

correlation analysis, as not all deprived people live in areas of high deprivation nor are they all likely to purchase analgesics containing opioids. Other limitations related specifically to the WIMD have been published elsewhere (Welsh Government 2011). The current study could be improved by analysing OTC sales and deprivation data at LSOAs level, but this was not achievable as both prescription and OTC sales data were only available in LHB format.

2.4.2.5 Trainings and sales protocols

In community pharmacies in the UK, Medicine Counter Assistants (MCAs) are often involved in the sales and supply of OTC medicines (Banks et al. 2007; Ward et al. 1998). In order to ensure MCAs can safely and effectively assist with the sales of non-prescription medicines it is a requirement that all MCAs have undergone, or be undertaking an accredited training programme before commencing their role (General Pharmaceutical Council [GPhC] 2011). In addition to the minimum training requirements, extra in-house materials may be provided in some pharmacies to engage their staff in further learning and/or promote company-specific policies. For example, pharmacy staff may be encouraged to recommend own-brand medicine over a proprietary equivalent to drive profit or the patient referral criteria/protocol for a condition may be different from one company to another. It was possible that these variations in pharmacy training and sales protocol for MCAs may have confounded the sales picture, particularly as not all codeine and DHC containing analgesics or generic products were included in the study. The exact impacts of these variations on OTC sales could not be determined and should be investigated further.

2.4.3 Comparison with existing literature

2.4.3.1 Impact of voluntary and legislative changes

Restriction of medicine pack size as a strategy to reduce the misuse and abuse potential of OTC medicines have previously been implemented in the UK. One notable example was the pack size reduction of paracetamol containing products in 1998 (Committee on Safety of Medicines [CSM] 1997) following an increase in number of deaths and reports of deliberate self-harm by

paracetamol poisoning (Bray 1993; Hawton et al. 1997). Several studies investigated the impact of the new legislation and found that limiting OTC pack size of paracetamol also reduced the quantity of non-prescription tablets/capsules sold (Hawton et al. 2001, 2004, 2013). A more recent example would be the pack size restriction of OTC pseudoephedrine and ephedrine containing products in April 2008 and it too demonstrated a reduction in OTC sales 12 months after the pack size restriction (MHRA 2009c). The outcomes of these prior regulatory efforts are in line with those observed in the current study and indicate pack size restriction was at least one of the reasons for the decline in OTC sales of opioid containing analgesics.

The sales data for Wales suggest the 2005 voluntary agreement affected the sales of soluble but not non-soluble codeine containing analgesics. This was unsurprising because the only opioid containing analgesics that had a pack size greater than 32 tablets were soluble preparations. Non-soluble codeine containing analgesics appeared to be unaffected probably because they were already limited to a maximum pack size of 32 tablets due to a legal restriction on the quantity of paracetamol that could be sold OTC (RPS 2011a). Other compound analgesics, such as those containing ibuprofen or aspirin combined with codeine, were not confined to a maximum pack size of 32 tablets but no large packs of these products were available in the UK (Anon. 2002). A similar observation of a reduction in large (60 tablets packs) but not small pack sizes (32 tablets packs) of codeine containing analgesics have also been reported by others following the 2005 voluntary agreement (Reed et al. 2011).

The beginning of a year-on-year decline in the sales of non-soluble codeine and DHC containing analgesics occurred in 2007. This coincided with the publication of a professional document by the RPSGB (2007), which recommended OTC sales of opioid containing analgesics were to be limit to one pack, of any pack size, per purchase. Furthermore, the updated guidance also stated soluble co-codamol that contained 100 tablets per pack should be reserved for dispensing use only. These recommendations were reported to be viewed authoritatively by medicine counter assistants who are often involved in the sales of non-prescription analgesics (Cooper 2011, 2013b). As such,

sales that could have otherwise involved multiple or large packs of these products might have therefore been prevented. The simultaneous reductions in both number of packs and tablets/capsules sold which began in 2007 indicate there was a direct relationship between the two variables. This possibly reflects the impact of the 'one pack per purchase' policy on the sales of codeine and DHC containing analgesics.

As mentioned earlier, multiple factors could have contributed to the reduction of codeine and DHC containing analgesics sold. Besides an increased awareness about the misuse and/or abuse potentials of these medicines among pharmacy (Anon 2007a, 2007b; Colquhoun 2008; Dickman 2008; Dunkley 2007) and medical professionals (Ford and Good 2007a, 2007b; Hanoch 2007; Matheson 2007), pharmacy counter assistants also reported to have received additional training on the subject matter (Cooper 2011, 2013b). Furthermore, community pharmacies adopted strategies to prevent inappropriate sales, such as monitor the frequencies of purchase, use technology to notify sales that involve multiple packs, make records of OTC transactions and inform nearby pharmacies of suspicious requests (Cooper 2011, 2013b). A national awareness campaign on the appropriate use of OTC analgesics was also launched and warned of the dangers of addiction to OTC analgesics (British Pain Society 2010). Lastly, the introduction of legislative changes in 2009 was accompanied by wide spread communications within the pharmacy profession aimed to raise awareness of the legislative changes (Anon. 2009a, 2009b, 2009c; Maguire 2010; RPSGB 2009). Whilst the impact of these measures have not been fully evaluated, it was likely that at least some of these activities have deterred customers from purchasing and/or altered pharmacy staff behaviour when faced with requests for OTC codeine or DHC containing analgesics.

2.4.3.2 Influence of deprivation

Research examining the association between socioeconomical deprivation and use of OTC medicines have utilised various measures of deprivation or consumption of OTC medicine and thus direct comparison between the studies is difficult (Boardman et al. 2005; Poretous et al. 2005). In addition, a patient's perception of his or her needs for an OTC medicine may be different

depending on the ailment or medicine in question and could influence the decision whether to self-medicate or obtain a prescription from their GP. The link between deprivation and use of different types OTC medicines must therefore be assessed with care.

Of the data that are published, Boardman et al. (2005) and Poretous et al. (2005) reported that a poorer self-reported health status was linked to an increase in OTC medicine use. However, no significant correlation was observed between health deprivation and use of non-prescription opioid analgesics in the current study. Increased use of OTC medicines was found to be associated with affluence in English (Boardman et al. 2005) and Scottish (Porteous et al. 2005) populations as well as in GP attendees (Bradley 1998; Urquhart et al. 2004). A need to pay for prescription levy, as an indicator for affluence, was also found to be significantly associated with increased OTC medicine use (Urquhart et al. 2004; Wazaify et al. 2005). McIntyre et al. (2003) reported that parents or carers of young children living in more affluent areas were more likely to purchase OTC medicines for future needs. Increased education has been associated with increased OTC medicine use (Porteous et al. 2005).

Most notably, many of the studies mentioned above reported a positive correlation between affluence and use of OTC medicines. However, their results should be compared cautiously with those of the current study not only because none of them investigated the use non-prescription opioid analgesics, but also a low deprivation index does not mean a population is necessarily more affluent. The fact that there appears to be no association between deprivation and OTC supply of opioid analgesics only serve to suggest increased socioeconomical deprivation was probably not a major contributing factor to non-prescription opioid analgesic use in the Welsh population.

The reason as to why there had been a larger quantity of opioid containing analgesics sold OTC in the more deprived compared with the less deprived LHBs is uncertain. However, socioeconomical deprivation has been shown to be associated with higher prevalence of pain (Aggarwal et al. 2003; Brekke et

al. 2002; Blyth et al. 2001) and may be a possible explanation for what had been observed. Had there been a higher prevalence of pain among the more deprived population this could also explain the unintended finding that, in a separate analysis involving the same prescription and deprivation data, a significant positive correlation ($p<0.001$) was observed between opioid analgesics supplied on prescription and all of the four deprivation components and overall deprivation (results not shown).

Given the emerging misuse and abuse potential associated with OTC analgesics containing opioids, one might be tempted to attribute their high consumptions in these more deprived areas to inappropriate use drawing on the known link between social deprivation and illicit drug use (Galea et al. 2004; Lloyd 1998). Such speculation, however, is unfounded as user demographic can differ from one substance to another and few OTC codeine dependent users actually reported concurrent illicit drug use (Cooper 2011; Grieve 2009; Nielsen et al. 2010, 2012). Investigations into the demographic features of codeine dependent users in Australia revealed codeine dependent users are more likely to have lower education, less likely to be in full-time employment and more likely to report fair to poor health than non-dependent codeine users (Nielsen 2010). Whether the same features could be extrapolated for the UK population is unknown and will require further investigation.

A number of studies outside of the UK reported a link between use of OTC codeine analgesics and a range of mental health problems and it has been suggested practicing self-medication enable individuals to cope with mental health symptoms (McAvoy et al. 2011; Nielsen et al. 2010). These findings were in agreement with those of a survey study conducted in the UK, which found 54% of codeine dependent participants reported as suffering from coexisting problems such as anxiety, panic attacks, depression, alcoholism or addiction to other drugs/medicines (Grieve 2009). This apparent link between mental illness and use of OTC opioid containing analgesics potentially explains the absence of an association between health deprivation and OTC sales reported in the current study, as none of the indicators considered by

WIMD to calculate the health deprivation scores were related to mental health problems (Welsh Government 2011).

2.4.3.3 Abolition of NHS prescription charge

Significant changes in healthcare policy have taken place in Wales during the six-year study period and one of the developments was the abolition of NHS prescription co-payment levy in April 2007 (Cohen et al. 2010). Studies have found that for some patients the prescription levy can act as a significant barrier to the use of prescribed medicines (Schafheutle et al. 2002, 2004; The Prescription Charges Coalition 2014). Whilst it was possible that this may have had an influence on the quantity of medicines prescribed, a study has found that there had only been a modest change in the overall dispensing rate 12 months post-abolition (Cohen et al. 2010). The present study supports this finding as codeine and DHC containing analgesics have demonstrated a similar prescribing trend in Wales before and after the policy change. As such, the likelihood that individuals have shifted from purchasing OTC opioid containing analgesics to obtaining them on prescription because of free prescriptions was probably small. Furthermore, OTC-to-prescription switching would not explain why there had been a reduction in quantities of soluble codeine containing sold in tablets but not in the number of packs sold.

2.4.4 Implication of findings

In light of the emerging issues of misuse and abuse of OTC analgesics containing opioids, regulatory measures introduced in 2005 (voluntary agreement) and 2009 (legislative changes) justified their continued non-prescription availability in the UK. Perhaps from a regulatory prospective, a reduction in their OTC sale indicated the policy interventions have been successful in reducing the likelihood of harm caused by these medicines. However, many important aspects related to the inappropriate use and/or OTC sale of these products remain to be addressed (Cooper 2013b, 2013c, Mackridge et al. 2013, Burton 2012).

One aspect that has been repeatedly mentioned is the absence of reliable data on what scale addiction to OTC analgesics really is among the UK population

(APPDMG 2009; Cooper 2011; 2013a; NTA 2011). This information on prevalence would allow changes in trends to be monitored, effectiveness of interventions to be evaluated and, ultimately, inform regulatory decisions as to whether analgesics containing an opioid should continue to be available without a prescription. While pharmacy sales data provided useful insights into the supply of OTC codeine and DHC containing analgesics in the primary care and the impact of relevant policy changes, their contribution to understanding the scale of the addiction problem is limited. The hidden nature of addiction to OTC medicine presents many challenges for researchers and policy makers (APPDMG 2009), and identifying a way to accurately quantify prevalence of users having problems with OTC analgesics should be a priority. In England, the commissioning guidance on the treatment of OTC and prescription medicine dependence (Public Health England [PHE] 2013b) urged local authorities to work with primary care service providers to monitor prescribing and purchasing pattern of opioid containing drugs. The utilisation of OTC medicines sales data is likely to play a vital role in fulfilling these goals.

The introduction of smaller pack sizes of OTC opioid containing analgesics meant the relative costs of these products have increased. This could be viewed favourably as it might have a deterrent effect upon individuals who misuse and/or abuse OTC codeine and DHC analgesics (Cooper 2011). However, it was also possible that the increased costs have deterred legitimate requests and limited people's ability and/or desire to practise self-medication. This illustrates a potential problem for the current pack size restriction policy and how it could exacerbate health inequalities. Furthermore, it highlights pharmacy sales data's inability to identify how much of a reduction in sales had impacted on inappropriate as oppose to appropriate self-medication.

As noted by Bond and Hannaford (2003) and Walker (2000), a weakness associated with the current regulation of OTC medicine is the lack of comprehensive post-market surveillance data. Given the increased regulations and heightened vigilance that have made opioid analgesics more difficult to obtain in high street pharmacy settings (Cooper 2013b), it was unsurprising that some dependent users reported to have turned to alternative sources of

supply, such as from internet pharmacies (Cooper 2011; Grieve 2009; Nielsen et al. 2010; APPDMG 2009). The anonymous and borderless nature of the internet makes the detection and monitoring of inappropriate use of opioid containing analgesics even more difficult, and reports of unchallenged sales involving multiple packets and repeated requests are concerning (APPDMG 2009; Cooper 2011; Nielsen et al. 2010). The missing sales information from internet pharmacies could have a consequential impact on the evaluation of the regulatory measures. Furthermore, the increase in OTC sales of generic and own-brand of opioid analgesics (IRI UK 2009), for which data were unavailable to public health organisations, represents another unknown source of non-prescription supply and should be included in future studies.

Pharmacy sales data revealed significantly greater quantities of OTC opioid containing analgesics have been sold in the three most rather than the three least socioeconomically deprived LHBs in Wales. More research is needed to understand exactly why this was the case. Interestingly, the present study unintentionally found that one of the most deprived LHBs, Blaenau Gwent, was also obtaining the highest quantities of opioid analgesics on primary care prescriptions in Wales. Recent evidence suggest many codeine or DHC dependent users have initially been prescribed with opioid-based painkillers for genuine medical reasons but these were subsequently replaced by taking an OTC analgesic after prescription treatment had ended (APPDMG 2009; Cooper 2011; Nielsen et al. 2010). Whether or not this was taking place in Blaenau Gwent was unknown but the possible link between the high level of prescribing and OTC use of opioids should be investigated. This demonstrates the strength of dual monitoring of both OTC sales and prescribing data to identify usage pattern that might not have otherwise been picked up by examining either dataset alone.

Drug misuse referral data for Wales indicate the number of treatment referrals for cases involving ‘Other Opiates’, such OTC preparations containing codeine and DHC, remained unchanged from 114 referrals in 2005 to 116 referrals in 2011 (Welsh Government, personal communication). In England, the number of people presented at drug treatment services with problems specifically

related to OTC opioid have, on the other hand, increased year on year over the same period (NTA 2011). These observations suggest despite an increase in regulation of the non-prescription sales of these products from pharmacies problems relating to their use continued to affect some individuals. Whether or not, over time, the increased regulation concerning the non-prescription supply of OTC opioid containing analgesics would translate to a fall in the number of people addicted to OTC analgesics remains a question to be answered and long term monitoring will be needed.

2.5 Summary

In the 12 months following the 2005 voluntary agreement, OTC sales of soluble codeine containing analgesics in number of tablets/capsules sold have significantly reduced but the number of corresponding packs sold remained unaffected. Sales of non-soluble codeine and DHC containing preparations were both unaffected by the 2005 voluntary agreement but year-on-year reductions in sales were observed between 2007 and 2010. In the 12 months following the legislative changes in 2009, a significant reduction in quantities sold for all formulations of codeine or DHC containing analgesics compared to the previous 12-month period was observed except for soluble codeine preparations.

Analysis of employment, education, income, health, and overall deprivation against sales of OTC opioid containing analgesics at LHB level indicate there was no association between increased socioeconomical deprivation and non-prescription analgesic use. However, it was found the sales of OTC opioid containing analgesics were significantly greater in the three most deprived than the three least deprived LHBs in Wales. Further research is needed to investigate whether the reductions in OTC sales have actually translated into a fall in number of people dependent to OTC opioid containing analgesics.

Chapter 3:

Impact of regulatory changes on supply of pseudoephedrine, ephedrine and phenylephrine

Impact of regulatory changes on supply of pseudoephedrine, ephedrine and phenylephrine

3.1 Introduction

Minor ailments have been defined as conditions that are self-limiting and/or conditions that can be diagnosed easily by patients themselves (Proprietary Association of Great Britain [PAGB] 2010). Coughs, constipation and colds are some conditions defined as 'minor' in the published literature (Banks 2010; Pillay et al. 2010). When it comes to minor ailments, many people use no medication, for example, because they are often not considered serious or perceived to require no treatment (PAGB 2005a). However, up to 41% of people claim to self-medicate with non-prescription medicines prior to seeking advice from healthcare professionals (Banks 2010; Porteous 2006) and do so most often by making purchases from community pharmacy (PAGB 2005a).

The main reasons for self-medicating with an OTC medicine include patient autonomy, convenience and potential financial-savings for the users (Banks 2005, Brass 2001; Ryan and Yule 1990) especially for individuals who have to pay for NHS prescriptions (Schafheutle et al. 1996, 2002, 2004). Self-medication is also promoted by other interested parties, including the government who have a desire to reduce NHS drug spending (Aronson 2004; PAGB 2011a, 2011b), need to reduce the burden on the NHS by making better use of pharmacists' and doctor's skills (Bellingham 2002; Royal Pharmaceutical Society of Great Britain [RPSGB] 2003) and the goal of pharmaceutical companies' to increase sales of their products and thereby increase profit (Blenkinsopp 2004).

Nasal congestion symptoms are commonly encountered in the primary care with 15% of adults and children in the United Kingdom (UK) (Banks 2010). Whilst it is usually considered to be a self-limiting condition that can be treated safely with over-the-counter (OTC) medicines (PAGB 2010), many patients choose to consult their general practitioner (GP), costing the National Health Service (NHS) up to £17.4 million in prescribing costs every year (Pillay et al. 2010). The onset of nasal congestion could be due to a number of causes, such

as a common cold (Blenkinsopp et al. 2009; National Institute for Health and Care Excellence [NICE] 2011), influenza infection (Eccles 2005) or hay fever (NICE 2012a), all of which are health conditions frequently experienced in primary care (PAGB 2005a). Nasal congestion can also be associated with nasal allergies other than hay fever (Blenkinsopp et al. 2009), nasal polyps, sinusitis (NICE 2009a) or changes in atmospheric humidity (British National Formulary [BNF] 2013). Studies have found over 50% of sufferers who reported nasal congestion have self-medicated with OTC medicines (PAGB 2005a).

3.1.1 Nasal decongestants

There is a wide range of pharmacological treatments for nasal congestion available OTC. Common active ingredients and the background to their use are discussed below.

3.1.1.1 Ephedrine

Ephedrine is a sympathomimetic that possesses both alpha- and beta-adrenergic activity (Sweetman 2007) and is indicated for the reversal of hypotension and nasal congestion (BNF 2013). Its usefulness is due to its stimulation of the central nervous system which increases cardiac output and induces peripheral vasoconstriction (Sweetman 2007). Other uses of ephedrine such as a bronchodilator or for the treatment of diabetic neurophatic oedema are becoming obsolete due to the availability of other, more effective treatments (BNF 2013).

When ephedrine is used as a nasal decongestant, it can be given orally or applied topically and is suitable for individuals over six years of age. The BNF (2013) only acknowledges the use of ephedrine as a nasal decongestant via the topical route due to its unwanted systemic effect on the cardiovascular system if given orally (Blenkinsopp et al. 2009). Furthermore, the BNF (2013) recommends the use of ephedrine containing nasal drops be limited to short-term use for no longer than seven days as they can give rise to rebound congestion (rhinitis medicamentosa) on termination of treatment. The oral forms of ephedrine can be found in multi-constituent products, in combination

with other active ingredients such as chlorphenamine, paracetamol or diphenhydramine, for the purpose of treating coexisting symptoms such as headaches or excessive nasal secretions that are frequently associated with a cold or a flu (Sweetman 2007). As of April 2010, there were seven proprietary brands of ephedrine containing preparations available in the UK. All except one (CAM Mixture) were multi-ingredient products (Chemist and Druggist: Monthly Pricelist April 2010). Their OTC indications included treatment for cold or flu symptoms, wheezing and bronchitis (Chemist and Druggist: Guide to OTC Medicines + Diagnostics, September 2008).

3.1.1.2 Pseudoephedrine

Pseudoephedrine (PSE) is a stereoisomer of ephedrine with notably fewer central nervous system effects and therefore its use may be preferable in many patients (Sweetman 2007; Blenkinsopp et al. 2009). PSE is only available orally in the UK and, therefore, unlike topical ephedrine it does not cause rebound congestion after prolonged use (BNF 2013). According to the BNF (2013) the only licensed indication for PSE is the symptomatic relief of nasal congestion and its use in children under six years old is not recommended (NICE 2011). In the UK, PSE can be found in single ingredient as well as multi-ingredient preparations (Sweetman 2007). The latter are often combined with ingredients such as paracetamol or ibuprofen for treating concurrent symptoms associated with a cold, flu or allergy (Chemist and Druggist: Guide to OTC Medicines + Diagnostics, September 2008).

3.1.1.3 Phenylephrine

Phenylephrine (PE) is a sympathomimetic that possesses predominantly alpha-adrenergic activity (Sweetman 2007). Its usefulness as a nasal decongestant is not formally acknowledged in the BNF (2013) due to its unproven efficacy (Eccles 2007; Hatton et al. 2007; Horak et al. 2009; Kollar et al. 2007). Despite the lack of evidence, PE-based products have long been available OTC because they were licensed many years ago at a time when robust evidence for efficacy was not required (Eccles 2007). As a nasal decongestant, PE may be given orally or applied topically in the form of nasal drops; the former route is not associated with rebound congestion after prolonged use but can give rise to

unwanted cardiovascular side effects, such as hypertension (Sweetman 2007). Similar to ephedrine and PSE containing products, PE is frequently found in preparations with other active ingredients intended to treat a range of common cold and flu symptoms (e.g. Beechams All-In-One), but is also available as a single-ingredient product (e.g. Sudafed Non-Drowsy Congestion Relief). The use of PE use in children under six years old is not recommended due to the unfavourable balance of benefits and risks (NICE 2011).

3.1.1.4 Other nasal decongestants

Oxymetazolin (OXY) and xylometazolin (XLY) are sympathomimetics with marked alpha-adrenergic activity but, unlike ephedrine, PSE and PE, they are used only topically as nasal sprays or nasal drops (Sweetman 2007). OXY and XLY are considered to be more potent topically than ephedrine-based products and are active over a longer relief period with the effect lasting between 5 and 10 hours. However, in practice, they are unsuitable for long-term use (no longer than seven days) due to the likelihood of rebound congestion (Blenkinsopp et al. 2009). In the UK, OXY and XYL are classified as General Sales List (GSL) medicines therefore availability and sales are not restricted to pharmacy settings and may be purchased from any retail outlet (RPS 2011a). OTC products containing either of these two ingredients are marketed in the UK for nasal congestion due to allergic rhinitis, sinusitis or the common cold. As with other sympathomimetic drugs, they are not recommended for children under six years of age (NICE 2011).

Another popular OTC treatment for nasal congestion is steam inhalation using volatile substances, such as eucalyptus oil, peppermint oil and menthol. These substances are used by dissolving them in warm water and inhaling the moist air. Alternatively, they may be applied to clothing or handkerchiefs and inhaled when required (Blenkinsopp et al. 2009; NICE 2011). Lozenges or pastilles containing peppermint oil and related cooling compounds have also been formulated and they induce the decongestant effect through menthol vapours reaching the nasal cavity via the nasopharynx during swallowing (Eccles 1994). Aromatic decongestants may not be suitable for infants and the BNF

(2013) advise saline nasal drops (sodium chloride 0.9%) be used instead (NICE 2011).

The use of topical saline preparations as an adjunct therapy has been found to be beneficial for nasal congestion symptoms and is well-tolerated (Harvey et al. 2009). Its mechanism of action is unknown but is thought to involve cleansing of the nasal passage, removal of inflammatory mediators and the promotion of ciliary beat frequency (Rabago and Zgierska 2009). In the UK, topical saline preparations are available in a wide range of formulations such as sprays, pumps, nebulisers or solutions. Both saline and inhalation based products are readily available for purchase OTC as GSL medicines and are indicated for nasals congestion due to a cold, influenza, hay fever or catarrh (Chemist and Druggist: Guide to OTC Medicines + Diagnostics, September 2008).

3.1.2 Changes to Over-the-Counter sale and supply

In March 2007, the Medicines and Healthcare products Regulatory Agency (MHRA), the government agency responsible for regulating the safety and effective use of human medicines and healthcare devices in the UK, launched a public consultation and collated views on changing the legal status of OTC products containing PSE and ephedrine from P to POM (MHRA 2007a). The consultation was triggered by two events that took place at around the same time; first of which was the reclassification of methylamphetamine to a class A controlled drug (Anon. 2006) and the second was the discovery of illicit manufacturing of methylamphetamine using OTC medicines containing PSE and ephedrine (Hampshire Constabulary 2007; Association of Chief Police Officers [ACPO] 2007).

Methylamphetamine, commonly known as methamphetamine, crystal meth or ice, is a highly addictive central nervous system stimulant that can cause long-term physical and psychological damage to the user (Darke et al. 2008). The manufacture of methylamphetamine was a serious issue for the MHRA to consider not only because OTC products containing ephedrine and PSE had been used as precursors in the illicit manufacture, but the process was

relatively straight forward and could be undertaken by anyone with low a level of skill and in a domestic environment (Commission on Human Medicines [CHM] 2007; ACPO 2007). There was also an anecdotal report of test purchases of large quantity of oral nasal decongestants from pharmacies that went unchallenged and this also raised some concerns (Anon. 2007c).

The MHRA undertook a public consultation on the reclassification of PSE and ephedrine containing products (MHRA 2007a). The consultation attracted a response from a range of interested parties, including law enforcement agencies, patient and substance misuse organisations, the medical profession, the pharmacy profession and the industry. Among those who supported a change of legal status from P to POM were those who agreed that the continued availability of OTC ephedrine and PSE posed a significant risk that could increase the use of methylamphetamine. Others objected to the proposal on the basis that the move could negatively impact on GP workload (Walker 2007), reduce patient choice (Angwin 2007) and showed a perceived lack of trust in the pharmacy profession (Styles 2007).

Having taken into account the scale of the problem and the potential for harm from methylamphetamine in the UK, the CHM concluded that the legal status of medicinal products containing PSE and ephedrine should remain as a P medicine providing the risk of misuse in the illicit manufacture of methylamphetamine was contained. To support the decision, a voluntary pack size restriction on PSE and ephedrine containing products was agreed between the product manufacturers and the MHRA in August 2007, which saw maximum quantity of PSE and ephedrine limited to 720mg and 180mg per pack, respectively. Furthermore, purchases of these products were restricted to one pack per transaction (Anon. 2007d). These changes generated a considerable amount of attention within the pharmacy profession and were accompanied by plans to increase awareness of misuse and promote widespread training of pharmacy staff (Anon. 2007e, 2007f, 2007g, 2007h).

Following the voluntary agreement to restrict the pack size of PSE and ephedrine containing products, a further public consultation in October 2007

considered specific proposals to make the sale and supply of these products subject to prescription control (MHRA 2007b). The intention was to ensure the limit on pack size was implemented by all manufacturers. At the time, respondents to the consultation were generally supportive of the proposal albeit some concerns over the date of implementation and restriction to one pack per sale (MHRA 2008b). Subsequently, legislation was enacted on 1 April 2008 (MHRA 2008c) and it became unlawful to sell or supply:

- any preparation containing more than 720mg or 180mg of PSE or ephedrine, respectively, without a prescription,
- a combination of products that between them add up to more than 720mg of PSE or 180mg of ephedrine without a prescription in one transaction, and
- any PSE-containing products together with an ephedrine product without a prescription

3.1.3 Concerns

In the four years up to 2011, following the introduction of OTC sales restrictions on PSE and ephedrine containing products, the various measures implemented to help to minimise the risk of their misuse have been reported to be successful and no trigger has yet prompted a further review of their availability OTC by the MHRA (MHRA 2012b). For example, UK-wide sales figures of PSE containing products have indicated a year-on-year decline from 2008 up to 2011 (MHRA 2009c, 2010, 2011a, 2012b). However, whether the sales of these products in Wales followed the same UK-wide trend is unknown and would be of interest to study. In addition, concerns raised at the time of the consultation regarding increased GP workload and prescribing costs as a result of stricter control of OTC nasal decongestants (Royal College of Physicians 2007; Royal College of General Practitioners 2007) have not been examined. The impact of increased regulation of OTC nasal decongestants on other primary healthcare services, such GPs, would be of interest to government, medicine regulators and healthcare professionals.

3.1.4 Aims

The aims of this study were to determine the impact of pack size restriction on (a) OTC sales of PSE, ephedrine and PE containing preparations; and (b) quantify the prescribing of nasal decongestants on primary care prescriptions in Wales.

3.2 Method

3.2.1 Study design

This ecological study involved the retrospective analysis of pharmacy wholesale data and primary care prescription data for Wales. Changes in quantities sold for selected, OTC PSE, ephedrine and PE containing preparations, before and after the imposition of legal restrictions on sale of PSE and ephedrine OTC, were determined. In addition, any changes in the quantity of nasal decongestants supplied on primary care prescriptions in Wales were also determined.

3.2.2 Data

3.2.2.1 Primary care prescription data

Prescription data for Wales were extracted from the NHS Wales prescription database using CASPA.net (Comparative Analysis System for Prescribing Audit) and was the same data source as described in Chapter 2 (Section 2.2.2.1). The data were obtained for the period between April 2004 and March 2011 (84 months) on a monthly basis and represented prescribing by GPs. In the current study, the quantity supplied on prescription was presented as the number of prescription items.

3.2.2.2 Pharmacy wholesale data

Pharmacy wholesale data were extracted using the IMS Health Dataview application from the Regional Sales Analysis (RSA) database. This was the same database as described in Chapter 2 (Section 2.2.2.2) and the purchase of medicines by pharmacies from wholesalers was utilised as a surrogate for pharmacy-to-patient sales (herein referred to as the pharmacy sales data). In the

present study, pharmacy wholesale data for Wales were extracted as the monthly number of packs sold for the selected OTC preparation between April 2004 and March 2011 (84 months). The quantities supplied in packs were also converted into the weight of active ingredient sold based on the pack size information that were also available in the RSA database. *Chemist and Druggist: Monthly Pricelist April 2010* was used as a reference source to determine the amount of PSE, ephedrine or PE contained in a particular product. Calculations of the weight of the active ingredient were undertaken in Microsoft Excel spreadsheet.

3.2.3 Medicines studied

3.2.3.1 Medicines supplied on NHS prescription

Prescription medicines studied included all preparations listed under the following chapters of BNF 65 (2013) and indicated for the symptomatic relief of nasal congestion:

- Aromatic inhalations (3.8)
- Systemic nasal decongestants (3.10)
- Topical nasal decongestants (12.2.2)

In addition, a manual search of the prescription database was undertaken by the researcher to identify any nasal decongestants not listed under the relevant BNF chapters. As an example, PE capsules were not listed in BNF 65 chapter 3.10 but were available in the Wales prescription database for extraction. The active ingredient contained in manually identified preparations and their corresponding clinical indications were confirmed using *Martindale: The Complete Drug Reference* (Sweetman 2007) and *Chemist and Druggist: Monthly Pricelist (April 2010 issue)*. Both proprietary and non-proprietary preparations were included in the study and they are shown in Appendix 10 and Appendix 11.

3.2.3.2 Over-the-Counter medicines

All proprietary PSE, ephedrine or PE containing products that were sold OTC during the period of the study in the UK were identified using May 2004, April 2006, April 2008 and April 2010 issues of *Chemist and Druggist: Monthly Pricelist*. Next, the main active ingredient responsible for producing the nasal decongestant effect was identified on individual product basis and preparations for which sales data was available in the RSA database were extracted for OTC sales analysis. The preparations included both P and GSL products in oral dosage forms (tablets, capsules, effervescent powders or liquids). Furthermore, a manual search of the RSA database was undertaken by the researcher after the initial selection to identify if there were other preparations that could be purchased without a prescription and none were identified. Lists of all OTC PSE and PE containing products included in the pharmacy sales data analysis are shown in Appendix 12 and Appendix 13, respectively. Data for none of the OTC ephedrine containing products sold in the UK were available in the RSA database and thus were not included in the current study.

3.2.4 Data processing and organisation

Prescription and pharmacy wholesale data for Wales were transferred from their respective database into Microsoft Excel spreadsheet as described in Appendix 8 and Appendix 9. The quantities supplied OTC and prescribed on prescription were arranged into 12-month blocks, from April to March for each year, to allow the comparison between the periods before and after implementation of the legal policy. There were four 12-month blocks prior to the legal restriction on OTC pack size (April 2004 to March 2008) and three 12-month blocks after (April 2008 to March 2011). All processed or reorganised data were manually screened for error before transferring to statistic software for analysis.

3.2.5 Analysis

3.2.5.1 Descriptive analysis

The supply of OTC PSE and PE in Wales was presented as 12-monthly totals from April 2004 to March 2011 in i) number of packs and ii) weight of the active ingredient supplied in grams. Prescription supplies of nasal

decongestants were presented only as the number of items supplied. The median and the interquartile range (IQR) for the component month for each of the 12-month periods were also determined.

3.2.5.2 Impact of regulatory changes on Over-the-Counter sales

Changes in the supply of PSE, PE and other nasal decongestants, on prescription and OTC from pharmacies, were determined between two consecutive 12-month periods and any difference was explored using Wilcoxon's signed-rank test. A p-value < 0.05 was considered to be statistically significant. Statistical analyses were performed using PASW version 18 (PASW Inc., Chicago, IL, USA).

3.3 Results

3.3.1 Over-the-Counter supply

The number of packs and weight of active ingredient supplied each for PSE and PE containing products are shown in Figure 3.1. Overall, OTC supply of PSE containing products declined in Wales between 2004 and 2011. This corresponded to a 48% (49,543/103,173) reduction in number of packs sold and a 53% (32,699/61,323) reduction in weight of PSE sold. Over the same period, PE containing products demonstrated a 40% (81,024/204,015) reduction in the number of packs sold but the cumulative weight reduced only by 6% (772/12,953).

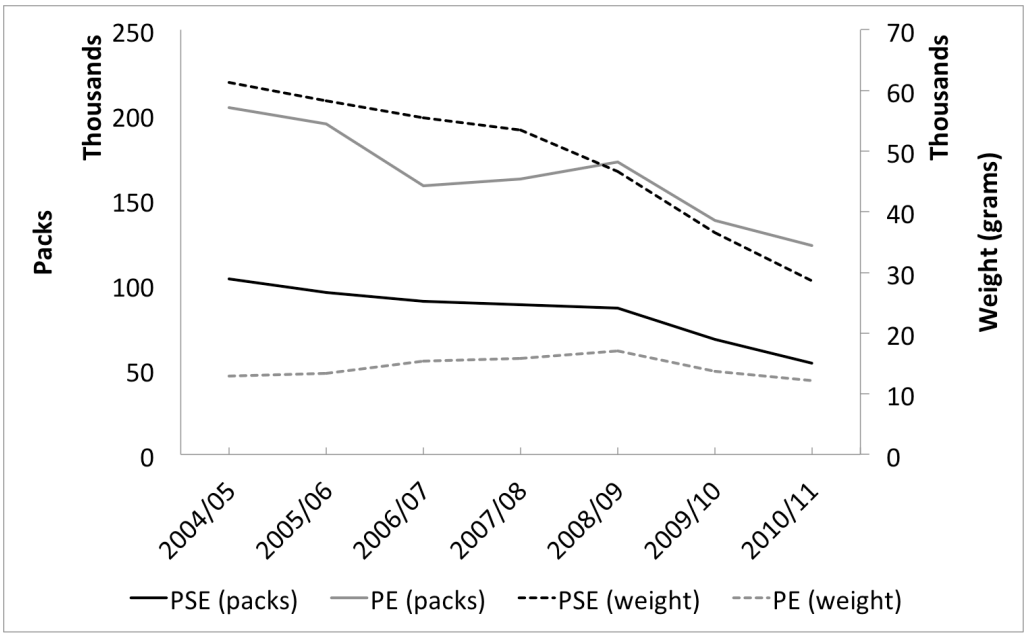


Figure 3.1 Twelve-monthly sales of over-the-counter pseudoephedrine (PSE) and phenylephrine (PE) containing preparations in Wales

3.3.1.1 Pseudoephedrine

OTC supplies of PSE containing products and their respective median and IQR for each 12-month period are shown in Table 3.1.

Table 3.1 Total supplies (median, interquartile range) of over-the-counter pseudoephedrine containing products in Wales for each 12-month period (April to March) between 2004 and 2011. Quantities supplied were compared between two consecutive periods and an asterisk (*) marks any significant difference (p<0.05)

	Packs	p-value	Weight (grams)	p-value
2004/05	103 173 (8 733, 4 171)		61 323 (5 069, 1 713)	
2005/06	95 465 (7 900, 2 516)	0.239	58 313 (4 825, 1 143)	0.388
2006/07	90 015 (7 409, 4 222)	0.182	55 432 (4 956, 2 071)	0.209
2007/08	88 354 (5 667, 4 635)	0.875	53 428 (3 985, 2 541)	0.875
2008/09	86 185 (5 618, 4 133)	0.388	46 629 (3 106, 2 152)	0.023*
2009/10	67 684 (4 185, 3 084)	0.023*	36 608 (2 233, 1 629)	0.028*
2010/11	53 630 (3 641, 1 773)	0.006*	28 624 (1 977, 908)	0.006*

Year-on-year there were reductions in number of packs sold, from 2005/06 to 2010/11 of 7% (7 708/103 173), 6% (5 450/95 465), 2% (1 661/90 015), 2% (2 169/88 354), 21% (18 501/86 185) and 21% (14 054/67 684), respectively. Year-on-year percent reductions in the weight of PSE sold, from 2005/06 to 2010/11, were 5% (3 010/57 313), 5% (2 881/55 432), 4% (2 004/55 432), 13% (6 799/46 629), 21% (10 021/36 608) and 22% (14 904/28 642), respectively. A marked decline in supply was noted from 2008 (Figure 3.1), which coincided with the implementation of legal restrictions on the sale of OTC PSE and ephedrine containing products.

No significant difference in the number of packs nor weight of PSE supplied was found compared to the previous 12 months for 2005/06, 2006/07 and 2007/08 (all p> 0.05). In 2008/09, the weight of PSE supplied was significantly less than in 2007/08 (p=0.023) although there was no reduction in the number of packs supplied (p=0.388). This coincided with the first 12-month period after the legal policy was introduced. Thereafter, in the last two years of the

study (2009/10 and 2010/11), the supply of PSE in terms of both the number of packs and weight were both significantly less than the previous 12-month period (Table 3.1).

3.3.1.2 Phenylephedrine

Sales of PE containing products and their respective median and IQR for each 12-month period are shown in Table 3.2.

Table 3.2 Total supplies (median, interquartile range) of over-the-counter phenylephrine containing products in Wales for each 12-month period (April to March) between 2004 and 2011. Quantities supplied were compared between two consecutive periods and an asterisk (*) marks any significant difference ($p<0.05$)

	Packs	p-value	Weight (grams)	p-value
2004/05	204 015 (18 230, 15 275)		12 953 (1 121, 1 009)	
2005/06	194 625 (14 805, 15 176)	0.480	13 416 (1 161, 1 305)	0.530
2006/07	158 315 (12 934, 12 004)	0.023*	15 367 (1 229, 1 146)	0.530
2007/08	162 296 (10 607, 15 170)	0.875	15 859 (1 001, 1 535)	0.937
2008/09	172 310 (7 841, 16 037)	0.388	17 040 (764, 1 563)	0.388
2009/10	137 895 (8 117, 13 112)	0.182	13 712 (814, 1 344)	0.272
2010/11	122 991 (5 619, 10 671)	0.182	12 181 (572, 1 061)	0.182

Wilcoxon's signed rank test indicated no significant difference ($p> 0.05$) between any two consecutive 12-month periods from 2004/05 to 20010/11 for the supply of PE containing products. The only exception was in 2006/07 when there was a significant reduction in number of packs sold in comparison to 2005/06 ($p=0.023$).

3.3.2 Prescription supply

The supply of non-systemic nasal decongestants (aromatic inhalation [BNF section 3.8] + topical nasal preparations [BNF section 12.2.2]) and PSE containing nasal decongestants on primary care prescriptions are shown in Figure 3.2.

Figure 3.2 Total 12-monthly items of non-systemic nasal decongestants (aromatic inhalation [BNF section 3.8] + topical nasal preparations [BNF section 12.2.2]) and pseudoephedrine (PSE) containing products supplied on primary care prescriptions in Wales

Overall, the numbers of items of non-systemic nasal decongestants supplied on prescription between 2004 and 2011 remained steady. The volume supplied in each 12-month period fluctuated between 30,000 and 35,000 items. In contrast, PSE containing decongestants reduced by 38% (10,412/27,354) from 27,354 items to 16,942 items over the same period.

In comparison to non-systemic and PSE containing nasal decongestants, supplies of ephedrine and PE containing products on prescription were low. For example, in the final 12 months of the study up to March 2011, there were less than 1% of PSE and non-systemic decongestants supplied on prescription.

Throughout the entire study period, the highest total quantity of ephedrine containing products prescribed and supplied in any 12-month period was 225 items in 2004/05 and 105 items in 2010/11 for PE containing products.

Table 3.3 shows the total supply, median and IQR for non-systemic and PSE-containing decongestants supplied on prescription for each of the 12-month periods between 2004 and 2011.

Table 3.3 Total items (median, interquartile range) of non-systemic (aromatic inhalation [BNF section 3.8] + topical nasal preparations [BNF section 12.2.2]) and pseudoephedrine (PSE) containing nasal decongestants dispensed in Wales for each year (April to March). Supplies were compared to with the previous 12-month period and any significant difference ($p<0.05$) is marked by an asterisk (*)

	Non-systemic decongestants	p-value	PSE	p-value
2004/05	32 311 (2 409, 913)		27 354 (2 221, 685)	
2005/06	32 721 (2 720, 462)	0.875	29 850 (2 293, 1 155)	0.019*
2006/07	30 801 (2 535, 546)	0.060	27 165 (2 302, 483)	0.023*
2007/08	33 909 (2 781, 478)	0.010*	28 177 (2 313, 646)	0.347
2008/09	34 478 (2 846, 360)	0.530	26 453 (2 161, 425)	0.136
2009/10	34 020 (2 781, 414)	0.182	22 467 (1 892, 509)	0.002*
2010/11	33 495 (2 740, 258)	0.347	20 825 (1 672, 424)	0.023*

Year-on-year analysis of non-systemic nasal decongestants indicated there was generally no significant difference ($p>0.05$) in the number of items prescribed between any two 12-month periods except in 2007/08 there was a significant increase ($p=0.010$). For PSE containing decongestants, there was a significant increase in numbers of items supplied compared to the previous year in

2005/06 (p=0.019) whilst there were significant reductions in 2006/07 (p=0.023), 2009/10 (p=0.002) and 2010/11 (p=0.023).

3.4 Discussion

The results from the present study indicate that the total weight of PSE supplied OTC fell significantly in the first 12 months following the introduction of policy restrictions but the overall numbers of packs sold were unaffected. This was not an unexpected outcome as pharmacy retailers and product manufactures were likely to have stopped large pack sizes during that period. Upon closer inspection of the current pharmacy sales data, it was noted products that contained greater than 720mg of PSE were discontinued after April 2008. This suggests the legal restrictions on PSE and ephedrine containing products had an immediate impact on the OTC market.

In contrast, during 2009/10 and 2010/11, the total weight as well as the number of packs of PSE containing products sold, simultaneously declined compared to the previous 12 months. This suggests there was an overall reduction in the number of packs sold from pharmacies. This could have been the result of both legal and non-legal measures that were being promoted at the time. For example, sales of a PSE and ephedrine containing products in the same transaction were no longer permitted without a prescription. Multiple pack purchases were also unlikely as the total quantity of PSE or ephedrine would have exceeded the legal limit. Non-legal measures, including the increased awareness and training among pharmacy staff about the misuse potential of PSE and ephedrine containing products and sales alerts, may have contributed to an increase in the number of refused sales (Anon. 2007i, 2008a; LearnSomething 2007). Furthermore, educational material on how to identify unusual product requests were developed (RPSGB 2008). The increase in staff vigilance may have also prevented inappropriate sales of PSE and ephedrine containing products but could also have deterred legitimate requests.

A decline in the sales of PSE containing products have been reported across the UK following the sales restriction policy. The reported reductions varied from 7% to 26%, year-on-year, between 2009 and 2012 (MHRA 2009c, 2010,

2011a, 2012b). The findings from the current study suggest that OTC sales in Wales followed the same trend and the levels of reduction were comparable to that seen across the UK as whole. A recent report suggested that the UK-wide decline in the sales of PSE containing products reached a plateau in 2012 (MHRA 2012b). Whether or not this has also occurred in Wales is unclear and will require further monitoring.

Attempts to explain the reduction in sales of PSE containing product on the basis that there was a shift to consumers using PE based products appeared not to be the case. The absence of a shift could have been due to the unproven efficacy of PE in relieving nasal congestion symptoms (Horak et al. 2009) or consumers being simply unwilling to use a different preparation to the one they were used to. However, it was possible that sales of other OTC nasal decongestants which were not included in the current study, such as topical preparations, increased and warrants further investigation. The introduction of free prescriptions in Wales in 2007 (Cohen et al. 2010) probably contributed little or no impact on the reduction of PSE sold OTC as items of nasal decongestants supplied on prescription have remained steady throughout the study.

The decline in sales of PSE containing products was not accompanied by an increase in primary care prescribing of nasal decongestants over the same time period. As a consequence, there is no evidence to substantiate the concerns that individuals would seek to obtain a prescription for PSE or ephedrine containing nasal decongestants from their GPs. Consequently, the restrictions to reduce access to PSE and ephedrine containing products OTC in 2008 did not result in additional drug costs to the NHS as some initially suggested (Anon. 2007j, Berg 2007). The present study has shed little light as to what caused the decline in the prescribing of PSE containing nasal decongestants during the study period. It is possible this was due to a general increase in awareness among GP prescribers regarding illicit manufacturing of methylemphetamine from PSE or ephedrine containing products (Anon. 2007k).

There were two other changes to the sales of OTC products containing nasal decongestants during the study which could also have influenced the results. The first change was in March 2008 when the MHRA announced OTC cough and cold preparations containing PSE or PE should no longer be used in children younger than two years old (Anon. 2008b; MHRA 2008d). The second was in February 2009 when the MHRA extended this recommendation to include children under six years of age, and advised the use of PSE and ephedrine decongestants to be reserved as second-line treatment for children aged between six and twelve years (Anon. 2009d; MHRA 2009d). On reviewing the products included in the current study, several of them would have been affected by these announcements, including Benylin 4 Flu tablet and liquid, Day Nurse capsule and liquid, Lemsip Sinus capsule and Sudafed Non-Drowsy tablet. The current study was, however, unable to identify what proportion of the OTC sales were related to paediatric use and therefore the influence of this updated practice guidance on sales is unknown.

3.4.1 Study Limitations

3.4.1.1 Ecological study

The pharmacy sales data used in the current study were useful for quantifying the supply trends but were unable to provide an explanation for the changes observed. A qualitative study exploring the views of consumers' and the pharmacy staffs' may have helped to identify the factors responsible for the changes and would aid future regulatory decisions.

The appropriateness of OTC sales and prescription supplies of the nasal decongestants under study could not be determined from the work undertaken. In order to investigate whether pharmacists and their staff were making legal and clinically appropriate supplies of nasal decongestants OTC would require an observational study with a pre-determined assessment criteria for the OTC sales of nasal decongestants.

3.4.1.2 Prescription data

The prescription data obtained from the NHS prescription database were comprehensive and are routinely used to study patterns of prescribed medicines in primary care. However, the current study only included prescriptions that are written by GPs and excluded those written by non-medical prescribers, such as independent nurse or pharmacist prescribers (discussed in detail in Section 4.4.2.2). As a result, the prescription figures reported in the present study were probably underestimates of the actual prescribing figure.

Unlike the OTC sales data, which were presented as the total number of packs and weight of active ingredients sold, the unit of measure used for the prescription data was the number of prescription items supplied. Given that GP prescribers could have requested more than one pack of nasal decongestants to be supplied to a patient per item, a direct comparison between quantities of medicine sold OTC and those supplied on prescription in those units of measure could have been problematic. However, this was not considered a major issue for the current study because the purpose of the prescription data was to detect a shift in the use of nasal decongestants following introduction of the legal policy rather than for it to be directly compared with OTC supply.

3.4.1.2 Pharmacy wholesale data

Pharmacy wholesale data were obtained from the RSA database and represented the sales of medicines from pharmaceutical wholesalers to 87% (614/708) of all NHS-contracted community pharmacies in Wales. As a result of the missing data for the remaining 13% of community pharmacies, wholesale figures reported in the current study are probably underestimates of the actual supply picture. Details relating to the coverage and accuracy of the RSA dataset are discussed in Sections 2.4.2.2 and 4.4.2.4, respectively.

One important assumption about using pharmacy sell-in data as a proxy for actual pharmacy-to-patient sales was that a pharmacy would have sold most, if not all, of the stock it had purchased within a four-week period. The approach of using pharmacy sell-in data as a marker of sales has been adopted by other

studies in the UK investigating medicine utilisation in the primary care setting (Cohen et al. 2010; Davis et al. 2009; Dhippayom and Walker 2006).

In contrast to pharmacy-to-patient sales data, one notable confounder for sell-in data is its vulnerability to factors unrelated to actual customer demand. For example, the timing of stock purchase could have been skewed by promotional activities by the manufactures or bulk-buying discount offered at a particular time of the year. Advance purchase in anticipation of demand, particularly for seasonal items such as to cold and flu products, was also possible. While these scenarios might have been the case for the products monitored in the present study, the sales figures were quantified in a 12-monthly format and therefore any seasonal variations would have been accounted for in the analysis.

There has been one report of the illegal production of methylamphetamine in the UK using PSE containing nasal decongestants bought over the internet (MHRA 2011a). The supplies of these products obtained via the online route were raised as a concern at the time of reclassification in 2007 (Anon. 2007l). Pharmacy wholesales data utilised in the current study only included data for pharmacies located in Wales. Therefore, it is possible that supplies for products monitored in the current study could also have been obtained from online pharmacies located elsewhere in the UK or overseas. Given the recognised potential of growth and the indication that pharmacy users are increasingly turning to internet pharmacies to purchase medicines (Bloodworth 2012), the online retail sector could account for a significant proportion of OTC sales in the future and this needs to be investigated further.

3.4.1.3 Medicines studied

During the six-year study period wholesale data for 25 and 66 proprietary OTC products containing PSE and PE, respectively, were obtained. Whilst this data had included many leading brands of OTC nasal decongestants sold in the UK, not all of the products on the market were included in the study.

An analysis of proprietary PSE and PE containing products available OTC in the UK between 2004 and 2010 showed product coverage in the current study

was 40% (25/65) for PSE and 84% (66/79) for PE containing products (Chemist and Druggist: Monthly Pricelist May 2004, April 2006, April 2008, April 2010 issue). As a result, the sales figures reported are likely to be underestimates of the actual supply in Wales.

Another notable omission for the current study was that sales data for ephedrine containing products were not available in the RSA database. Consequently, these preparations were not investigated. Other nasal decongestants that could have been bought OTC, such as topical sympathomimetics, inhalation-based products or own-brand (generic) products, were also not monitored in the present study. These sales data potentially hold explanations for the decline in the sales of PSE containing decongestants. Future studies should utilise data with a more comprehensive coverage of products to ensure a full overview of the OTC market is possible. Other potential confounding issues related to Medicine Counter Assistant (MCA) training and sales protocol have been discussed in Section 2.4.2.5.

3.5 Summary

In the three-year period following the introduction of legal restrictions on the sales of PSE and ephedrine containing products in the UK, the supply of OTC PSE based products in Wales have significantly reduced. The magnitude of the reductions were consistent with those observed for the UK as a whole, providing reassurance that the legal measures introduced in 2008 have had the desired impact in Wales. Furthermore, the reduction in OTC sales of PSE containing products was not accompanied by an increase in GP prescribing of nasal decongestants on primary care prescriptions. This suggests that concerns related to the increase in GP workload and primary care prescribing that would adversely impact the NHS drugs bills have not materialised.

Chapter 4:

Reclassification of ophthalmic chloramphenicol

Reclassification of ophthalmic chloramphenicol

4.1 Introduction

4.1.1 Reclassification of medicines

The practice of self-medication using over-the-counter (OTC) medicines is an important element of self-care and is often the starting point for individuals to maintain and/or improve their health status (Yiangou 2011). In order for patients to undertake appropriate self-medication, medicines need to be accessible without the need of a prescription. Whilst the policy regarding availability of OTC medicines varies from country to country (Blenkinsopp and Bond 2005), in the United Kingdom (UK), medicines which are classified as Pharmacy (P) medicines are available for sale from pharmacies only and those classified as General Sales List (GSL) medicines can be purchased from general retail outlets by self-selection (Human Medicines Regulations 2012). Medicines under both the P and GSL categories are free from prescription control, whereas Prescription-Only Medicines (POM) can only be obtained on a prescription.

As mentioned in Chapter 1 (Section 1.3), the range of medicines available OTC could be expanded through medicine reclassification (MHRA 2012a). This involves a medicine being 'switched' from POM to P status or from P to GSL status. Among the drivers for a wider range of OTC medicines are patients' desire for greater autonomy and choices of medicines (Brass et al. 2009; Hanna and Hughes 2011), pharmacists' wish to extend their clinical role in the care of their patients (Bellingham 2002; Tasker et al. 2008; Weidmann et al. 2011), desire for greater profits by the pharmaceutical industry (Blenkinsopp 2004; Bond 2001) and government's need to reduce drug spending by the National Health Service (NHS) (Blenkinsopp and Bradley 1996; Bond and Hannaford 2003; Brass et al. 2009). The decision to reclassify a medicine and making it more widely available depends on the balance of risks and benefits associated with the increased access of the drug in question (Table 4.1). This assessment of risks versus benefits is undertaken by the

Medicines and Healthcare Products Regulatory Agency (MHRA), which is the medicine regulator in the UK (MHRA 2012a).

Table 4.1 Considerations of risks and benefits associated with making a medicine available without a prescription (Source: Brass et al. 2009)

Risk considerations	Benefit considerations
Unintended misuse	Improved access to effective drugs
Intentional misuse with therapeutic intent	Improved clinical outcomes
Accidental ingestion	Improved public health
Intentional overdose	Enhanced involvement by consumers in their health care
Worsened outcomes due to self-management	Economical benefits of non-prescription availability

There have been many successful POM to P switches in the last decade (Proprietary Association of Great Britain [PAGB] 2011a). These reclassification initiatives were supported by the publication of several health strategies by the Department of Health (DH), which pledged to improve public's access to non-prescription medicines by increasing the range of treatment available from pharmacies and the number of reclassified medicines each year (DH 2000, 2003a, 2003b, 2005, 2008). This commitment by the UK government was recently reiterated in a plan to reduce the processing time of reclassification applications in order to maintain a steady stream of newly reclassified medicines (Anon. 2012b, 2012c).

By making more medicines available OTC, the government hope it would allow individuals to engage better in practicing self-care, make better utilisation of pharmacists' clinical skills, knowledge and resources, and reduce the number of minor ailments seen by doctors in order to free up their time for patients with more serious health problems (Blenkinsopp and Bond 2005).

However, it should noted that these potential benefits associated with medicine reclassification are not routinely evaluated. As a consequence, whether or not many of the reclassified medicines in the UK have had the desired, positive impact on patients' health and the wider healthcare system are not always clear.

In 2002, Royal Pharmaceutical Society of Great Britain (RPSGB), the then professional body and regulator of pharmacists in the UK, published a long list of potential candidates for POM to P switches to support government's reclassification policy (RPSGB 2002). The therapeutic class of medicines proposed for reclassification was wide ranging, covering both minor ailments such as dyspepsia and chronic conditions such as hypertension. Over the years, many of the medicines suggested for deregulation at the time have since became available OTC in the UK (PAGB 2011a).

Whilst the reclassification effort has traditionally focused on medicines used in minor and self-limiting conditions, medicines for long-term use, such as simvastatin for the primary prevention of cardiovascular event (RPSGB 2004), and diseases normally managed by general practitioners (GPs), such as tamsulosin for the symptom of benign prostatic hyperplasia, have also been reclassified (PAGB 2012). This emerging trend of reclassification for medicines used in chronic diseases is in line with the strategic intent of the UK government, which was to enable patients to practice self-medication for even long-term conditions (DH 2008).

The present study examined one particular medicine that was the first of its therapeutic class to become reclassified from POM to P status in the UK and it is discussed in the next section.

4.1.2 Ophthalmic chloramphenicol and reclassification

Chloramphenicol is a broad-spectrum antibiotic that is effective against a large number of gram-positive and gram-negative bacteria (Sweetman 2007). Use of chloramphenicol via the systemic route is limited due to the potential of a rare but serious side effect relating to bone marrow toxicity (Dameshek 1952;

Sweetman 2007). Consequently, indiscriminate use of chloramphenicol in minor infections is discouraged (Havener 1994). Nonetheless, chloramphenicol remains to be a potential treatment for life threatening infections such as typhoid fever or bacterial meningitis (British National Formulary [BNF] 2013; Sweetman 2007).

As a topical preparation, ophthalmic chloramphenicol are widely used because of their broad antibacterial action against common ocular pathogens (Chalita et al. 2004). In comparison to other topical antibacterials, chloramphenicol possesses the highest overall efficacy among ciprofloxacin, ofloxacin, norfloxacin, bacitracin, tetracycline, neomycin, erythromycin, tobramycin and gentamicin against ocular bacteria obtained from clinically symptomatic eyes (Egger et al. 2001). Due to their superior bactericidal activity, the BNF has been and continues to recommend ophthalmic chloramphenicol as the antibiotic of choice for superficial eye infections, such as bacterial conjunctivitis (BNF 2013). In England, prescription statistic indicates that two-thirds of all prescriptions for ocular antibiotics were for ophthalmic chloramphenicol (Sheikh and Hurwitz 2001).

In the UK, ophthalmic chloramphenicol in an eye drops formulation was first reclassified from POM to P status in June 2005. Optrex Infected Eyes® was the first proprietary product to be sold on the OTC market. The ointment formulation was subsequently reclassified in July 2007 and was available under a number of different brands (Brochlor®, Galpharm Vision® and Optrex Infected Eyes®). The licensed indication of OTC ophthalmic chloramphenicol was for the treatment of acute bacterial conjunctivitis in adults and children over two years of age. It was the first antibiotic to receive non-prescription status in the UK albeit for ophthalmic use only (Adcock 2005).

Infective conjunctivitis is the most common eye infection encountered in primary care in the UK accounting for up to 40% of all eye related GP consultations (McDonnell 1988; Sheldrick et al. 1993). Before ophthalmic chloramphenicol was available OTC, pharmacists had few non-prescription medicines available to them to manage patients with minor eye infections

(Hardy et al. 1993a). At the time, preparations containing propamidine (Brolene® eye drops) or dibrompropamidine (Golden Eye® ointment) were the only topical antibacterials that could be sold without a prescription. Although these products have frequently been used in managing patients with non-urgent ocular infections in a pharmacy setting (Hardy et al. 1993a; Seston et al. 2001), the lack of evidence for their effectiveness (BNF 2013) was a concern for many pharmacists (Hardy et al. 1993a). As a consequence, the majority of patients with infective conjunctivitis were referred to their GPs instead (Seston et al. 2001). It was found that most of these primary care cases of suspected infective conjunctivitis were managed by a prescription for ophthalmic chloramphenicol (Sheldrick et al. 1993). The inability to counter-prescribe ophthalmic chloramphenicol was a major frustration for many pharmacists and, unsurprisingly, it was one of the most frequently suggested candidates for medicine reclassification (Bond et al. 1993).

Following a wide spread public consultation in 2004 (MHRA 2004), the proposal to make ophthalmic chloramphenicol available OTC as P medicine was welcomed by various representatives of healthcare professionals, including nurses, GPs and ophthalmologists (MHRA 2005b). At the time, it was thought the benefit of timely access to effective treatment outweighed the risks associated with wider availability, such as antibiotic resistance (Brennan 2005), potential of misdiagnosis (Rumney 2005) and unnecessary medicalisation of what is, in most patients, a self-limiting condition (Tuft 2005). The theoretical risk of bone marrow toxicity associated with the use of topical chloramphenicol was also considered during the consultation process (MHRA 2004). However, evidence from large national and international case-controlled studies suggested the risk were extremely low (Lancaster et al. 1998; Laporte et al. 1998; Wiholm et al. 1998).

4.1.3 Recent findings

Since the launch of OTC ophthalmic chloramphenicol two important issues have emerged. First, there is an increasing body of evidence that suggests topical antibiotics are of limited benefit in patients with acute infective conjunctivitis (Everett et al. 2006; Jefferies et al. 2011; Rose et al. 2005; Rose

2007). As a result of these findings, the latest recommended strategy for managing infective conjunctivitis has changed from empirical prescribing to advise patients to practice simple self-care measures, such as hand washing, regular cleansing and lubrication of the eyes (National Institute for Health and Care Excellence [NICE] 2012b). An alternative approach involving 'no or delayed antibiotic' has also been suggested (Drugs and Therapeutics Bulletin [DTB] 2011). Adopting these management strategies is associated with the added benefit of minimising the risks of promoting bacterial resistance and reducing unnecessary medicalisation of patients (Everett et al. 2006). Findings from a recent study suggest these two updated advice for the management of infective conjunctivitis may have reduced the prescribing of ophthalmic chloramphenicol by GPs in England (Davis et al. 2009). However, whether or not these evidences had the same impact on the sales and supply of OTC ophthalmic chloramphenicol from pharmacies is unclear.

Secondly, a substantial increase in primary care supply of ophthalmic chloramphenicol three years after the reclassification has been observed in Wales (Walker and Hinchliffe 2009, 2010). In England, pharmacy sales data for ophthalmic chloramphenicol also demonstrated a marked increase in OTC supply during the first two years following reclassification (Davis et al. 2009). This increase in total overall use could not be explained by a shift in sale to another OTC product or by a change in how antibiotics were prescribed by GPs (Walker and Hinchliffe 2009). As a result, concerns have been raised regarding pharmacists over supplying OTC ophthalmic chloramphenicol (Behjat-Amery 2012) and whether or not they were aware of the latest practice recommendations (Davies et al. 2009). It may be argued that the increased sales of OTC ophthalmic chloramphenicol during the early years after reclassification was due to the launch a new product and is a reflection of normal market growth. However, whether or not the increasing sales trend has continued five years after its OTC availability is not known.

4.1.4 Aims

The aim of the current study was to (a) determine the quantity of ophthalmic chloramphenicol supplied OTC from community pharmacies in Wales and (b) examine the impact of OTC availability on primary care prescriptions five years after reclassification. The temporal relationship between ophthalmic chloramphenicol supplied OTC and on primary care prescriptions was also examined to explore whether their supplies occurred at the same time.

4.2 Method

4.2.1 Study design

The study had an ecological design (Schoenbach and Rosamond 2000) and involved a retrospective analysis of pharmacy wholesale data, retail data from a multiple chain pharmacy and primary care prescription data for ophthalmic chloramphenicol preparations in Wales.

4.2.2 Data

The data utilised in the present study were obtained from three different sources as outlined below:

4.2.2.1 Primary care prescription data

Prescribing data for Wales was obtained from the NHS Wales prescription database and was the same prescription data as utilised in the Chapter 2 (Section 2.2.2.1). In the present study, data were extracted as the number of items prescribed in a monthly format for each of the 22 Local Health Boards (LHBs) in Wales for the period between June 2004 and December 2010 (79 months).

4.2.2.2 Pharmacy wholesale data

Pharmacy wholesale (or buy-in) data were extracted from the Regional Sales Analysis (RSA) database and this was the same pharmacy sales database as utilised in Chapter 2 (Section 2.2.2.2). The RSA database contained sales information of medicines from wholesalers to pharmacies rather than actual point of sales data. In the present study, the pharmacy wholesale data were

extracted in a monthly format for the period June 2005 to December 2010 (66 months) for each of the 22 LHBs in Wales. The amalgamation of the 22 to seven new LHBs in Wales in October 2009 has been described elsewhere in this thesis (Section 2.2.2.2).

4.2.2.3 Pharmacy retail data

Company A was a national, multiple-chain pharmacy in the UK which did not contribute data to the RSA database. Under an arrangement with Public Health Wales (PHW) and the Welsh Government, pharmacy retail data for the 94 community pharmacies owned by Company A in Wales were obtained for the period between January 2008 and December 2010. This dataset represented actual pharmacy-to-patient sales data and complemented the missing portion of the pharmacy wholesale data in the RSA database. Sales figures for chloramphenicol eye drops, between June 2005 and December 2007, and eye ointment, between July and December 2007, were not available. Sales during these periods were estimated using linear regression as described in Section 4.2.4.

The data obtained from Company A included the weekly number of items sold from each of their pharmacies together with postcode information. Each of Company A's pharmacies was allocated to their corresponding LHBs using a list of pharmacy contractor's in Wales provided by PHW (personal communication). The weekly retail figures were aggregated into their corresponding month to conform to the format of pharmacy wholesale data which was available on a monthly basis.

4.2.3 Medicines studied

4.2.3.1 Prescription medicines

All ophthalmic chloramphenicol preparations listed under section 11.3.1 (Anti-bacterial eye preparations) of the BNF 65 (2013) were included in the present study. A manual search of the NHS prescription database was also undertaken by the researcher to identify any other ophthalmic preparations that contained

chloramphenicol. A list of product included in the analysis is shown in Appendix 14.

4.2.3.2 Over-the-Counter medicines

Chemist and Druggist: Monthly Pricelist (June 2011 issue) was used to identify all available proprietary ophthalmic chloramphenicol preparations sold OTC in the UK. A list of all available OTC products can be found in Appendix 15. At the time of the study, OTC ophthalmic chloramphenicol was only available as a P and not as a GSL medicine.

After the identification of all available products in the UK a manual search of the RSA database was undertaken and matching preparations found in the RSA database were included in the present analysis. Preparations listed in the RSA database by their generic name, such as chloramphenicol 0.5% eye drops, were excluded from the analysis. This was due to the uncertainty as to whether such product was sold OTC or used to dispense a prescription. A list of the ophthalmic chloramphenicol preparations extracted from the RSA database is shown in Appendix 16.

Pharmacy retail data supplied by Company A included every brand (including own-brand) of ophthalmic chloramphenicol preparations sold from its pharmacies and were included in the analysis. A list of all preparations sold from Company A's pharmacy is shown in Appendix 17.

4.2.4 Estimation of Over-the-Counter supply

The sales of ophthalmic chloramphenicol from Company A, between June 2005 and December 2007 for eye drops (30 months) and July and December 2007 for eye ointment (6 months), were estimated using linear regression. The line of best fit generated from the linear regression model was extrapolated backwards based on cumulative sales between January 2008 and December 2010 from Company A. The availability of data for the eye drops and the eye ointment are illustrated in Table 4.2 and Table 4.3, respectively.

Table 4.2 Availability of prescription, pharmacy wholesale and Company A retail data for over-the-counter chloramphenicol eye drops. Sales from Company A's pharmacy between June 2005 and December 2007 were estimates (shaded grey) calculated from the available data between January 2008 and December 2010. Check mark (✓) indicates a complete set of data for the corresponding period. Asterisk (*) marks the first 12-month period post-reclassification of the eye drops formulation

	Prescription	Pharmacy wholesale	Company A retail
2004/05	✓		
2005/06*	✓	✓	Estimates
2006/07	✓	✓	
2007/08	✓	✓	
2008/09	✓	✓	✓
2009/10	✓	✓	✓

Table 4.3 Availability of prescription, pharmacy wholesale and Company A retail data for over-the-counter chloramphenicol eye ointment. Sales from Company A's pharmacy between July and December 2007 were estimates (shaded grey) calculated from the available data between January 2008 and December 2010. Check mark (✓) indicates a complete set of data for the corresponding period. Asterisk (*) marks the first 12-month period post-reclassification of the ointment formulation

	Prescription	Pharmacy wholesale	Company A retail
2004/05	✓		
2005/06	✓		
2006/07	✓		
2007/08*	✓	✓	Estimates
2008/09	✓	✓	✓
2009/10	✓	✓	✓

The linear regression model was defined by the equation:

$$Y_i = b_0 + b_1 X_i$$

where Y_i was the estimated cumulative sales each month; X_i was the number of months after reclassification of eye drops or ointment (June 2005 and July 2007 are denoted as month 1, respectively) and b1 and b0 represented the gradient and y-axis intercept for the line of best fit, respectively. The coefficient of determination (R^2) was reported to indicate the goodness of fit for the model together with the corresponding p-value. The linear relationship between cumulative sales of OTC ophthalmic chloramphenicol from Company A and number of months after reclassification was verified using the available pharmacy wholesale data. This involved estimating the cumulative wholesale figures for the eye drops, between June 2005 and December 2007, and the eye ointment, between July and December 2010, based on available wholesale data between January 2008 and December 2010, and comparing the estimated to the actual observed cumulative sales.

To calculate the total quantity of OTC ophthalmic chloramphenicol sold in Wales, the estimated sales during the data-missing period and actual sales from Company A were combined with the pharmacy wholesale figures.

4.2.5 Data processing and organisation

The data utilised in the present study were obtained from multiple sources and it was necessary for them to be processed and organised into a suitable format before statistical analysis could be undertaken. These processes are described below.

Prescription and pharmacy wholesale data were manually transferred from their respective database into Microsoft Excel spreadsheet as illustrated in Appendix 8 and Appendix 9, respectively. Retail data for Company A were supplied already in a Microsoft Excel spreadsheet. Once all the data were in Microsoft Excel spreadsheet they were organised into a number of 12-month blocks to allow comparison before and after the reclassification. The 12-month

period for the supply of eye drops were defined as between June and May and the ointment between July and June.

There were six 12-month blocks for both eye drops and ointment supplied on prescription (2004/05 to 2009/10); five 12-month blocks for eye drops sold OTC (2005/06 to 2009/10) and three 12-month blocks for ointment sold OTC (2007/08 to 2009/10). All processed and reorganised data were manually screened for errors before transferring to the statistical software for analysis (PASW v18).

4.2.6 Analysis

4.2.6.1 Descriptive analysis

The supplies of OTC and prescription ophthalmic chloramphenicol were expressed as the total number of packs sold and total number of items dispensed, respectively. For each of the 12-month periods, the total supply was reported together with the median and the interquartile range (IQR) for the component month. Box-plots were used to visualise the distribution of the data and an example is shown in Figure 4.1.

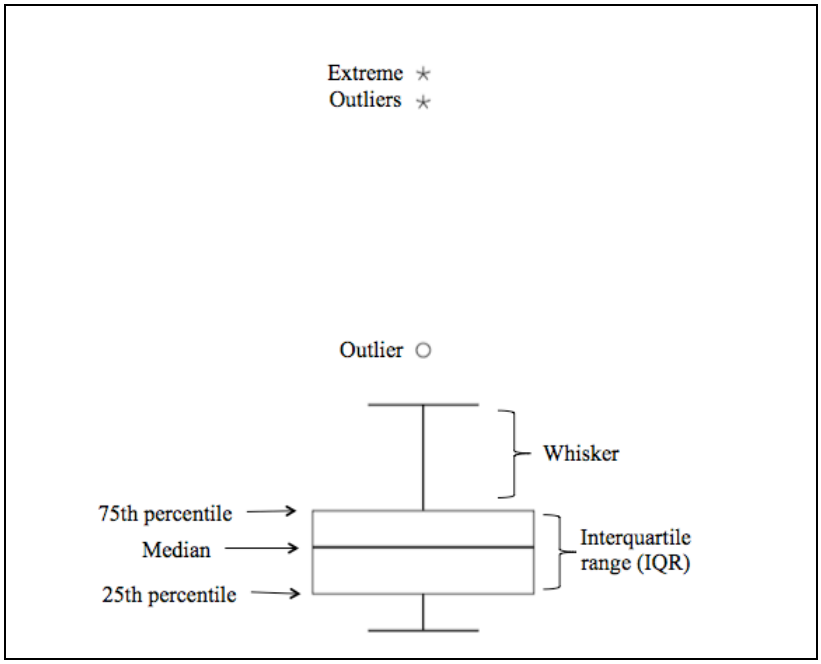


Figure 4.1 An example demonstrating the components of a boxplot

The line across the inside of the box indicated the median value of the data. Upper and bottom edge of the box indicated the 75th and 25th percentile of the data and the range between the two edges represented the IQR. The ends of the vertical lines (whiskers) extended to 1.5 times the height of the box or, if no value was within that range, to the minimum and maximum values of the data. Values that were beyond the upper and lower quartile by one and a half IQRs were classified as outliers, indicated by circles. And if values were more than three IQRs away, they were classified as extreme outliers, indicated by asterisks.

4.2.6.2 Impact of reclassification

The impact of reclassification of ophthalmic chloramphenicol on GP prescribing was explored using Wilcoxon's sign rank test by comparing the quantities supplied on prescription during the 12-month period before reclassification with those after the reclassification. For the eye drops, quantities supplied in 2004/05 were compared to those in 2005/06, 2006/07, 2007/08, 2008/09 and 2009/10. For the eye ointment, quantities supplied in each of the three 12-month periods before reclassification (2004/05, 2005/06, 2006/07) was compared to those supplied in the 12-month periods after (2007/08, 2008/09, 2009/10).

4.2.6.3 Association between Over-the-Counter and prescription supply

Correlation between quantity supplied on prescription and sold OTC for ophthalmic chloramphenicol was examined using Pearson's product-moment correlation. Calculations were based on actual prescribing and pharmacy sales data for ophthalmic chloramphenicol between January 2008 and December 2010 (36 months).

All data analysis and statistics were performed using PASW version 18 (PASW Inc., Chicago, IL, USA). A p-value < 0.05 was considered to be statistically significant.

4.3 Results

4.3.1 Estimation of Over-the-Counter sales from Company A

The linear regression model generated cumulative sales equations for the eye drops ($R^2 = 0.998$, $P < 0.0001$) and the eye ointment ($R^2 = 0.995$, $P < 0.0001$) sold by Company A and estimated the cumulative sales for the respective periods when no retail data was available. The linear equation used to model the cumulative sales of the eye drops was:

$$Y_i = -34526 + 1135 \text{ (month[s] after reclassification of the eye drops)}$$

And the linear equation used to model the cumulative sales of the eye ointment was:

$$Y_i = -3731 + 482 \text{ (month[s] after reclassification of the eye ointment)}$$

Based on the linear equations, the estimated total sale for the eye drops from Company A was 35,185 packs between June 2005 and December 2007. The estimated total sale for the eye ointments was 2,892 packs between July and December 2007. The total cumulative sales of ophthalmic chloramphenicol OTC in Wales (pharmacy wholesale + Company A [actual and estimated OTC sales]) are shown in Figure 4.2.

Validation of the linear regression model using the pharmacy wholesale data indicated that the estimated cumulative sale for the eye drops ($R^2 = 0.998$, $p < 0.0001$) between June 2004 and December 2007 was 102,694 packs. This equates to a 4% (4,184/102,694 packs) overestimation of the actual cumulative sales during the corresponding period. Estimated cumulative sale for the eye ointment ($R^2 = 0.995$, $p < 0.0001$) between July and December 2007 was 12,312 packs and was 13% (1,441/10,871) more than the actual cumulative wholesale supply during the corresponding period.

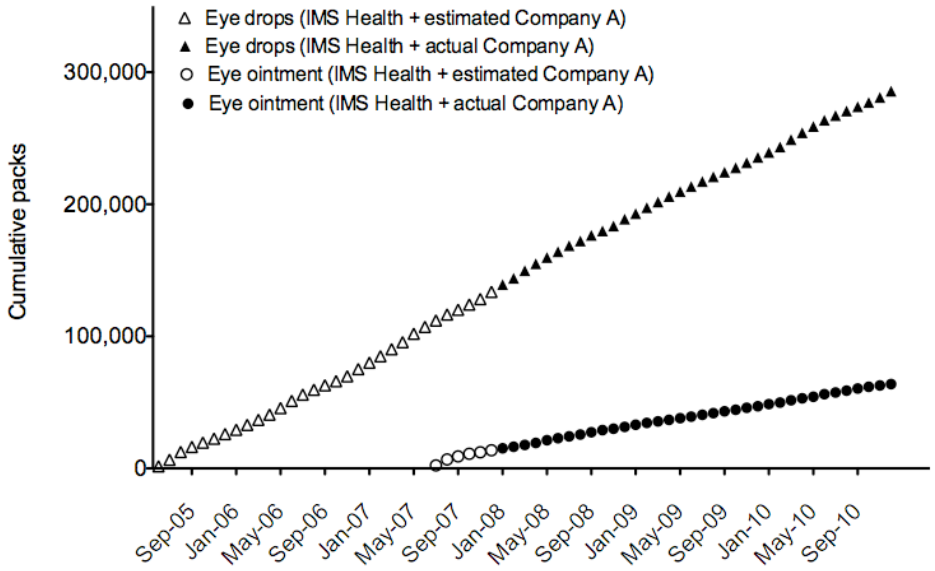
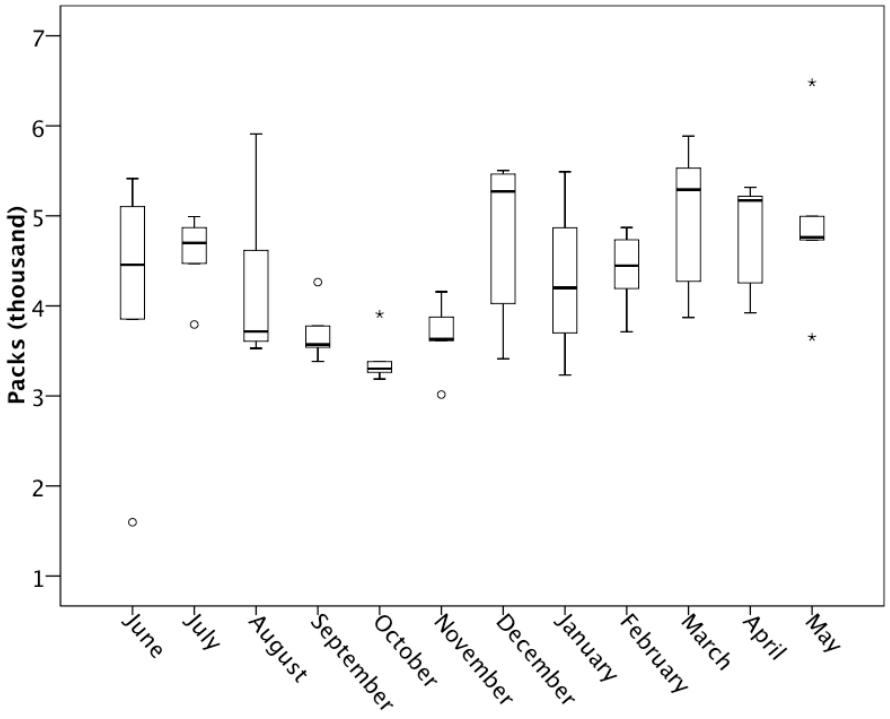


Figure 4.2 Cumulative sales of over-the-counter chloramphenicol eye drops and eye ointment in Wales between June 2005 and December 2010. Data including estimated sales from Company A are indicated by (△) for the eye drops and (○) for the eye ointment. Solid-filled symbols (▲) and (●) represent actual sales data

4.3.2 Over-the-Counter ophthalmic chloramphenicol

Over the six-year study period, sales of OTC chloramphenicol eye drops demonstrated a marked seasonal variation with the highest number of packs sold (median, IQR) in March (5291, 1258) and the lowest in October (3303, 119). In contrast, sales of the ointment formulation between 2007/08 and 2009/10 revealed no discernible trend (Figure 4.3)

a)



b)

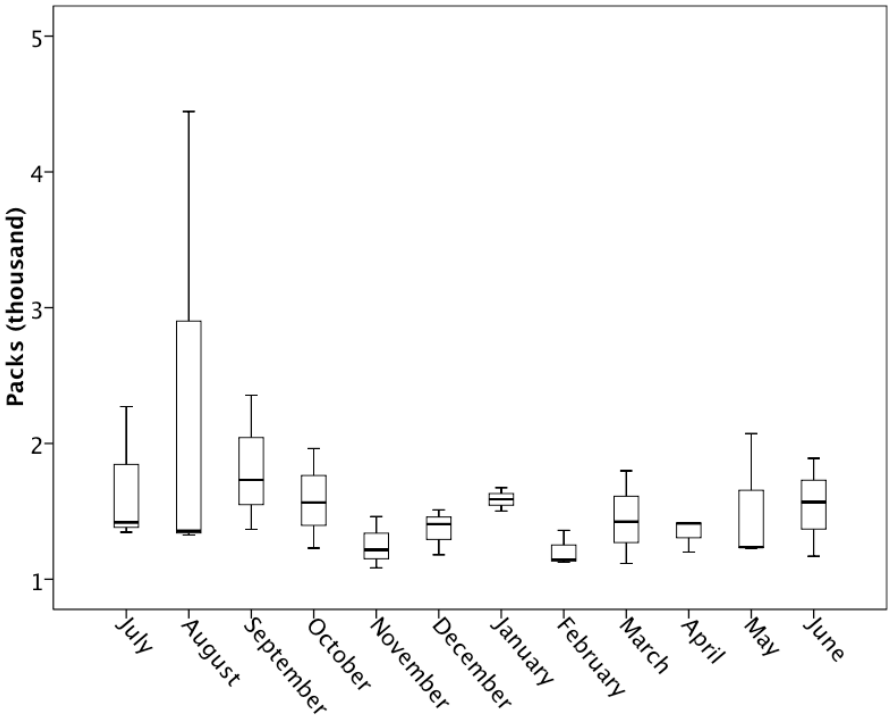


Figure 4.3 Boxplot showing the median and the interquartile range (IQR) for each of the month for ophthalmic chloramphenicol (a) eye drops and (b) eye ointment sold in Wales between June 2005 to May 2010 and July 2007 to June 2010, respectively. Circles (○) and asterisks (∗) indicate outliers and extreme outliers, respectively

Quantities of OTC ophthalmic chloramphenicol sold each month, their cumulative total for each 12-month period together with the median and IQR for the component month are shown in Table 4.4 and Table 4.5.

Table 4.4 Sales of over-the-counter chloramphenicol eye drops in number of packs sold for Wales (IQR = interquartile range)

	2005/06	2006/07	2007/08	2008/09	2009/10	Median (IQR)
June	1 597	5 413	5 103	4 457	3 854	4 457 (1249)
July	4 991	4 700	4 869	4 472	3 793	4 700 (397)
August	5 909	3 716	4 617	3 608	3 529	3 716 (1009)
September	3 777	3 383	3 539	4 264	3 571	3 571 (238)
October	3 262	3 188	3 908	3 381	3 303	3 303 (119)
November	3 015	3 613	4 156	3 633	3 875	3 633 (262)
December	3 412	5 464	5 504	5 271	4 026	5 271 (1438)
January	3 232	4 867	5 489	4 201	3 700	4 201 (1 167)
February	3 712	4 871	4 734	4 447	4 192	4 447 (542)
March	3 871	5 291	5 886	4 272	5 530	5 291 (1 258)
April	3 923	5 317	5 170	4 256	5 218	5 170 (962)
May	4 995	6 480	4 733	3 652	4 763	4 763 (262)
Total	45 696	56 303	57 708	49 914	49 354	
Median	3 745	4 869	4 802	4 260	3 865	
IQR	936	1651	748	802	667	

Table 4.5 Sales of over-the-counter chloramphenicol eye ointment in number of packs sold for Wales (IQR = interquartile range)

	2007/08	2008/09	2009/10	Median (IQR)
July	2 272	1 419	1 346	1 419 (463)
August	4 445	1 357	1 326	1 357 (1 560)
September	2 355	1 732	1 367	1 732 (494)
October	1 963	1 565	1 229	1 565 (367)
November	1 217	1 084	1 462	1 217 (189)
December	1 511	1 406	1 180	1 406 (166)
January	1 502	1 674	1 589	1 589 (86)
February	1 127	1 360	1 144	1 144 (117)
March	1 424	1 116	1 798	1 424 (341)
April	1 418	1 200	1 411	1 411 (109)
May	2 073	1 229	1 237	1 237 (422)
June	1 568	1 170	1 891	1 568 (361)
Total	22 875	16 312	16 980	
Median	1 540	1 359	1 357	
IQR	700.3	263	258.8	

The sales of chloramphenicol eye drops demonstrated a 21% (12,012/57,708) increase from 45,696 packs in 2005/06 to a peak of 57,708 packs in 2007/08. This was followed by a statistically significant reduction to 49,914 packs in 2008/09 ($p=0.012$) and a further reduction to 49,315 packs in 2009/10 ($p>0.05$). The sales of the ointment were highest in 2007/08, which coincided with the 12-month period immediately after becoming available OTC, at a total of 22,875 packs. During the second 12-month period post-reclassification, sales declined significantly by 29% (6,563/22,875) to 16,312 packs in 2008/09 ($p=0.015$) and thereafter remained steady in 2009/10.

4.3.3 Prescription ophthalmic chloramphenicol

Similar to preparations sold OTC, a marked seasonal pattern was also observed for chloramphenicol eye drops supplied on prescriptions during the study. The month of highest supply (medians, IQR) was March (8,470, 861) and lowest was August (5,637, 353). The supply of ointment on prescription demonstrated no discernible seasonal pattern over the study period (Figure 4.4).

The monthly items of chloramphenicol eye drops and ointment supplied on prescription in Wales, their 12-monthly totals, median and IQR for the component month are shown in Table 4.6 and Table 4.7, respectively.

The quantity of chloramphenicol eye drops supplied on prescription was the highest in 2004/05 (86,916 items), the 12-month period immediately before the reclassification of ophthalmic chloramphenicol eye drops. In the 12 months immediately after (2005/06), a significant reduction ($p=0.015$) in items prescribed was observed compared to the previous year (80,844 items) and further reduced ($p>0.05$) in 2006/07 (78,308 items). This declining trend reversed in 2007/08 with a significant increase in items prescribed ($p=0.010$) compared to the previous 12 months; back to the level comparable to that seen prior to reclassification (84,305 items). Thereafter, the year-on-year supply on prescription remained steady for 2008/09 ($p=0.638$) and 2009/10 ($p=0.530$).

For the eye ointment, the quantities prescribed followed a decreasing trend from 2004/05 (57,516 items) to 2007/08 (47,192 items). Reductions were statistically significant in 2005/06 ($p=0.023$) and 2007/08 ($p=0.002$) compared to the previous 12 months. A significant increase in ointment prescribed was observed in 2008/09 ($p=0.028$).

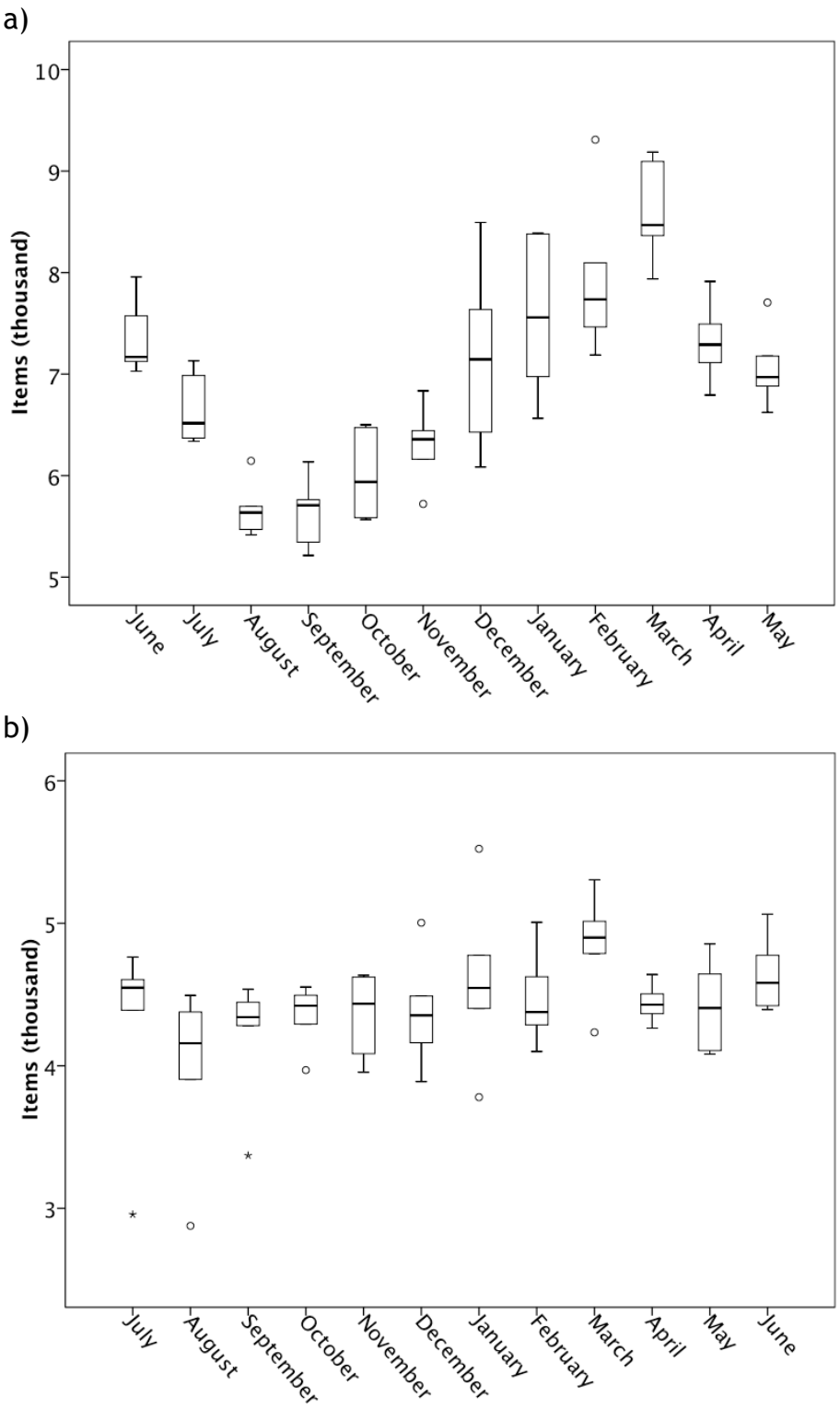


Figure 4.4 Boxplot showing the median and the interquartile range (IQR) for each of the month for ophthalmic chloramphenicol (a) eye drops and (b) eye ointment prescribed in Wales between 2004 and 2010, respectively. Circles (○) and asterisks (∗) indicate outliers and extreme outliers, respectively

Table 4.6 Number of items of chloramphenicol eye drops supplied on primary care prescriptions in Wales and their respective 12-monthly totals together with median and interquartile range (IQR) for the component month

	2004/05	2005/06	2006/07	2007/08	2008/09	2009/10	Median (IQR)
June	7 180	7 958	7 029	7 126	7 157	7 574	7 169 (342)
July	6 480	6 338	6 369	6 986	6 553	7 131	6 517 (481)
August	5 696	5 697	5 577	6 145	5 416	5 470	5 637 (200)
September	5 763	5 685	5 214	5 344	6 135	5 731	5 708 (326)
October	5 727	5 568	5 586	6 500	6 473	6 148	5 938 (771)
November	6 395	6 161	5 721	6 442	6 320	6 835	6 358 (230)
December	7 272	6 429	6 085	7 018	8 494	7 637	7 145 (970)
January	8 380	6 977	6 975	8 390	8 139	6 565	7 558 (1344)
February	9 309	7 835	7 188	8 096	7 464	7 639	7 737 (523)
March	9 096	8 521	8 364	7 938	8 418	9 187	8 470 (575)
April	7 913	6 793	7 208	7 373	7 114	7 493	7 291 (326)
May	7 705	6 882	6 992	6 947	6 623	7 178	6 970 (233)
Total	86 916	80 844	78 308	84 305	84 306	84 588	
Median	7 226	6 611	6 672	7 002	6 869	7 155	
IQR	2 342	1 808	1 529	1 340	1 612	1 369	

Table 4.7 Number of items of chloramphenicol eye ointment supplied on primary care prescriptions in Wales and their respective 12-monthly totals together with median and interquartile range (IQR) for the component month

	2004/05	2005/06	2006/07	2007/08	2008/09	2009/10	Median (IQR)
July	4 763	4 497	4 390	2 957	4 605	4 599	4 548 (187)
August	4 494	4 340	4 378	2 877	3 976	3 905	4 158 (446)
September	4 537	4 446	4 282	3 371	4 328	4 355	4 342 (130)
October	4 495	4 293	4 486	3 970	4 553	4 357	4 422 (184)
November	4 635	4 622	4 506	3 955	4 085	4 365	4 436 (438)
December	5 004	4 391	4 162	3 889	4 490	4 318	4 355 (264)
January	5 523	4 631	4 775	4 461	4 403	3 780	4 546 (322)
February	5 007	4 625	4 421	4 334	4 287	4 101	4 378 (275)
March	4 862	5 305	5 014	4 235	4 938	4 788	4 900 (189)
April	4 488	4 371	4 641	4 504	4 264	4 366	4 429 (133)
May	4 644	4 594	4 856	4 217	4 107	4 082	4 406 (467)
June	5 064	4 666	4 499	4 422	4 775	4 394	4 583 (307)
Total	57 516	54 781	54 410	47 192	52 811	51 410	
Median	4 704	4 546	4 493	4 094	4 366	4 356	
IQR	501	254	361	900	446	300	

4.3.4 Overall supply trend in primary care

The combined prescription and OTC supply of chloramphenicol eye drops, each year, from 2004/05 to 2009/10 is shown in Figure 4.5 (part a). Overall, there was an increase in use of the eye drops, prescribed and sold, from 86,916 units in 2004/05 to a peak of 142,013 units in 2007/08. Thereafter, supplies plateaued in 2008/09 (134,220 units) and 2009/10 (133,942 units). The highest proportion of eye drops supplied OTC occurred in 2006/07, which saw an equivalent of 71% (56,303/78,308) of the respective number of items supplied on prescription. The supply of chloramphenicol eye drops in primary care by the end of the study period was 54% higher (47,026 units/86,916 units) than it was at the beginning of the study (2004/05).

Chloramphenicol eye ointment became available OTC in July 2007 and their total quantity supplied on prescription and sold OTC for each 12-month period are shown in Figure 4.5 (part b). The highest proportion of ointment sold OTC compared to items supplied on prescription occurred in 2007/08, where the sales represented 48% (22,875/47,192) of the respective prescription volume. Sales in 2008/09 and 2009/10 fell to 31% (16,312/52,811) and 33% (17,061/51,410) of their respective prescription volumes. The overall impact of the OTC availability of chloramphenicol ointment in 2007 was to increase its primary care supply in Wales by 29% (15,657/54,410) compared to the previous year. Thereafter, the overall, combined supply each year remained consistently higher than in any 12-month period prior to 2007 when the ointment was only available on prescription.

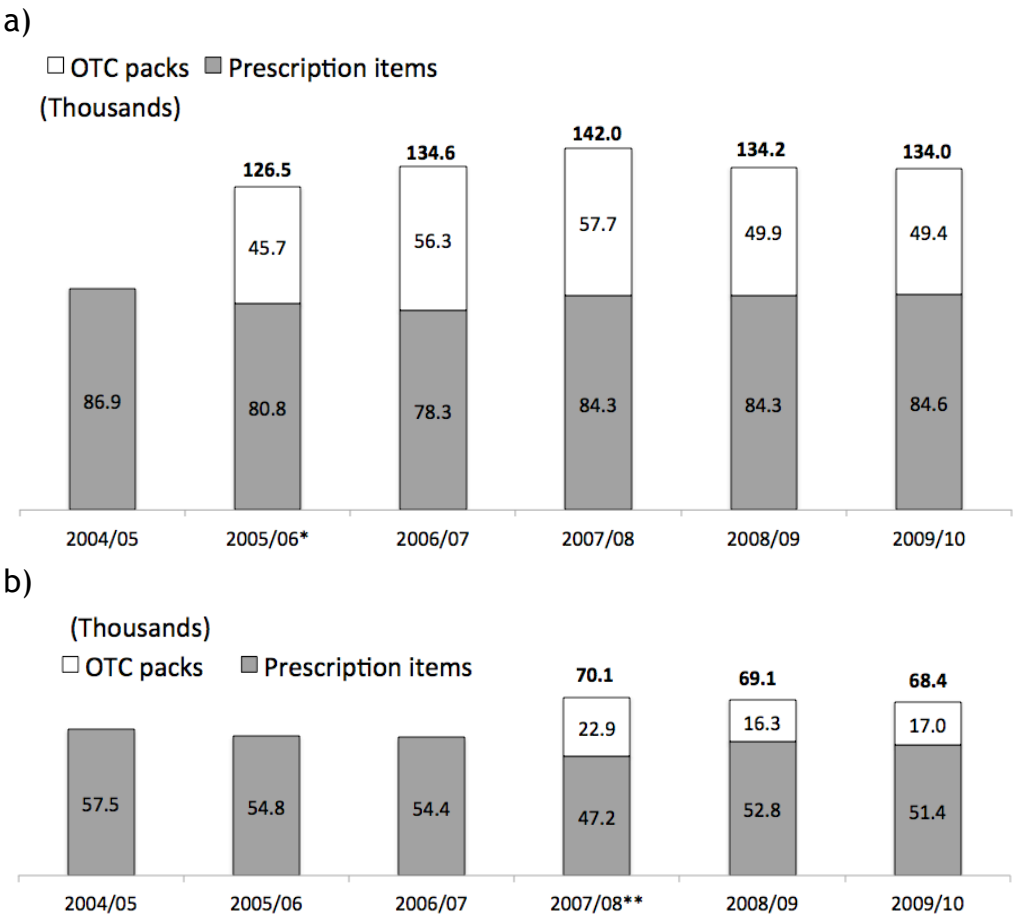


Figure 4.5 Number of items or packs of chloramphenicol (a) eye drops (June to May) and (b) eye ointment (July to June) supplied on prescription or sold over-the-counter for each 12-month period in Wales, respectively. The combined total supply each year is indicated on each column head in bold. The asterisk (*) and double-asterisk (**) mark the period when the eye drops and eye ointment became available OTC, respectively

The combined quantities of eye drops and ointment supplied OTC and on prescription for each 12-month period is shown in Figure 4.6. The peak supply of all ophthalmic chloramphenicol was observed in 2007/08.

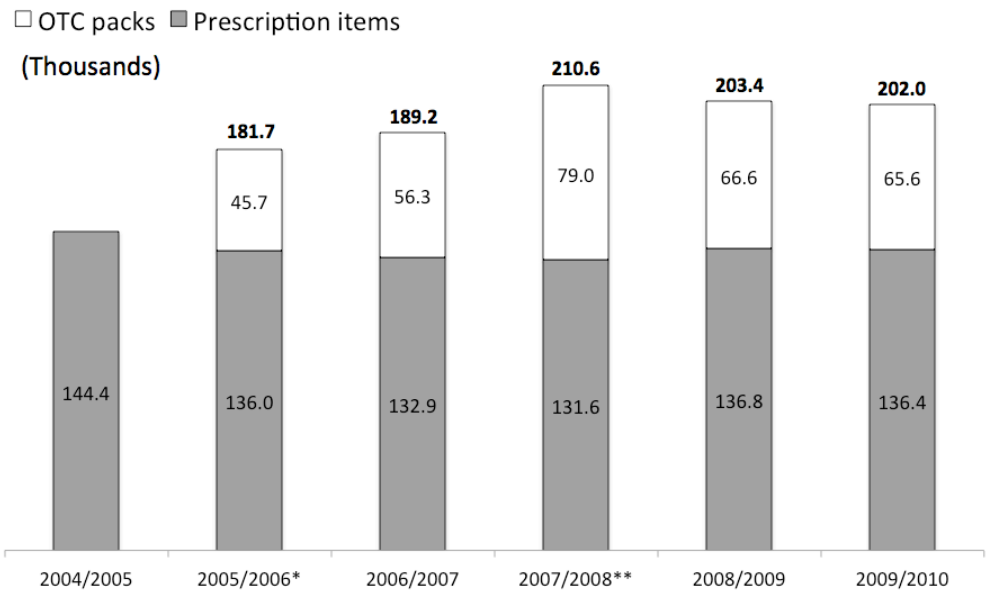


Figure 4.6 Supply of ophthalmic chloramphenicol (eye drops + ointment) on prescription and that sold over-the-counter (OTC) in Wales. The combined total supply each year (June to May) is indicated on each column head in bold. The asterisk (*) and double-asterisk (**) mark the period when chloramphenicol eye drops and ointment became available OTC, respectively

4.3.5 Impact of reclassification

The results from Wilcoxon's sign rank test are summarised in Table 4.8. The largest year-on-year reduction in the supply of prescription eye drops occurred in 2005/06 when the equivalent OTC pack became available from pharmacies. This represented a significant reduction ($p=0.015$) of 7% (6,072/86,912) decline in the number of items prescribed compare to the previous year. In the following 12-month period (2006/07) there was a further 3% (2,536/80,844) reduction in the quantities prescribed compared to the previous 12-month period. Quantity prescribed during the 2006/07 period was also significantly less ($p=0.003$) than that supplied prior to reclassification. No other significant difference in the number of prescribed items was observed between 2004/05 and any other 12-month periods ($p>0.05$).

The largest year-on-year decrease in the ointment formulation supplied on prescription occurred in 2007/08 when equivalent OTC pack became available from pharmacies. During 2007/08, there was a 13% (7,218/54,410) reduction in number of items prescribed and was significantly less than any other periods

prior to the reclassification of the ointment (2004/05, p=0.003; 2005/06, p=0.003; 2006/07, p=0.002). The quantity prescribed in 2009/10 was also significantly less than any other periods prior to reclassification (2004/05, p=0.002; 2005/06, p=0.012; 2006/07, p=0.034). Quantity of ointment prescribed in 2008/09 were significantly less (p=0.005) than that in the 2004/05 period only.

Table 4.8 Total numbers of items of chloramphenicol eye drops and ointment supplied on primary care prescriptions in Wales and their respective median and interquartile range (IQR) for the component month

	Eye Drops (June - May)		
	Total	**Median (IQR)**	**p-value***
2004/05	86 916	7 226 (2 342)	
2005/06	80 844	6 611 (1 808)	**0.015**
2006/07	78 308	6 672 (1 529)	**0.003**
2007/08	84 305	7 002 (1 340)	0.308
2008/09	84 306	6 869 (1 612)	0.347
2009/10	84 588	7 155 (1 369)	0.814
	Ointment (July – June)		
	Total	**Median (IQR)**	**p-value***
2004/05	57 516	4 704 (501)	
2005/06	54 781	4 546 (254)	
2006/07	54 410	4 493 (361)	
2007/08	47 192	4 094 (900)	**0.003, 0.003, 0.002**
2008/09	52 811	4 366 (446)	**0.005**, 0.060, 0.158
2009/10	51 410	4 356 (300)	**0.002, 0.012, 0.034**

* P-values reported for the eye drops were comparison with the 2004/05 period; ointment were compared with the 2004/05, 2005/06 and 2006/07 periods, respectively. A p-value < 0.05 is indicated in bold.

4.3.6 Association between Over-the-Counter and prescription supply

The number of items of combined chloramphenicol eye drops and ointment dispensed on prescription and sold OTC each month, between January 2008 and December 2010, are shown in Figure 4.7. Pearson's product moment correlation coefficient (r) revealed a significant and positive correlation (r=0.7, p<0.001) between the supplies of ophthalmic chloramphenicol (eye drops and

ointment combined) on prescription and that sold OTC from community pharmacies in Wales.

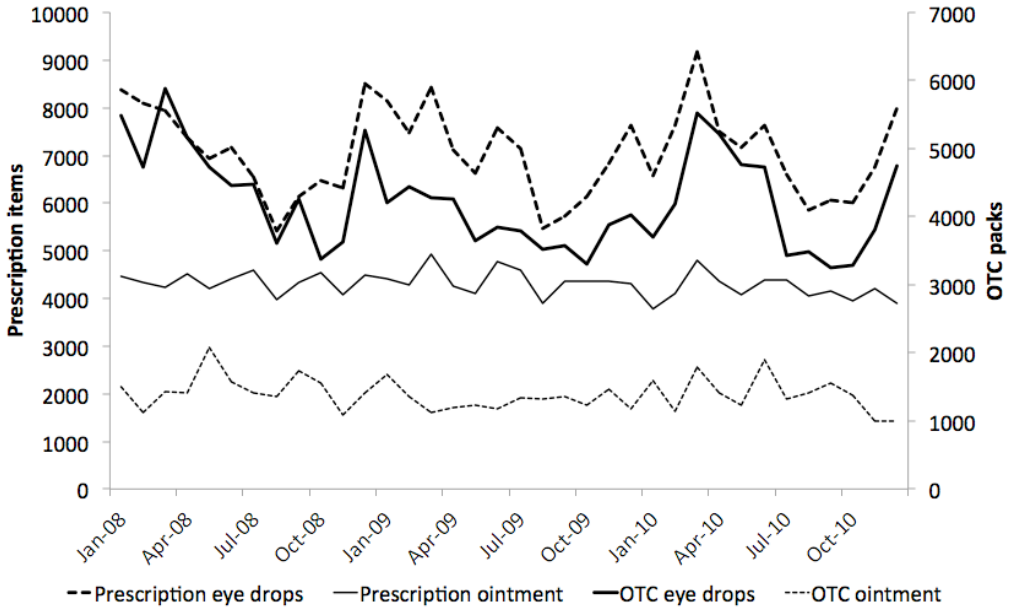


Figure 4.7 Number of items and packs of ophthalmic chloramphenicol supplied on prescription and sold over-the-counter (OTC), respectively, between January 2008 to December 2010

4.4 Discussion

4.4.1 Main findings

The pharmacy sales data presented in this study are the most comprehensive dataset studied to date for chloramphenicol products and include data from all NHS-contracted community pharmacies in Wales. The study successfully quantified the supply of OTC ophthalmic chloramphenicol following reclassification and investigated the impact on primary care prescription over a five-year period. The results demonstrated the OTC availability of ophthalmic chloramphenicol contributed to an increase in supply in primary care that is greater than previously reported (Walker and Hinchliffe 2010). In addition, the year-on-year growth in the sales of OTC eye drops plateaued in 2008 and no further growth was observed. In contrast, the sales of non-prescription

chloramphenicol ointment declined year-on-year since becoming available OTC.

It would appear that despite relatively large numbers of packs of both chloramphenicol eye drops and ointment sold OTC, this had no impact on the items dispensed on prescription for ophthalmic chloramphenicol over the five-year period studied. As a consequence there has been no cost saving on drug expenditure for the NHS in Wales as was anticipated with the increased availability of a medicine (Bond and Hannaford 2003; Blenkinsopp and Bradley 1996). When the temporal relationship between OTC sales of ophthalmic chloramphenicol and items dispensed on prescription was explored, a positive relationship was identified. This may, in part, suggest community pharmacists and GP prescribers were responding to similar presenting symptoms although whether or not prescribing and/or OTC sales were appropriate is unclear.

4.4.2 Study limitations

4.4.2.1 Ecological study

The present study was limited by its ecological nature, and consequently it was not possible to identify the factors that contributed to the increased supply of OTC ophthalmic chloramphenicol. This could be explored by a cross-sectional survey study to examine influence of various factors, such as demographic features of the individuals who bought ophthalmic chloramphenicol, their ocular history and presenting symptoms, the expertise and characteristics of the pharmacist or pharmacy staff consulted.

4.4.2.2 Prescription data

Primary care prescribing data were extracted from an established and routinely used database which included details of NHS prescriptions dispensed by every community pharmacy in Wales. Whilst this source of data was comprehensive in capturing prescriptions issued by GPs, the study did not include prescriptions issued by non-medical prescribers, such as nurse or pharmacist prescribers (National Prescribing Centre 2012). Given the omission of

prescriptions issues by non-medical prescribers, it is likely that the prescribing of ophthalmic chloramphenicol reported in the current study was an underestimate of the actual figure. Whilst data obtained from NHS Wales Informatics Service indicate NHS prescriptions written by non-medical prescribers in Wales only account for 1% of all primary care prescriptions dispensed (personal communication), whether or not this was the case for ophthalmic chloramphenicol is unclear and will require further investigation.

4.4.2.3 Estimation for Over-the-Counter supply

Pharmacy sales data in the RSA database represented the sales of selected medicines from wholesalers to community pharmacies. Although the RSA database offered a good coverage and captured data from 87% of all community pharmacies in Wales, sales data from one major pharmacy chain (Company A) was not included. The missing data were obtained direct from the pharmacy chain concerned and complemented the wholesale data obtained from IMS Health.

Unlike the pharmacy wholesale data, which were available for the entire post-reclassification period (2005 to 2010), sales data from Company A were only available for a three year period from 2008 to 2010. Consequently, the quantity of ophthalmic chloramphenicol sold from Company A for both the eye drops and ointment following reclassification and up to 2008 had to be estimated. It was possible that the sales pattern during the early years of a new product could have been different to that seen during the period when Company A sales data were available. This potential confounder was explored and tested using the available pharmacy wholesale data.

The results based on the available pharmacy wholesale data revealed the linear regression model overestimated the cumulative sales of the eye drops by 4% (1,407 packs) and the ointment by 13% (376 packs). As a result, the predicted sales figures for OTC ophthalmic chloramphenicol sold from Company A during the data missing period could have also been overestimated. However, the number of packs of ophthalmic chloramphenicol overestimated by the linear regression model were relatively small compared to the overall volume

of sale during the entire study period and therefore the impact on the results was probably minimal.

4.4.2.4 Pharmacy wholesale data

The data from IMS Health have been widely used by the pharmaceutical industry to map market trends. The majority of the data (97%) is extracted from invoices with a small percentage of data (3%) derived from a sample of approximately 300 independent retailers. Each geographical area is consisted of a different amount of projected information but in most cases the difference is estimated to be small. IMS Health have declared data may be on some occasions edited to compensate for grey market trading. For example, edits are made when very large volume of a product are purchased by one pharmacy address for onward supply to other pharmacies within the same company. Editing sales data in this scenario avoids distorting the local sales picture. Similarly, when a larger independent pharmacy chain buys for a purchasing group, sales are also reallocated across the businesses in the purchasing group. IMS Health claims these procedures ensure wholesale data are geographically accurate.

One important difference to note between the pharmacy data utilised in the present study is that data from Company A represented transactions between the pharmacy and customers, whereas data from IMS Health represented supplies from wholesalers to pharmacies. As with previous studies that employed IMS Health data (Walker and Hinchliffe 2010; Davis et al. 2009; Deslandes et al. 2011), the latter is thought to be a good proxy for pharmacy-to-customer sales for a number of reasons. Firstly, community pharmacies rely on a regular turn-over of stock to facilitate cash flow which generates revenue for future purchase of stock. Therefore, it is imperative that pharmacy businesses avoid accumulation of unsold stock and minimise stock wastage where possible. Secondly, the limited amount of space for on-site storage means a large quantity of backup stock is unlikely to be kept in a pharmacy. This may be particularly the case for chloramphenicol eye drops as they are required to be stored in a fridge where space is usually at a premium. Therefore advance purchase for on-site storage is unlikely. Finally, promotions offered by

wholesalers to pharmacies, such as bulk-purchase discounts at a particular time of the year, could potentially distorted sales. However, there was no evidence of this taking place from the available pharmacy wholesale data.

4.4.2.5 Range of Over-the-Counter products

As of January 2011, there were seven proprietary brands of chloramphenicol eye drops and five proprietary brands of eye ointment available OTC in the UK (Chemists and Druggists, January 2011 Issue). Of these the pharmacy wholesale data have captured the sales of five brands of the eye drops and four brands of the eye ointment. The two brands of chloramphenicol eye drops that were not included in the present study (Numark 0.5% Antibiotic Eye Drops® and I-Care Antibiotic Eye Drops®) were less widely known, one of which was sold only by selected independent pharmacies and the other was not sold by any Boots or Company A pharmacies in Wales. Whilst the market share for these two brands appears to be low, their contributions to the supply of ophthalmic chloramphenicol in Wales are not known.

4.4.2.7 Proprietary and non-proprietary ophthalmic chloramphenicol

In the RSA database wholesale data for both proprietary and non-proprietary (generic) ophthalmic chloramphenicol preparations were available. The proprietary products were identifiable by brand/product name and therefore whether they were sold OTC could be determined. On the other hand, generic ophthalmic chloramphenicol preparations were listed in the RSA database by drug name only (i.e. chloramphenicol eye drops 0.5%). Consequently, it was not possible to ascertain whether such products were sold OTC or used to dispense a prescription. For this reason, only OTC proprietary preparations were included in the current study. Whilst it was possible that even an OTC pack could have been used to dispense a prescription for ophthalmic chloramphenicol, this occurrence was considered to be rare due to the higher cost normally associated with a branded product than a generic equivalent. The possibility remains that sometimes a large chain multiple pharmacy may use its own-brand ophthalmic chloramphenicol preparations to dispense a prescription. However this was not an issue for the sales data provided by Company A as the data represented actual pharmacy-to-patient sales.

The prescribing of a proprietary ophthalmic chloramphenicol preparation on NHS prescriptions was another concern for the present study and this was explored by analysing NHS prescription data for Wales. The results suggest between 2005 and 2010, the mean number of items of proprietary chloramphenicol eye drops and eye ointment dispensed on NHS prescriptions were 31 and 34 items per year, respectively. These numbers were small compared to the 83,613 items of eye drops and 51,062 items of ointment dispensed per year over the same period (results not shown). These findings provided some reassurance that only very few packs of OTC proprietary ophthalmic chloramphenicol have been used to dispense a prescription and the majority were sold for non-prescription use.

4.4.2.8 Unit of measure

The unit of measure used for the prescription data was the number of prescription items dispensed. In contrast, pharmacy sales data was reported in number of product packs sold. Theoretically, more than one pack of chloramphenicol eye drops or eye ointment could be supplied against one prescription item if the total quantity requested by the prescriber required multiple packs to fill. However, as a single pack of the eye drops and the eye ointment is the usual quantity of ophthalmic chloramphenicol supplied per item on prescriptions (Walker and Hinchliffe 2010), the impact of the difference in units of measure was probably small on the results.

4.4.2.9 Temporal correlation

Although a positive relationship was observed between OTC sales and items supplied on prescription, this needs to be interpreted with caution as it only serves to demonstrate an association between the two variables but provides no explanation for the observation. Whether or not community pharmacists and other GP prescribers are capable of making clinically appropriate supplies of ophthalmic chloramphenicol remains to be studied. To date, there has been no published study evaluating the appropriateness OTC sales of ophthalmic chloramphenicol by pharmacists from community pharmacies.

4.4.2.10 Licensed indication

The licensed indication of OTC ophthalmic chloramphenicol was limited to the treatment of acute infective conjunctivitis in adults and children over two years of age, whereas that obtained on a prescription was not subject to the same restrictions (BNF 2013). Therefore, it was probable that the prescribing data had included supplies of ophthalmic chloramphenicol that are otherwise contraindicated in an OTC sales context. What proportion of the prescribed ophthalmic chloramphenicol in primary care in Wales was due to this could not be determined as data on prescribing by age group was not available.

4.4.2.11 Training and sales protocol

The potential issues relating to Medicine Counter Assistant (MCA) training and sales protocol have been discussed in Section 2.4.2.5.

4.4.3 Comparison with existing literature

The high levels of OTC sales for ophthalmic chloramphenicol reported in the current study is somewhat different to that seen with other reclassified medicines in the UK. For example, in March 2004, omeprazole was reclassified from POM to P status indicated for the relief of heart-burn symptoms associated with acid-reflux (Royal Pharmaceutical Society [RPS] 2011b). In the first 12-month after the reclassification, the total quantity of omeprazole supplied OTC was reported to be equivalent to 1% of the number of items dispensed on primary care prescriptions in Wales (Dhippayom and Walker 2006). In another study, Deslandes et al. (2011) investigated the sales of OTC azithromycin following its reclassification from POM to P status in 2008. It was reported that its supply OTC declined during the two years following reclassification and in 2010 the quantities sold across the UK were less than one pack per 10,000 population. Lastly, simvastatin, a lipid-lowering agent, was reclassified from POM to P status in the UK for the primary prevention of cardiovascular events in 2004 (DTB 2005). However, five years after becoming available OTC the medicine manufacture decided to discontinue the OTC product because of poor sales (Anon. 2010a).

Patients' perception and understanding about infective conjunctivitis could have played a role in driving the non-prescription sales. In a qualitative study

conducted by Everitt et al. (2003), it was found the majority of study participants were confident in making a diagnosis of infective conjunctivitis. The infection was considered to be relatively minor but perceived there was a need for treatment in order to clear the infection. Whilst the present study was unable to identify the exact reasons behind the increased sales of OTC ophthalmic chloramphenicol, it was likely the improved access to treatment presented the opportunity for the self-management of infective conjunctivitis compared to when it was only available on a prescription. The apparent high volume of non-prescription sale reflected the finding that many individuals prefer to self-manage a minor condition rather than consult a GP (Porteous et al. 2006). Furthermore, the removal of patient barriers such as the need to make a GP appointment (Seston et al. 2001), convenience (Schafheutle et al. 1996) and reduced cost of travelling to and from doctor's surgery (Ryan and Yule 1990) may have provided further incentives for people to practice self-medication, even if they had to purchase the treatment themselves in a country with no co-payment prescription levy.

A number of factors have been identified that could influence pharmacists' adoption of a newly reclassified medicine (Kennedy and Moody 2000; Paudyal et al. 2012a). In particular, the evidence of safety and efficacy of a product was one of the aspects considered by pharmacists when making OTC recommendations. In this regard, pharmacists' familiarity with ophthalmic chloramphenicol through dispensing prescriptions might have served as positive evidence for these desired properties and thereby promoted sales through better adoption. Sometimes a newly reclassified medicine is granted OTC availability at a lower dose and/or strength compared to same drug available on a prescription (Blenkinsopp and Bond 2005). The lack of evidence of efficacy for a new dose/strength has been found to deter some pharmacists from recommending such product (Paudyal et al. 2012b). This was not an issue for ophthalmic chloramphenicol as preparations available OTC and those on prescription were of identical dose and strength.

Prior to the availability of OTC ophthalmic chloramphenicol, patients presented at a community pharmacy with a suspected eye infection were often

treated with topical preparations containing propamadine or dibromopropamidine (Hardy et al. 1993a; Seston et al. 2001). However, many pharmacists were concerned with these preparations' limited benefit in bacterial infections (Hardy et al. 1993a) and expressed the desire to be able to counter prescribe ophthalmic chloramphenicol (Bond et al. 1993). It was therefore unsurprising to find pharmacists highly value the addition of OTC ophthalmic chloramphenicol to their armamentarium (Colquhoun et al. 2009). The perceived opportunity by pharmacists to extend beyond their traditional dispensing role to better care for their patients may have encouraged non-prescription sales.

Contrary to the reduction of ophthalmic chloramphenicol dispensed on primary care prescriptions in England (Davis et al. 2009), items dispensed in Wales remained steady throughout the five-year study period. One possible explanation for the difference in prescribing trend between the two countries was the abolition of the NHS prescription charge in Wales in April 2007. The removal of the prescription levy may have encouraged patients in Wales to obtain a free prescription of ophthalmic chloramphenicol from their doctors. This was illustrated in the present study by the observation of a small but distinguishable increase in eye drops dispensed on prescription 12 months after the prescription charge was abolished (June 2007 to May 2008). This phenomena is consistent with the observations made by others of a modest increase in prescription items following the abolition of prescription co-payment charges in Wales (Dhippayom and Walker 2008; Groves et al. 2010).

In comparison to England, it was cheaper for non-exempt patients to purchase OTC ophthalmic chloramphenicol (average price of eye drops and ointment were £4.72 and £5.24 respectively) than paying for the NHS prescription levy (£6.50/item in 2005 and £7.40/item in 2011). Consequently, this may have contributed to the reduction of primary care prescribing of ophthalmic chloramphenicol in England. The practice of self-medication using OTC medicines is known to be a common cost-reduction strategy adopted by patients (Schafheutle et al. 1996, 2002, 2004). Besides patients' own effort in trying to contain the cost of medicines, GPs may also recommend the purchase

of OTC medicines as a way to help to patients to overcome the prescription cost barrier (Wazaify et al. 2005; Weiss et al. 2001). This encouragement is, in part, driven by GPs' own agenda in trying to lessen their prescribing budgets by transferring the cost of medicines onto the patients (Schafheutle et al. 2004). It was possible that both patients and primary care prescribers in England had a financial inclination to promote the use of OTC ophthalmic chloramphenicol compared to GPs in Wales. The impact of the abolition of NHS prescription charge in Wales on the prescribing of ophthalmic chloramphenicol will need to be examined further.

It has been suggested that decrease in the prescribing of ophthalmic chloramphenicol in England was due to a change in the management strategy of infective conjunctivitis from empirical prescribing to no or delayed prescribing of antibiotics (Davis et al. 2009). Whether or not primary care prescribers in Wales were aware of these changes are unknown. Other reasons, such as a change in prescriber preference from prescribing one topical antibiotic to ophthalmic chloramphenicol, may have confounded the supply picture. This was investigated in a separate analysis where the prescribing of all other ophthalmic anti-bacterials listed in BNF section 11.3.1, from June 2004 to May 2010, was quantified for Wales. However, the results demonstrated that there was no marked change in the prescribing of other ophthalmic antibacterials (results not presented) and thus failed to explain the sustained high level of prescribing for ophthalmic chloramphenicol.

Walker and Hinchliffe (2009) reported a year-on-year increase in OTC sales of ophthalmic chloramphenicol eye drops in Wales during the three-year period post-reclassification. Likewise, Davis et al. (2009) reported a similar increase in England two year after reclassification. The present study demonstrated the sales of OTC chloramphenicol eye drops eventually stabilised four years post-reclassification. This length of time taken for OTC ophthalmic chloramphenicol to reach stability was longer than that seen with other reclassified medicines (Carlsten et al. 1996; Temin 1983). This demonstrates the need to monitor the sales of a reclassified medicine long-term in order to study the full impact of medicines reclassification on the OTC market.

4.4.4 Implications of findings

During the five-year period after the reclassification of ophthalmic chloramphenicol, their overall supply in primary care increased substantially before appearing to stabilise. The improved access to treatment for acute bacterial conjunctivitis appeared to have benefited new users who would not have otherwise consulted a GP about the condition. Despite the relatively large volume of ophthalmic chloramphenicol supplied OTC, there has been no impact on the supply of the same drug on primary care prescriptions in Wales even after five years. Consequently, the reclassification of ophthalmic chloramphenicol did not translate into any cost savings for the NHS drug budget or has reduced the workload of GPs in managing patients with infective conjunctivitis in Wales.

The latest evidence from published studies suggest a 'no or delayed antibiotic' approach to the management of acute infective conjunctivitis is likely to be appropriate for the majority of presentations in the primary care (DTB 2011; Everitt et al. 2006; Jefferis et al. 2011; Rose et al. 2005). In view of the latest advice, the updated practice guidance published by the RPS on the sale of OTC ophthalmic chloramphenicol was imperative (RPS 2011c). In the updated guidance for pharmacists, previously underemphasised information, such as the need to discuss with patients about the self-limiting nature of acute infective conjunctivitis and use non-medicinal measures to manage symptoms, were included. Whether or not these new recommendations will impact on pharmacists' counter-prescribing behaviour could be evaluated by further monitoring of the OTC sales of ophthalmic chloramphenicol.

The inappropriate supply of non-prescription ophthalmic chloramphenicol from pharmacies continues to cause concern among healthcare professionals (Behjat-Amery 2012; Davis et al. 2009; Price 2013). Whether or not community pharmacists possess the required clinical and communication skills to identify and appropriately manage cases of infective conjunctivitis remains unknown. In addition, it was not known from the sales data to what extent MCAs were involved in the sales of OTC ophthalmic chloramphenicol. Further

research on this matter would be helpful as MCAs have for many years been delegated with the task to conduct sales of OTC medicines and it has been shown they do not always comply with sales protocol (Watson et al. 2008). Other primary care prescribers, such as GPs, have been found to misdiagnose and mismanage a range of ocular conditions, including infective conjunctivitis (Buckley 1990; Harrison et al. 1988; Statham et al. 2008). While most unwarranted use of ophthalmic chloramphenicol pose little or no serious health risk to patients, it may however delay the diagnosis of an underlying disease and/or the timely commencement of proper treatment. The risk associated with the use of OTC medicine resulting in a delay in patients receiving appropriate treatment was illustrated in a study Hardy et al. (1993b), which found self-medication among hospital attendees for ocular conditions were considered to be ineffective or detrimental to their condition in 96% of the cases.

Given the conventional signs and symptoms relied upon by pharmacists and MCAs are diagnostically non-informative in distinguishing bacterial from viral form of infective conjunctivitis (Rietveld et al. 2004), it is not improbable that some of the increase in OTC sales have arisen because of misdiagnosis and therefore represent inappropriate use. This may not only have lead to the ineffective relief of symptoms in individuals but more importantly it may pose as a potential threat to the wider public health if antibacterial resistance develops (Price 2013). Therefore, the appropriateness for the supply of OTC ophthalmic chloramphenicol from pharmacies may need to be re-evaluated by the UK medicine regulator.

4.5 Summary

Following the reclassification of ophthalmic chloramphenicol in the UK in 2005, overall primary care supply of ophthalmic chloramphenicol in Wales increased, year-on-year, for three years before stabilising in 2008. Thereafter, the supply remained steady and showed no signs of decline until the end of the study period in 2010. Despite the high volume of ophthalmic chloramphenicol sold OTC it had no impact on prescription items over the entire study period. Whilst a temporal relationship was observed between OTC and prescription supplies of ophthalmic chloramphenicol, the appropriateness of supplies from

pharmacies remains unknown. The benefits and risks of having ophthalmic chloramphenicol available OTC and the impact of updated practice guidance on OTC sales need to be studied further to better understand its current, high level of use.

Chapter 5:

Detection of infective conjunctivitis outbreak

Detection of infective conjunctivitis outbreak

5.1 Introduction

Public health surveillance has been defined by the Word Health Organization (WHO) as the:

"*continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice*" (WHO 2013).

Compared to epidemiological research where the emphasis is usually on providing a snapshot of the health status of the population without a pre-determined set of actions or response, public health surveillance is characterised by its on-going nature, regular output and dissemination of health-related data in a timely basis. In addition, the outputs from these surveillance systems are usually actively monitored and interpreted against historical data or thresholds of health, and are directly linked to actions in order to respond to a public health threat (Department of Health [DH] Public Health England Transition Team 2012). The key objective of public health surveillance is to provide essential factual information that is required by public health agencies or decision makers to guide interventions, make policy decisions and evaluate public health services (Nsubuga et al. 2006).

The utility of public health surveillance data are wide-ranging and, depending on the actions that can be taken, they can be viewed as immediate, periodical or archival (Table 5.1). Each public health objective and the actions needed to make a successful intervention may require a different kind of surveillance information and system design. For example, the detection of acute infectious disease outbreaks or environmental hazards will require the active surveillance of related disease indicators to provide rapid information collection, transfer and analyses. This would allow identification of the problem and deployment of containment measures. In contrast, surveillance for chronic diseases or evaluation of the impact of policy change on health requires the gathering of

data over a long period of time since the associated changes occur more gradually, and may not require the same data collection mechanism as the detection of an immediate threat.

Table 5.1 Utility of public health surveillance data (Source: adapted from Thacker et al. 1998)

Immediate detection of	Epidemics
	Newly emerging health problems
	Changes in health practices
	Changes in antibiotic resistance
	Changes in distribution at risk for disease
Periodic dissemination for	Estimating magnitude of a health problem
	Assessing control activities
	Setting research priorities
	Determining risk factors for disease
	Facilitating planning
	Monitoring risk factors
	Monitoring changes in health practices
	Documenting distribution and spread of disease and injury
Store information for	Describing natural history of diseases
	Facilitating epidemiological and laboratory research
	Validating use of preliminary data
	Setting research priorities
	Documenting distribution and spread of disease and injury

The importance of public health surveillance to public health practice has been acknowledged by various strategic documents published in England and Wales (DH 2010; Welsh Government 2009a). Specifically, it was highlighted that the gathering of information and intelligence for health-related data from a range of systems was crucial to the success of health protection operations, such as emergency preparedness and development of evidence-based public health policies (DH Public Health England Transition Team 2012). A wide range of health-related data have been utilised for public health surveillance, which includes both data primarily intended for surveillance purposes as well as data that do not have surveillance as the main goal (Table 5.2 and Table 5.3). This chapter focuses on the role of public health surveillance specifically in the area of disease monitoring and outbreak detection.

Table 5.2 Sources of health-related data intended for surveillance purposes (Source: Department of Health Public Health England Transition Team 2012)

Data and systems primarily for surveillance purposes
Mortality data
Infectious disease reporting and analysis
Accidents and poisonings reporting and analysis
Environmental hazards reporting and analysis
Acute and chronic disease registers
Congenital anomaly registers
Behavioural monitoring and analysis
Monitoring systems for other determinants e.g. obesity, poor housing
Meteorological data analysis for health
Health-care seeking behaviour monitoring e.g. general practice attendance, telephone calls

Table 5.3 Sources of information and intelligence unintended for surveillance purposes but for service planning, management and evaluation purposes (Source: Department of Health Public Health England Transition Team 2012)

Public health information and intelligence for service planning, management and evaluation
Screening programme data
Drug misuse and treatment data
Immunization programme data
Hospital episodes statistics
General practice episode statistics
Termination of pregnancy statistics

5.1.1 Syndromic surveillance

In the United Kingdom (UK), a number of data sources are routinely used to monitor prevalence and incidence of infectious diseases in primary care. This includes reports of clinical diagnosis, microbiological results from patient samples, mortality and morbidity statistics (Health Protection Agency [HPA] 2010b). The surveillance systems that facilitate the collection of these data are well established and are now useful for monitoring long-term disease trends (Fleming 1999, Public Health Wales [PHW] 2011a). One common element with these surveillance datasets is that they all rely on individuals accessing a healthcare service, where his or her symptoms are assessed by a healthcare professional, before a diagnosis is recorded or passed on for laboratory investigation. This implies that (a) the presence of a disease can only be detected if and when an individual begins to access healthcare service where these data are collected and, (b) these traditional surveillance methods may not be able to detect the early stages of a disease outbreak when symptoms are less severe. More notably, a number of other factors could contribute to the time delay between the first onset of symptoms and reports of disease to public health agencies. For example, difficulty in accessing healthcare service, time required to conduct clinical assessment, unwillingness to seek medical attention at the first instance of experiencing symptoms (Banks 2010) and time

needed for transporting patient samples, can all affect the timeliness of detection by a surveillance system that relies on healthcare service based data. This potential time delay could negate public health planning efforts and hold back time critical countermeasures from being deployed that minimise the spread of a communicable disease outbreak.

Syndromic surveillance, also referred to as real-time surveillance (Harder et al. 2011), or electronic surveillance (Lombardo et al. 2003), is an investigational approach to outbreak detection that makes use of non-traditional health data based on generic symptoms or proxy measures that constitute a provisional, but not confirmed, diagnosis of a disease (Buehler et al. 2004). For example, data derived from clinical indicators such as emergency hospital patient admission record (Wagner et al. 2004) or physician consultation rate (Harcourt et al. 2011) are among some that have been used as inputs in syndromic surveillance programmes (Table 5.4). Other systems have utilised data derived from non-clinical sources, such as the sales of over-the-counter (OTC) medicines (Edge et al. 2006), number of telephone health help line calls (Cooper et al. 2007) or school absenteeism (Kara et al. 2011), as potential correlates for certain disease activities in the population (Table 5.4).

The key rationale behind these new approaches to disease surveillance is that such health indicators, although not based on confirmed aetiology, have been found to correlate with the levels of some common infections in the population (van den Wijngaard et al. 2011). Another reason why these datasets are considered to be beneficial is that that they may provide an earlier warning for emerging diseases than traditional surveillance systems (Dailey et al. 2007; Mandl et al. 2004). This is because the data input used by syndromic surveillance systems are often measures of events that might precede a clinical diagnosis, such as changes in health-seeking behaviour or the actions of a person suffering early disease onset (e.g. purchase non-prescription medications or miss school), thereby providing the first sign of an emerging disease outbreak (Henning 2004).

Table 5.4 Sources of health-related data used for syndromic surveillance

Sources of data for syndromic surveillance
Telephone health helpline (Cooper et al. 2007)
Emergency hospital attendance (Elliot et al. 2012)
Over-the-counter medicine sales (Edge et al. 2006)
School absence (Kara et al. 2011)
Employee absence (van den Wijngaard et al. 2011)
Prescription medication dispense (Chen et al. 2005)
Internet search and weblog (Johnson et al. 2004)
Hospital chief complaint (Wagner et al. 2003)
GP clinical diagnosis (Fleming and Elliot 2008)

The HPA collects a range of data from multiple sources for a variety of communicable diseases as part of its routine syndromic surveillance operation for England and Wales (HPA 2013a). This involves mainly data on general practitioner (GP) consultations (Fleming and Elliot 2008), telephone health help line calls (Cooper and Chinemana 2004), emergency department (Elliot et al. 2012) and out-of-hours GP service attendance (HPA 2013b). These syndromic surveillance systems have demonstrated their usefulness for the detection of gastrointestinal (GI) related (Cooper et al. 2006; Cooper et al. 2008; Smith et al. 2010) and seasonal influenza outbreaks (Cooper et al. 2007; Smith et al. 2006) in the UK population. More recently, these systems have been successfully used in 2009 to track the activity of large scale, unexpected outbreaks of pandemic influenza (Harcourt et al. 2011; Smith et al. 2011, HPA 2013c), monitor the impact of potential environmental hazards on public health (Elliot et al. 2010) and support public health protection during periods of heightened surveillance, such as for the London 2012 Olympic and Paralympic Games (Harcourt et al. 2012).

5.1.2 Pharmaceutical sales data

Outside of the UK, pharmaceutical sales data for OTC (or non-prescription) medicines has been utilised by syndromic surveillance systems for the detection of a range of disease outbreaks (Andersson et al. 2013; Buehler et al. 2008). For instance, in New York City, sales of anti-diarrhoeal medications and medications for influenza-like-illnesses (ILI) from pharmacies have been used as part of the routine surveillance program for seasonal influenza monitoring (Das et al. 2005). Another larger syndromic surveillance system, National Retail Data Monitor, has been collecting real-time sales of several thousand OTC health care products from 18,000 pharmacies across the United States for routine surveillance of respiratory-related outbreaks (Wagner et al. 2003). In 2009, during the H1N1 influenza pandemic, a national influenza surveillance program was established in Canada using the sales of respiratory-related OTC medicines collected from over 1,800 retail pharmacies. The system successfully tracked the activity of the pandemic and complemented other surveillance systems that operated at the time (Anon. 2009e). While national surveillance schemes such as those mentioned above have yet to be implemented and integrated into public health practice in most other countries, findings from many studies provided support for its contribution to healthcare (Andersson et al. 2013; Edge et al. 2006; Liu et al. 2013; Magruder et al. 2004; Ohkusa et al. 2005; Pelat et al. 2010; Vaergu et al. 2006). To date, successes in using OTC medicine sales data as a data input have been reported for the detection of GI-related outbreaks (Andersson et al. 2013; Das et al. 2005; Edge et al. 2006; Hogan et al. 2003; Pelat 2010), respiratory diseases (Magruder 2003; Magruder et al. 2004) and seasonal and non-seasonal outbreaks of influenza (Liu et al. 2013; Ohkusa et al. 2005; Sočan et al. 2012; Vaergu et al. 2006; Welliver et al. 1979).

A combination of factors makes OTC medicines sales data a potential attractive option for syndromic surveillance. First, it has been shown OTC medicines are commonly used for treating minor ailments (McIntyre et al. 2003; Vingilis et al. 1999), and many people self-medicate prior to seeking a consultation with a healthcare professional (Banks 2010; Urquhart et al. 2004). As a consequence, for some people the purchase of an OTC medicine may be

the first and only point of contact with healthcare services. This potentially provides an opportunity for early increase in disease cases to be identified before they are reported to other primary care or secondary care services.

Secondly, a wide range of medicines are available OTC and already a number of them have the potential to be linked to diseases that are of interest to public health. Examples include rehydration salts or anti-diarrhoeal products for cryptosporidium outbreaks; cough, cold and flu remedies for ILI or influenza outbreaks and ophthalmic chloramphenicol for infective conjunctivitis.

Thirdly, many large retail pharmacy businesses, through automatic and electronic systems, already collect, utilise and maintain OTC medicine sales data on a routine basis. Making use of these existing systems, infrastructures and equipment is more cost efficient than developing a system primarily intended for surveillance.

Fourthly, as medicine sales data is already routinely gathered the data collection process does not add any additional burden on the data providers, and the availability of historical data means baseline level of sales can be determined at the early stage of surveillance.

Finally, with the aid of computer technology, an electronic record is made instantly available at the time of each sale, including the type of product sold and the location of each sale. These records can be easily transmitted to facilitate real-time or near real-time monitoring which is difficult to achieve with surveillance data that are based on a confirmed clinical diagnosis.

The usefulness of OTC medicine sales data for early disease detection or the determination of an outbreak has not yet been established in the UK. Outside the UK, however, studies have been published and shed light on answers to some important questions about the application of such data in public health surveillance. For example, which products correlate with what type of disease (Li et al. 2005; Magruder 2003); how to identify meaningful categories of products for monitoring (Pelat et al. 2010; Wallstrom and Hogan 2007); how to

identify an unusual change in sales that correspond to a disease outbreak (Dailey et al. 2007); how to adjust for potential confounders that affect sales (Magruder 2004) and what criteria should be used to evaluate system performance (Buehler et al. 2004). One major barrier to using medicines sales data for diseases surveillance is the practical difficulties in obtaining the data. Pharmacy businesses also have concerns over security and the commercial sensitivities around supplying the data. In addition, there is currently little incentive for commercial companies to exploit medicine sales data for their public health potential.

5.1.3 Description of conjunctivitis outbreaks

The results from Chapter 4 indicate that sales of OTC ophthalmic chloramphenicol from community pharmacy were synchronised with the prescribing of the same drug by GPs in Wales. This was not unexpected given the majority of ophthalmic chloramphenicol supplied was likely to have been for the same indication in both settings i.e. the treatment for infective conjunctivitis. The possibility that sales of OTC ophthalmic chloramphenicol from community pharmacy may be an indicator of an outbreak of infective conjunctivitis in the community motivated the current study.

The Health Protection Team (HPT) is part of the Health Protection Division of PHW and is responsible for providing advice and support on community disease control issues as well as communicable disease management in Wales. One of its core functions is to investigate outbreaks of disease in healthcare premises or clusters of disease of unknown origin (PHW 2010a). Through a unique collaboration with PHW, the present study investigated whether the sales data for OTC ophthalmic chloramphenicol from community pharmacy was capable of detecting two known conjunctivitis outbreaks in Wales. Each of the outbreaks is described in more detail below.

5.1.3.1 Pontypool Outbreak (February 2010)

The first outbreak was reported to the HPT on 12th February 2010 (week 7, 2010) by the on duty nurse who was working at a GP practice located in Pontypool, Torfaen, Wales. At the time, it was reported that 13 children

(between the age of three and four years old as well as teenagers) with symptoms of acute infective conjunctivitis had been seen at the practice. The practice was advised by the HPT to be vigilant of any new cases of infective conjunctivitis and was reminded to disseminate infection prevention and control measures to those who might be affected. None of the 13 cases returned to the practice for further consultation. Following the initial report of the outbreak, a further eight new cases presented at the practice three days later on 15th February 2010. Individuals affected were children of 14 years of age all of whom attended a local school in Trevethin. After 15th February 2010 no new reports of infective conjunctivitis were notified to HPT. It was not known if any of the affected individuals had been supplied with a prescription for topical antibiotics. Laboratory results obtained from three of the affected children revealed the infections were of a bacterial origin.

5.1.3.2 Aberdare Outbreak (November 2010)

The second outbreak (Aberdare) was recorded by the HPT week commencing 15th November 2010 (week 46, 2010). The incident was reported by a school nurse who was working at a secondary school located in Aberdare, Rhondda Cynon Taf, Wales. The suspected outbreak involved five female students between the age of 13 and 15 years old who showed signs of acute infective conjunctivitis as identified by the school nurse. The five affected students were excluded from school and were advised to seek medical attention from their GPs but it was not known if a prescription for topical antibiotics had been supplied. In addition, the school and the carers or families of the five students were provided with advice on infection control and prevention measures, such as hand-washing and avoidance of sharing personal items. Since this initial incident, no other new cases was identified at the school nor was the HPT aware of any other outbreak in the nearby vicinity. No other action thereafter was taken by the HPT. It was suspected the infections were of bacterial origin due to sharing of eye make up between the students although no eye swab was taken.

5.1.4 Aims

By utilising pharmacy retail data obtained from Company A (Section 4.2.2.3), the aim of the present study was to determine whether pharmacy sales data for ophthalmic chloramphenicol were sensitive to and could detect the occurrence of two known conjunctivitis outbreaks in the local community. The specific objectives were:

(a) quantify the sales and prescribing of ophthalmic chloramphenicol from Company A pharmacy and by local GPs, respectively, in each of the areas where the outbreak had been reported and,

(b) determine if there was a statistically significant difference in the quantity of ophthalmic chloramphenicol supplied during the period of the outbreak and that during a non-outbreak period in previous years.

5.2 Method

5.2.1 Study design

The study had an ecological design (Schoenbach and Rosamond 2000) and involved the retrospective analysis of pharmacy retail data and primary care prescription data for ophthalmic chloramphenicol preparations supplied in Pontypool and Aberdare, Wales, during the period January 2008 to December 2010.

5.2.2 Data

Primary care prescription data for ophthalmic chloramphenicol were obtained from CASPA.net, a data store that contained NHS Wales primary care prescribing data. This was the same prescription data source as utilised through out the work presented in this thesis. Pharmacy retail sales data (herein refer to as pharmacy sales data) for OTC ophthalmic chloramphenicol were obtained from Company A, which was a national, multiple-chain pharmacy in the UK. This source of data was identical to that utilised in Chapter 4 (Section 4.2.2.3) and represented actual sales of ophthalmic chloramphenicol from pharmacy to patients. The data extraction processes for each of the areas studied is described separately below:

5.2.2.1 Pontypool

All GP practices located in the Pontypool area were identified using the NHS Wales Service Directory available online on NHS Wales website (NHS Wales 2011). This revealed a total of nine GP practices situated in the area at the time of the study (Figure 5.1). Forty-three GP prescribers were based at these nine surgeries during the study period and identified using the CASPA.net prescription database. Monthly prescribing data for each of the GP prescribers during the period from January 2008 to December 2010 were extracted.

Pharmacy sales data obtained from Company A were available from January 2008 to December 2010. Data supplied included the weekly number of packs of product sold for each Company A's 94 pharmacies across Wales together with postcode information. The location for each Company A pharmacy was cross-referenced to the Welsh Pharmacy Contractors List supplied by PHW. Any Company A pharmacy located in the Pontypool area was identified. This revealed one Company A pharmacy was in the area in question. Weekly sales figures for this pharmacy were extracted and aggregated into their corresponding month accordingly. The location of the pharmacy in relation to the nine GP practices in Pontypool is shown in Figure 5.1.

5.2.2.2 Aberdare

Using the same method as described above, a total of six primary care GP practices were identified in the Aberdare area at the time of the study (Figure 5.2). The CASPA.net prescription database indicated a total of 17 GP prescribers who based in the six GP practices. Monthly prescribing data for each of the GP prescribers were extracted for the period from January 2008 to December 2010. Similarly, a Company A pharmacy was located in the Aberdare area and its weekly sales figures were extracted and aggregated into their corresponding month accordingly. The location of the pharmacy in relation to the nine GP practices in Aberdare is shown in Figure 5.2.

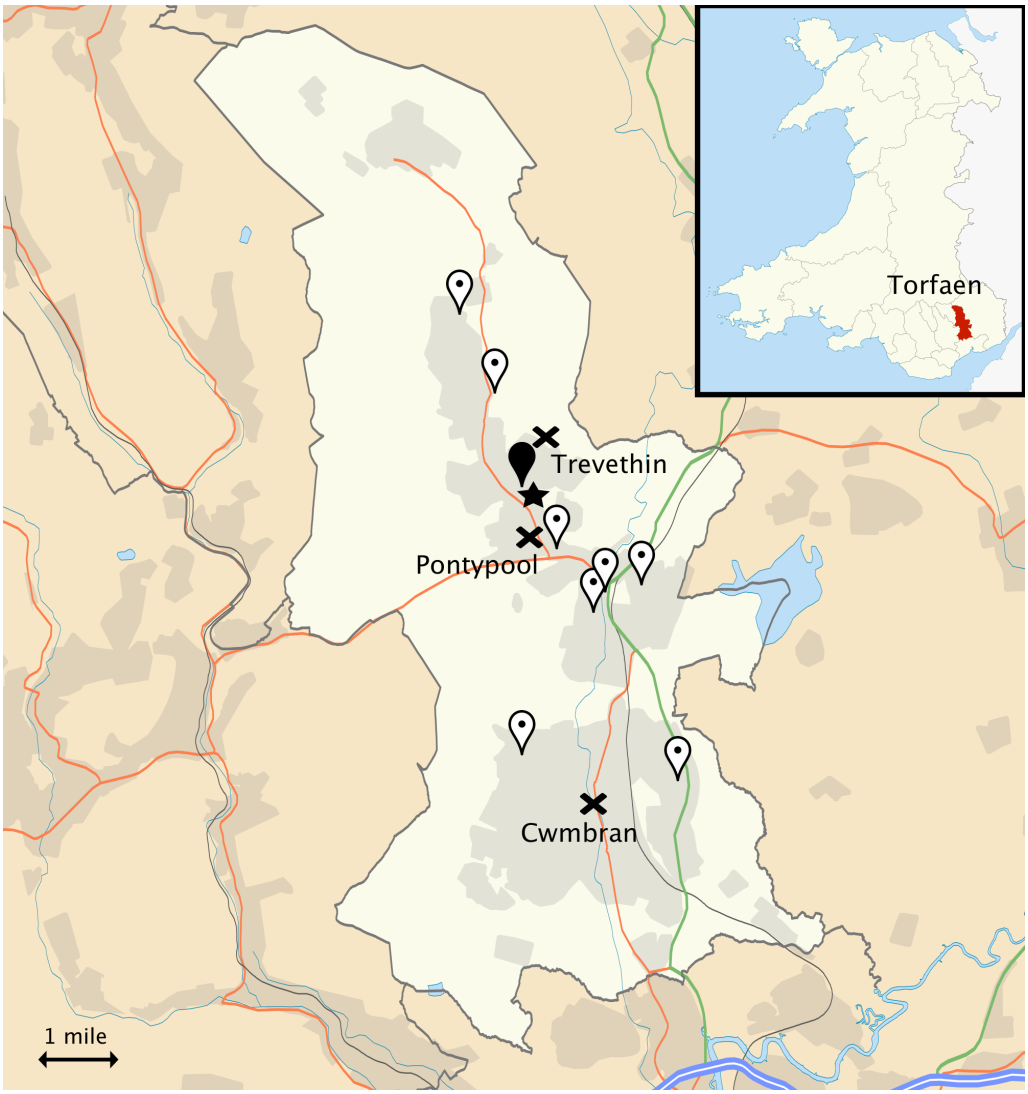


Figure 5.1 Locations of general practices (♀) in Pontypool, Torfaen, Wales, for which prescribing data were extracted from the NHS Wales prescription database. The solid-filled marker (♀) indicates the practice that identified and reported the outbreak. Star (★) marks the location of Company A pharmacy. Major towns and villages are indicated by a cross

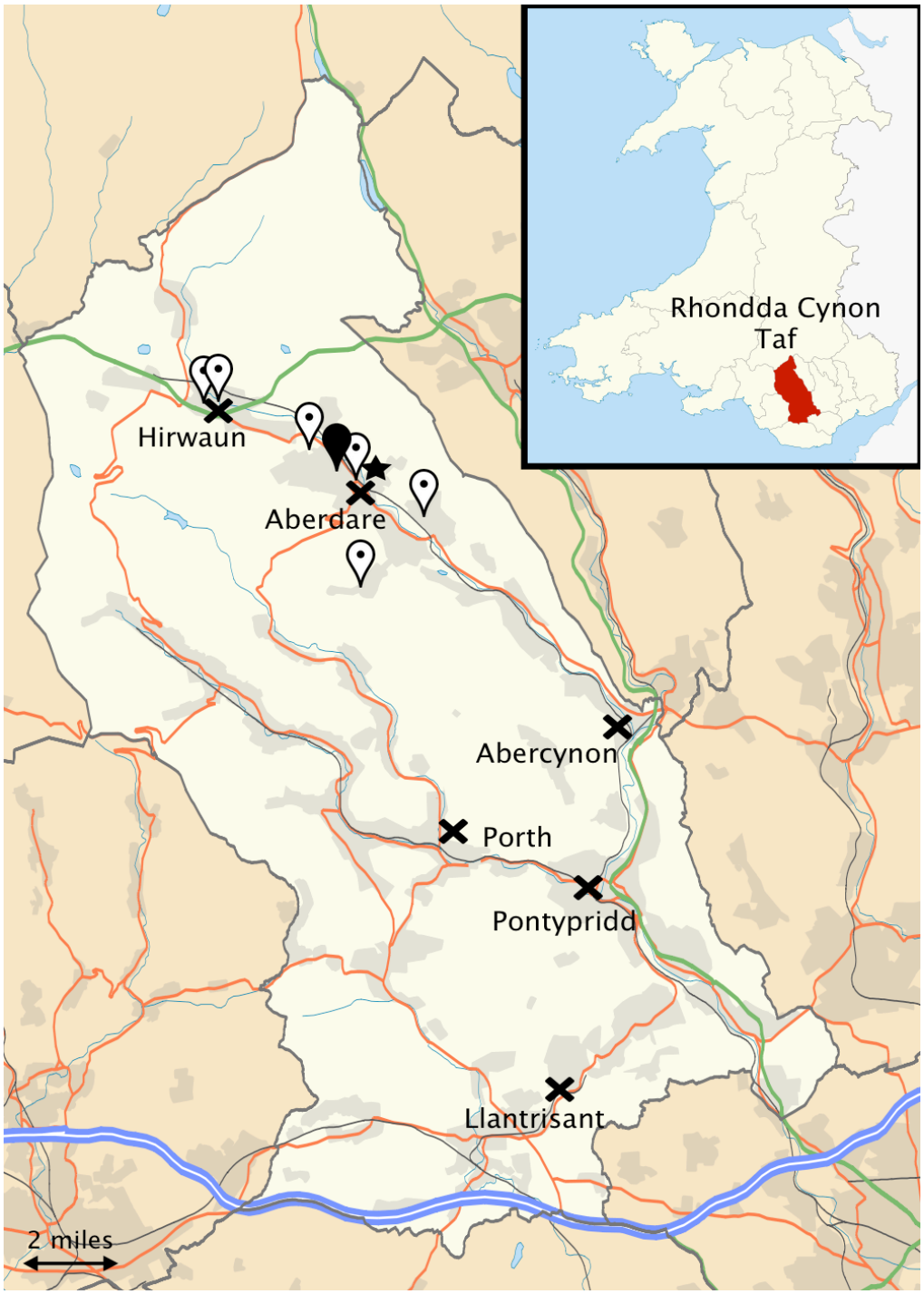


Figure 5.2 Locations of general practices (♀) in Aberdare, Rhondda Cynon Taf, Wales, for which prescribing data were extracted from the NHS Wales prescription database. The solid-filled marker (♀) indicates location of the school that was involved in the outbreak. Star (★) marks the location of Company A pharmacy. Major towns and villages are indicated by a cross

5.2.3 Medicines studied

5.2.3.1 Prescription medicines

Chloramphenicol containing preparations listed under section 11.3.1 (Anti-bacterial eye preparations) of the British National Formulary (BNF) 65 (BNF 2013) were included in the study. In addition, a manual search of the prescription database was conducted to identify any other ophthalmic preparations that also contained chloramphenicol to be subsequently included in the analysis. A list of prescribed products included in the current study can be found in Appendix 14.

5.2.3.2 Over-the-Counter medicines

Pharmacy retail data included all proprietary and Company A's own-brand of ophthalmic chloramphenicol preparations (eye drops and eye ointment) sold. A list of all ophthalmic chloramphenicol products sold from company A and included in the present study can be found in Appendix 17.

5.2.4 Data processing and organisation

Data utilised in the current study were obtained from different sources and had to be processed and organised into a suitable format before statistical analysis. Primary care prescription data were extracted from the NHS Wales prescription database and transferred to a Microsoft Excel spreadsheet (Appendix 8). Pharmacy retail data from Company A were supplied in a Microsoft Excel spreadsheet. All processed and reorganised data were manually screened for errors before transferring to the statistical software for analysis.

5.2.5 Analysis

The supply of ophthalmic chloramphenicol on prescription and the number of pack sold OTC in Pontypool and Aberdare were quantified for the period from January 2008 to December 2010. The year-on-year changes in the quantities supplied were visualised using box plots as described in Chapter 4 (Section 4.2.6.1).

Over the three-year study period, the numbers of items prescribed each month were presented on an unadjusted time series chart. Weekly sales of OTC ophthalmic chloramphenicol from Company A were presented on an unadjusted time series chart as well as on a four-week moving average chart. The purpose of presenting the weekly sales data in four-week moving averages was to aid the identification of sales trends.

The moving averages are the unweighted means of a constant number of past observations that are calculated based on values from the beginning to more recent observations of a time series. The number of observations used for computing the mean is called the order of the series. Since the order of the time series was an even number, the centred moving average method was used to determine the data points for the four-week moving average time series (Yaffee and McGee 1999).

5.2.5.1 Determine changes in prescription supply

To investigate the potential impact of the reported outbreaks on the prescribing of ophthalmic chloramphenicol, the total number of items supplied during the month of the outbreak in 2010, together with total quantities supplied in the corresponding month in 2008 and 2009, were determined for each of the respective areas. The median and interquartile range (IQR) for the number of ophthalmic chloramphenicol items prescribed per GP prescriber were also calculated for the month of the outbreak in 2010 and for the corresponding months of 2008 and 2009. Wilcoxon's signed rank test was used to identify any statistically significant difference between the quantities supplies per GP prescriber during the month of outbreak in 2010 and the corresponding month of 2008 and 2009.

5.2.5.2 Determine the changes in Over-the-Counter sales

Total packs of OTC ophthalmic chloramphenicol sold from Company A's pharmacy, during the period one week before to one week after the reported outbreak, were determined for each of the respective areas studied. For the Pontypool outbreak, the three-week period corresponded to week six, seven and eight of 2010. For the Aberdare outbreak the three-week period

corresponded to week 45, 46 and 47 of 2010. The median and IQR were also calculated for ophthalmic chloramphenicol sold per brand for the three-week period of 2008, 2009 and 2010 for each of the respective areas. Wilcoxon's signed rank test was used to identify any statistically significant difference between sales of ophthalmic chloramphenicol of two different three-week periods.

All data analysis and statistics were performed using PASW version 18 (PASW Inc., Chicago, IL, USA). A p-value < 0.05 was considered to be statistically significant.

5.3 Results

5.3.1 Pontypool

5.3.1.1 Over-the-Counter ophthalmic chloramphenicol

Weekly sales of ophthalmic chloramphenicol preparations from Company A pharmacy in Pontypool are shown in Figure 5.3. The number of packs sold varied from week to week and no seasonal or periodic trend was discernible. Transformation of weekly sales of ophthalmic chloramphenicol into four-week moving average also revealed no consistent pattern of sale between the different years (Figure 5.4).

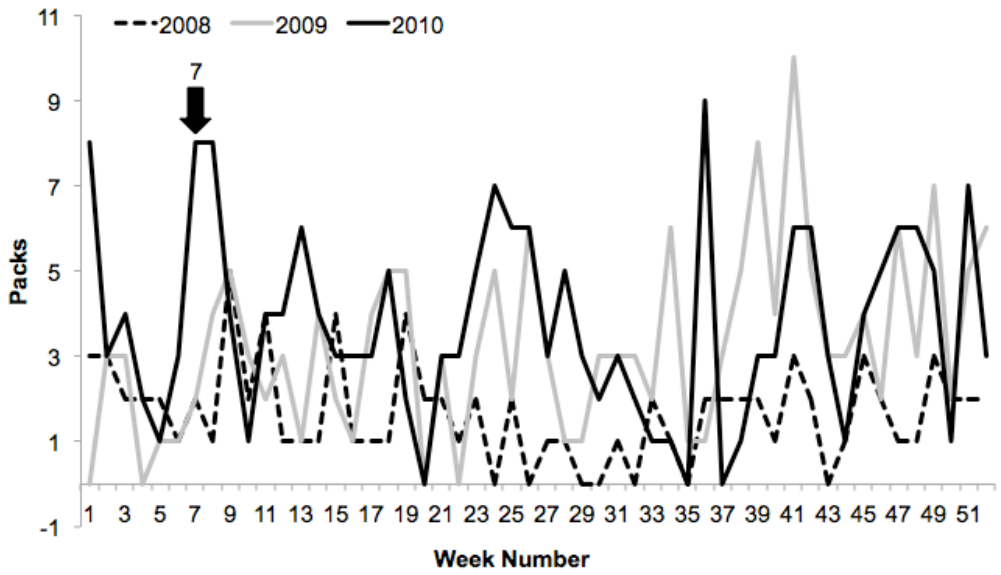


Figure 5.3 Weekly sales of over-the-counter ophthalmic chloramphenicol preparations (eye drops and ointment) from one Company A pharmacy located in Pontypool, Wales. The arrow marks the week (week number) of the reported conjunctivitis outbreak (2010)

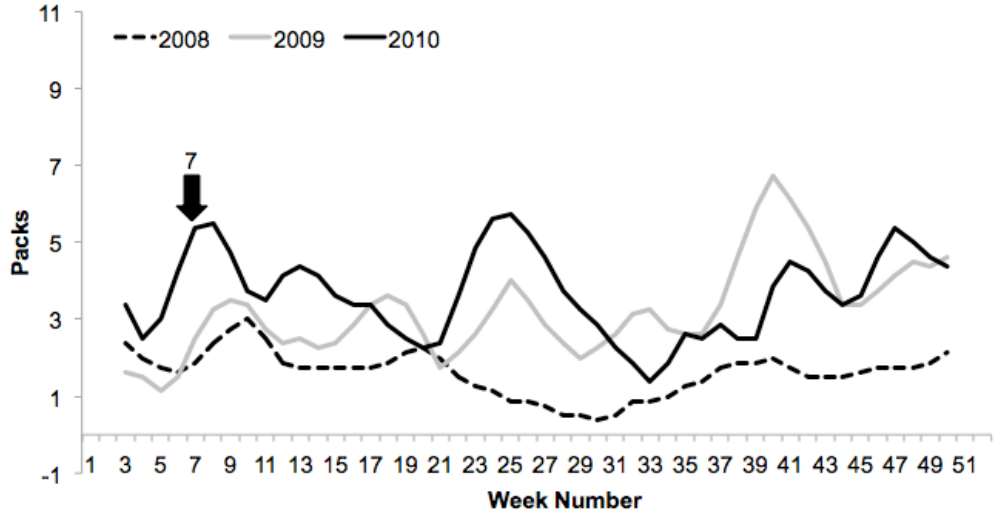


Figure 5.4 Four-week moving average chart for the sales of over-the-counter ophthalmic chloramphenicol preparations (eye drops and ointment) from one Company A pharmacy located in Pontypool, Wales. The arrow marks the week (week number) of the reported conjunctivitis outbreak (2010)

A sharp increase in the sales of OTC ophthalmic chloramphenicol was observed in week 7 of 2010. This rise in sales coincided with the report of conjunctivitis outbreak to PHW on the same week (Figure 5.3). A similar increase was not observed during the corresponding week in the previous

years. However, it was noted that although there was no change in sales in week 7 of either 2008 or 2009, a small increase in sales had occurred two weeks after in week 9 of 2008 and 2009. Overall, the sales of combined OTC ophthalmic chloramphenicol preparations increased, year-on-year, from 87 packs in 2008 to 197 packs in 2010. Significantly more packs (p-value, median, IQR) were sold in 2009 (0.011, 8, 3.75) and 2010 (0.002, 16.5, 6.75) compared to 2008 (Figure 5.5).

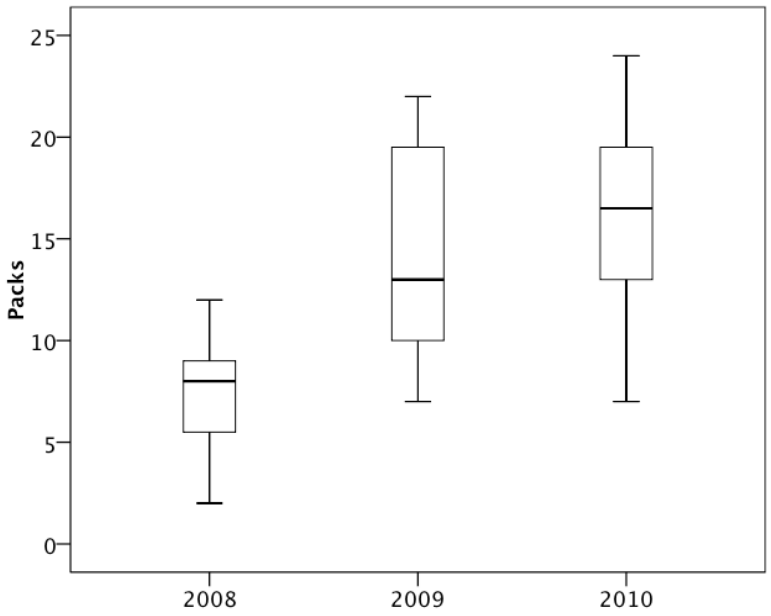


Figure 5.5 Boxplot showing the median and interquartile range for the number of packs of over-the-counter ophthalmic chloramphenicol (eye drops and ointment) sold from one Company A pharmacy located in Pontypool, Wales for the component month each year (January to December)

The total sales, median and IQR for OTC ophthalmic chloramphenicol sold OTC between week six and week eight of 2008, 2009 and 2010 in Pontypool are shown in Table 5.5. Sales of OTC ophthalmic chloramphenicol during the three week period that corresponded to the Pontypool outbreak in 2010 were significantly greater than those sold during the corresponding period in 2008 ($p=0.042$) when no conjunctivitis outbreak was known to have occurred. No significant difference was observed between the sales of ophthalmic chloramphenicol in 2010 and those sold during the corresponding period in 2009 ($p>0.05$).

Table 5.5 Total ophthalmic chloramphenicol (eye drops and ointment) supplied in Pontypool and Aberdare during respective periods of the reported conjunctivitis outbreaks, together with median (and interquartile range [IQR]) for the number of OTC packs sold per brand and items prescribed per GP prescriber for each of the areas. The quantity of ophthalmic chloramphenicol sold OTC or supplies on prescription in 2010 were compared to their corresponding quantity in 2008 or 2009 using Wilcoxon's sign rank test. A p-value < 0.05 is indicated in bold

		Total OTC packs† (Median, IQR); p-value	**Total prescribed items‡** (Median, IQR); p-value
Pontypool	**2008**	4 (0, 0.75); p = **0.042**	185 (3, 7); p = 0.467
	2009	7 (0, 1); p = 0.107	132 (2, 5); p = **0.003**
	2010	19 (0.5, 1.75)	200 (3, 6)
Aberdare	**2008**	9 (0.5, 1.75); p = 0.803	92 (4, 8.5); p = 0.553
	2009	8 (0, 1.5); p = 1.00	113 (5, 11.5); p = 0.528
	2010	8 (0.5, 1)	110 (5, 9)

† Period reported for Pontypool (week 6 to 8); Aberdare (week 45 to 47)
‡ Period reported for Pontypool (February); Aberdare (November)

5.3.1.2 Prescribed ophthalmic chloramphenicol

The numbers of items of ophthalmic chloramphenicol supplied on GP prescription in Pontypool are shown in Figure 5.6. During the three-year study period the items prescribed each year followed a similar pattern to one another with more items prescribed in January to March and less items prescribed in September to November. A peak in the prescribing of ophthalmic chloramphenicol was observed in February 2010. This coincided with the month in which the infective conjunctivitis outbreak in Pontypool was reported to PHW (week 7, 2010). The overall trend of ophthalmic chloramphenicol supplied on prescription in Pontypool remained steady, year-on-year, with 1,680 items in 2008, 1,614 items in 2009 and 1,656 items in 2010. No significant differences (p>0.05) were observed between any two 12-month periods (Figure 5.7).

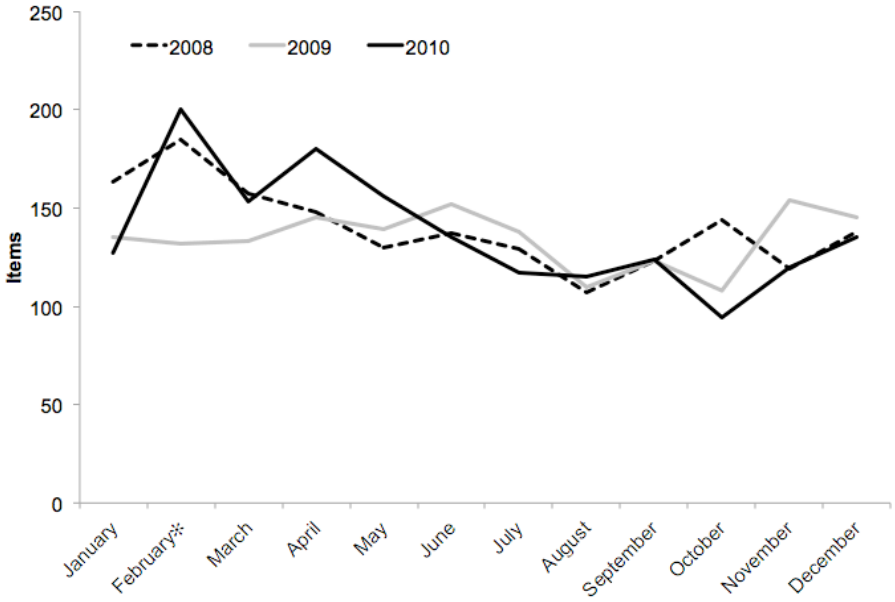


Figure 5.6 Monthly numbers of items of ophthalmic chloramphenicol preparation (eye drops and ointment) supplied on primary care prescriptions in Pontypool, Wales for each year. Asterisk (*) marks the month when the infective conjunctivitis outbreak was reported to Public Health Wales (2010)

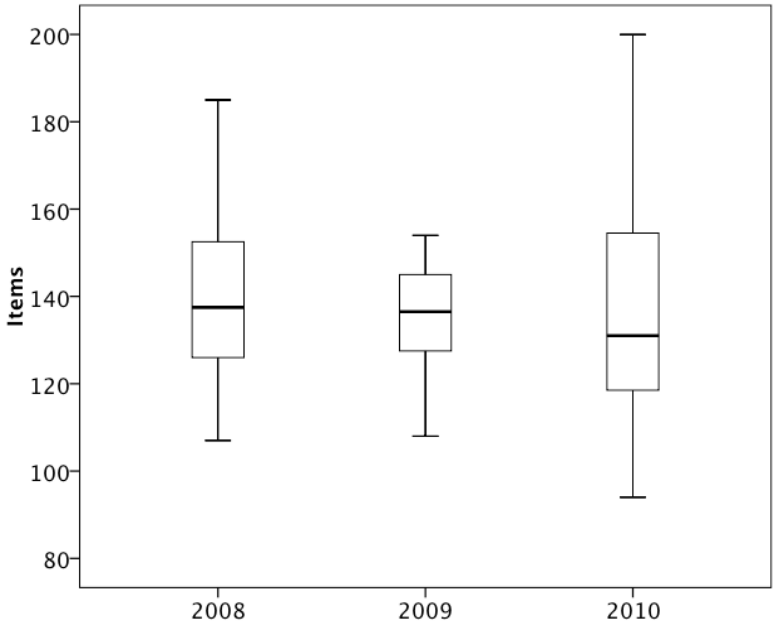


Figure 5.7 Boxplot showing the items of ophthalmic chloramphenicol preparations (eye drops and ointment) prescribed on primary care prescriptions in Pontypool, Wales for the component months each year (January to December)

The total items, median and IQR for ophthalmic chloramphenicol supplied on prescriptions during the month of the Pontypool outbreak are shown in Table

5.5. The number of items prescribed per GP prescriber in February 2010 was significantly higher (p=0.003) than the number of items supplied in the corresponding month of 2009 when no outbreak was known to have occurred. No significant differences in number of items prescribed were observed between February 2010 and February 2008 (p>0.05).

5.3.2 Aberdare

5.3.2.1 Over-the-Counter ophthalmic chloramphenicol

Weekly sales of OTC ophthalmic chloramphenicol from Company A pharmacy between January 2008 and December 2010 in Aberdare are shown in Figure 5.8. Both time-series charts (Figure 5.8 and 5.9) demonstrated no discernible seasonal pattern during the period studied. During the week of the reported outbreak in 2010 (week 46), there was no marked change in sales of OTC ophthalmic chloramphenicol. However, A noticeable increase in sales that was not present during week 12 of 2008 and 2009 was observed in 2010 (Figure 5.8).

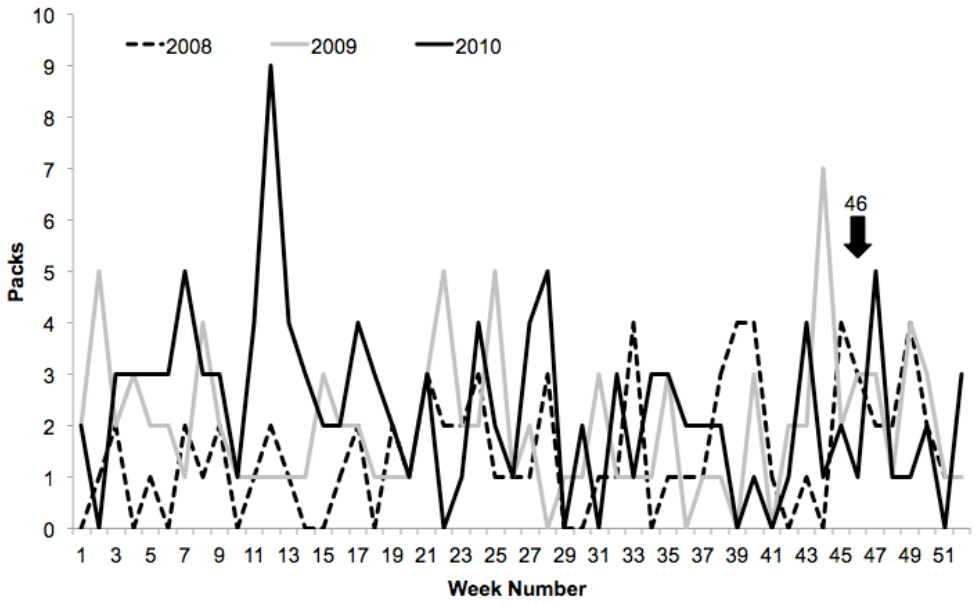


Figure 5.8 Weekly sales of over-the-counter ophthalmic chloramphenicol preparations (eye drops and ointment) from one Company A pharmacy in Aberdare, Wales. The arrow marks the week and week number when the suspected conjunctivitis outbreak was reported to Public Health Wales (2010)

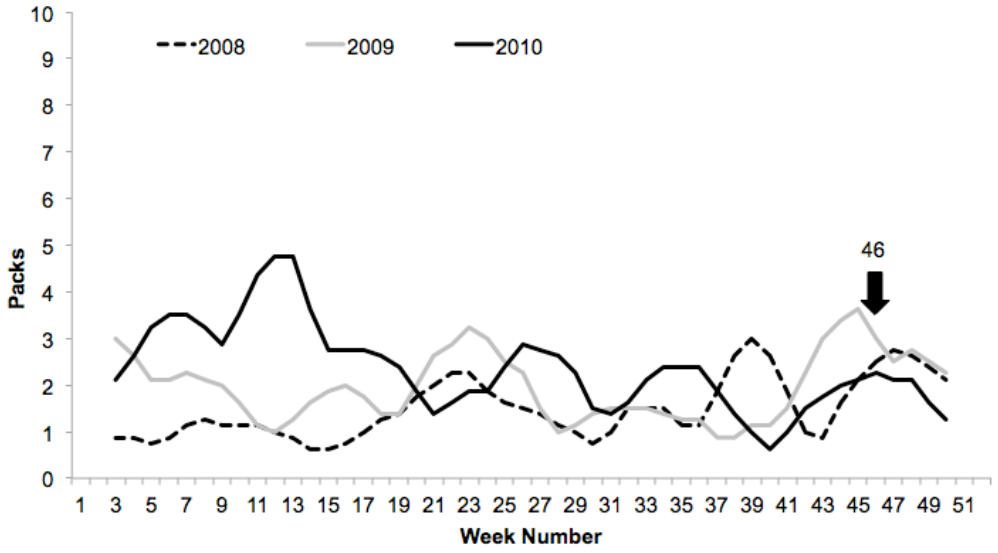


Figure 5.9 Four-week moving average chart showing the sales of over-the-counter ophthalmic chloramphenicol (eye drops and ointment) from one Company A pharmacy in Aberdare, Wales. The arrow marks the week when the suspected conjunctivitis outbreak was reported to Public Health Wales (2010)

Overall, the sales of ophthalmic chloramphenicol preparations increased, year-on-year, from 78 packs in 2008 to 120 packs in 2010. No significant difference ($p>0.05$) in the sales of OTC ophthalmic chloramphenicol was detected between any two 12-month periods. An outlying data point indicated higher than normal volumes of OTC ophthalmic chloramphenicol had been sold from Company A pharmacy during the month of March 2010 (Figure 5.10). This was confirmed by Wilcoxon's signed rank test, which showed the volume sold during March 2010 was significantly higher than that sold in the corresponding month in 2008 and 2009 ($p=0.019$ and 0.024, respectively). However, no conjunctivitis outbreak was known to PHW for the Pontypool area in March 2010.

The total sales, median and IQR for ophthalmic chloramphenicol sold OTC in Aberdare during the three-week period of 45, 46 and 47, each year from 2008 to 2010, are shown in Table 5.5. The numbers of packs sold during the three-week period were similar between each year and Wilcoxon's sign rank test indicated there was no significant difference ($p>0.05$) in quantities sold between the outbreak and non-outbreak periods.

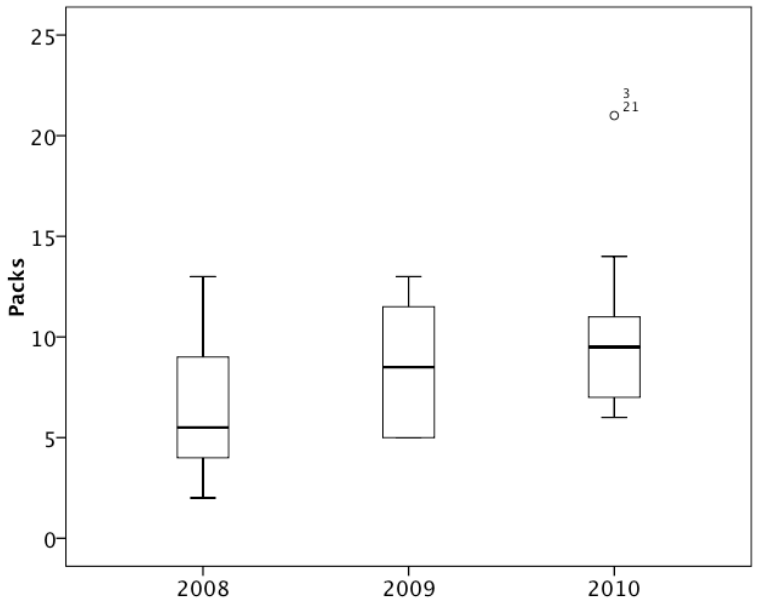


Figure 5.10 Boxplot showing the median and interquartile range (IQR) for the number of packs of over-the-counter (OTC) ophthalmic chloramphenicol (eye drops and ointment) sold from one Company A pharmacy located in Aberdare, Wales for the component months each year (January to December). Circles (○) indicate values that are beyond the upper and lower quartile by one and a half IQRs and are classified as outliers

5.3.2.2 Prescription ophthalmic chloramphenicol

The numbers of items of ophthalmic chloramphenicol supplied on primary care prescription in Aberdare are shown in Figure 5.11. During the three-year study period, prescribing of ophthalmic chloramphenicol showed a similar pattern in 2008 and 2010 with more items prescribed in December to February and fewer in August to November.

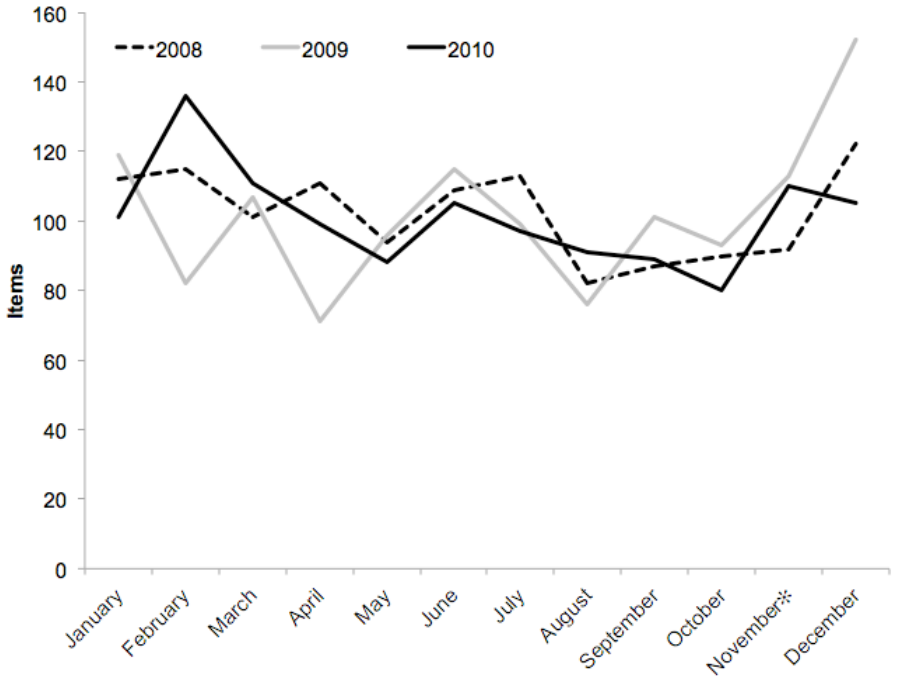


Figure 5.11 Monthly numbers of items of ophthalmic chloramphenicol preparation (eye drops and ointment) supplied on primary care prescriptions in Aberdare, Wales for each year. Asterisk (*) marks the month when the infective conjunctivitis outbreak was reported to Public Health Wales (2010)

Overall, the total quantity of ophthalmic chloramphenicol prescribed each year remained steady from 2008 to 2010 with a total of 1,228 items, 1,224 items and 1,212 items supplied, respectively. No significant differences ($p>0.05$) in quantity prescribed were observed between any two 12-month periods. However, an outlying data point indicated that a higher than normal volume of prescribing occurred during the month of February 2010 (Figure 5.12). The volume of prescribing during this month was significantly higher than that during the corresponding month in 2009 ($p=0.028$) but indifferent to 2008 ($p>0.05$). To the knowledge of PHW, no known conjunctivitis outbreak was reported for the area surrounding Aberdare in February 2010.

Results from Wilcoxon's signed rank test indicated no significant differences ($p>0.05$) in number of items prescribed were observed between November 2010 and other November months in any other years (Table 5.5). This indicates there was no difference in volume of ophthalmic chloramphenicol prescribed between the months of a known and no known conjunctivitis outbreak.

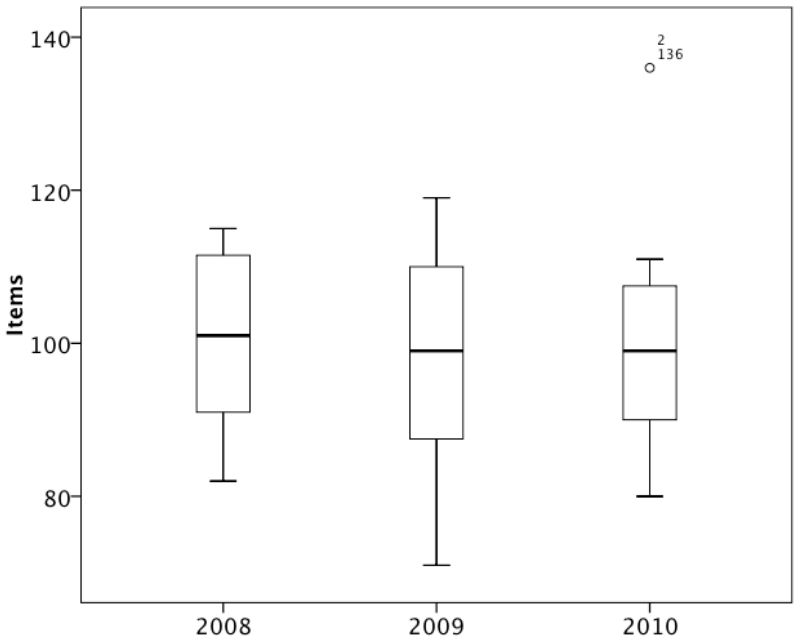


Figure 5.12 Boxplot showing the items of ophthalmic chloramphenicol preparations (eye drops and ointment) prescribed on primary care prescriptions in Aberdare, Wales for the component months each year (January to December)

5.4 Discussion

5.4.1 Main findings

This was the first study in Wales that explored the potential of OTC medicine sales data from community pharmacy for the detection of a small outbreak of conjunctivitis. The results showed that during the period of the outbreak in Pontypool, sales of OTC ophthalmic chloramphenicol were significantly higher than those sold in the corresponding period in one (2008) of the two non-outbreak years. Similarly, numbers of items for ophthalmic chloramphenicol prescribed by local GPs in the month of the outbreak were also found to be significantly higher than those prescribed in the corresponding month in one (2009) of the two non-outbreak years. In contrast, ophthalmic chloramphenicol supplied on prescription and sold OTC during the Aberdare outbreak demonstrated no significant difference to the quantity supplied during their corresponding period in the non-outbreak years.

Despite the positive findings with the Pontypool outbreak, the results need to be interpreted with caution for two reasons. First, the quantities of ophthalmic chloramphenicol supplied OTC and on prescription during the outbreak period were not consistently higher than that supplied during their corresponding non-outbreak periods. This reduces the confidence for medicine sales to detect the occurrence of conjunctivitis outbreaks in the community. Second, due to the low volume of ophthalmic chloramphenicol sold from Company A pharmacy in study area, the changes in sale was small and could have been caused by factors unrelated to the outbreak. As a result of these confounding issues, the current study was unable to determine conclusively if medicine sales data was capable of detecting local outbreaks of infective conjunctivitis.

In addition to the above, the current study illustrated there was no change in both the sale or prescribing of ophthalmic chloramphenicol during the outbreak in Aberdare. This suggests small outbreaks may be particularly difficult to identify using medicine sales data. Nonetheless, this exploratory study had a number of weaknesses in terms of study design and data collection which could inform future work. These will be discussed in the following section.

5.4.2 Study limitations

5.4.2.1: Prescription data

The prescription data used in the present study were obtained from the NHS Wales prescription database, which was a robust and routinely used data source for analysing primary care prescriptions dispensed by NHS-contracted community pharmacies in Wales. All ophthalmic chloramphenicol preparations that were prescribable on NHS prescriptions in primary care were included in the study.

The prescription data were derived from prescriptions written by all GPs whose practices were located in the immediate vicinity of the reported outbreaks. It was possible an individual who lived outside Pontypool or Aberdare visited the areas and obtained a prescription for ophthalmic chloramphenicol from a local GP for causes unrelated to the two outbreaks studied. How much of an impact

this confounder had on the prescribing figures is unknown for either of the areas studied.

Another potential confounder about the prescription data was that patients could have consulted a non-medical prescriber, such as an independent nurse or pharmacist prescriber, about their eye conditions. If this was the case, any prescription issued as a result would have not been included in the study and the quantities reported could be an underestimation of the real supply picture. The impact of the missing data on overall prescribing is likely to be small as information received from NHS Wales Information Services indicate items of ophthalmic chloramphenicol prescribed by non-medical prescribers only accounted for 1% of all primary care prescriptions in Wales (personal communication). However, despite the low levels of non-medical prescribing for ophthalmic chloramphenicol overall, it was unclear to what extent this was taking place during the two conjunctivitis outbreaks studied.

The prescription data obtained for the current study were aggregated figures for all ophthalmic chloramphenicol prescribed and differentiation between adult and paediatric prescribing was not possible. In both outbreaks the individuals reported to have been affected were mainly children between the age of ten and fifteen years old (personal communication), it was possible that the levels of prescribing for ophthalmic chloramphenicol in certain age groups had increased but not in others or, alternatively, had been masked by background levels of prescribing in others age groups. It may be worthwhile in future studies capturing age-specific data to avoid such problem.

Finally, the data available in the NHS Wales prescription database were only available as a total figure compiled on a quarterly or monthly basis, therefore separating the prescribing of ophthalmic chloramphenicol into shorter and more frequent time intervals was not possible. If weekly prescribing data had been available, it could have allowed short-lived changes in prescribing pattern to be identified as a signal of interest may be less likely to become diluted over time or masked by unrelated background supplies. Furthermore, weekly prescribing data would have been more comparable to pharmacy sales data as

this was also available on a weekly basis. These potential weaknesses had been identified before the study was undertaken but it was thought the number of individuals seeking treatment as part of an outbreak would be greater.

5.4.2.2: Pharmacy retail data

Company A pharmacy was a large, national chain pharmacy in the UK with a total of 94 community pharmacies across Wales. Despite their extensive network nationally, sales data obtained from Company A represented 11% (1/9) and 20% (1/5) of all the community pharmacy located in the Pontypool and Aberdare areas, respectively (NHS Wales 2011). This small number of pharmacy clearly would have reduced the sensitivity of the medicines sales data to detect any changes in OTC ophthalmic chloramphenicol sold in the local area. The possibility that individuals could have visited another pharmacy in or outside of either of the outbreak areas could have further contributed to the low number of sales observed in the present study.

Whilst a minimum recommended coverage of pharmacy or medicine market share required for a successful syndromic surveillance system based on pharmacy sales data has yet to be established, the pharmacies utilised in this study were probably inadequate to undertake any appropriate syndromic surveillance, particular when a coverage greater than that of the current study has been reported by others (Hogan et al. 2003; Kirian et al. 2010; Magruder 2004; Pelat et al. 2010; Wagner et al. 2003).

Although the incomplete capture of data could have limited the sensitivity and accuracy of the study in detecting small outbreaks of conjunctivitis (Wagner et al. 2003), it is worth noting that the study had intended to utilise pharmacy sales data available at the time. Whilst it appears relatively straightforward to recruit more pharmacies to capture the data, barriers such as the lack of an appropriate IT infrastructure and the confidentiality of the data precluded this. Furthermore, the additional time and resources required to obtain and analyse pharmacy sales data from all community pharmacies in areas studied were not permissible within the constraints of the current study.

5.2.4.3: Medicines studied

At the time of the study, the licensed indication of OTC ophthalmic chloramphenicol was for the treatment of acute infective conjunctivitis in adults and children over two years of age. The same medicine, however, when supplied on a prescription could be used in any age for a range of eye infections (BNF 2013). It was possible that during the period of the study ophthalmic chloramphenicol might have been prescribed to patients for other eye-related infections or for whom the OTC version was not suitable.

However, despite the differences in their licensed indications, the impact of this on the study findings was probably small as infective conjunctivitis has been found to be the commonest eye-related diagnosis made by GPs in primary care, and ophthalmic chloramphenicol has been identified as the largest contributor to prescriptions issued as a result of these consultations (Sheldrick et al. 1993). Moreover, the BNF (2013) has been and continues to recommend ophthalmic chloramphenicol as the first-line choice of treatment for uncomplicated cases of infective conjunctivitis by in the UK, which makes them the likely drug of choice for infective conjunctivitis encountered in the primary care.

Besides ophthalmic chloramphenicol, other anti-infective ophthalmic preparations that could have been purchased without a prescription, such as propamidine or dibrompropamidine containing products, were also available at the time of the study. While the sales of these anti-infectives might have been a more sensitive marker for incidences of infective conjunctivitis in the population, their use in infective conjunctivitis was not recommended (BNF 2013) and there were no published data at the time that suggested they would be effective.

The selection of ophthalmic chloramphenicol as the first candidate to be monitored for detecting outbreaks of infective conjunctivitis was a logical first step given its licensed indication for OTC use was exclusively for the treatment of acute infective conjunctivitis. Nonetheless, future studies may need to

collate sales data of other ophthalmic preparations that could be used to treat eye conditions easily confused with the symptoms of infective conjunctivitis.

5.4.2.4: Severity and prevalence of the outbreaks

The numbers of individuals reported to have been involved in both outbreaks were small. Information obtained from the public health nurses who responded to the two outbreaks at the time indicated the number of known affected individuals was 21 in Pontypool and 5 in Aberdare (personal communication). As a consequence, it was possible that there had not been enough additional supplies of ophthalmic chloramphenicol to cause an abrupt change in OTC sale or prescribing above their baseline level. Although it was possible that the actual number of people affected by the outbreak was greater than the official number of reported cases, to what extent under-reporting was occurring was also unknown and could not be estimated.

In addition to the low numbers of people affected, the nurse noted that the Pontypool outbreak may have been contained by itself as affected children who studied at the local school entered spring holiday period just as when the outbreak had begun. This was thought to be one of the reasons why the outbreak was not as widespread as it could have been. For the outbreak that took place in Aberdare, the public health nurse commented that, at the time, the school had been given advice to send any symptomatic children to their GPs, and infection control and prevention measures were promptly issued. These public health interventions were likely to have limited the numbers of those who would otherwise have been affected and minimised the spread of the outbreak.

Lastly, the symptoms of acute conjunctivitis experienced by those who were affected needed to be severe enough in order to prompt health-seeking behaviours, such as the purchase of OTC treatment from a pharmacy or obtain a prescription from a doctor. Given the symptoms normally associated with acute infective conjunctivitis are mild (Everitt et al. 2006; Rose et al. 2005), it was probable that some individuals, even though exhibiting the symptoms of infective conjunctivitis, had not sought any treatment and thus were not

captured by either the OTC sales data or the prescription data in either of the areas. Alternatively, they could have managed their symptoms using non-medicinal, conservative measures for infective conjunctivitis (National Institute for Health and Care Excellence [NICE] 2012b).

5.4.3 Comparison with existing literature

Acute infective conjunctivitis is the most common eye-related problem seen in the primary care responsible for up to 41% of all eye-related consultations in the general practice. Elderly patients and children are known to be most susceptible to the infection (Scott and Dhillon 1998). This epidemiological feature was possibly reflected by the fact that both of the outbreaks studied involved school age children. One of the reasons that infections among these two groups are more common is that person-to-person contact is high and hand hygiene often poor thereby facilitating person-to-person transfer. Both of the outbreaks took place in the early spring and winter months, thereby confining individuals to stay indoor and increasing the likelihood of transmission.

For both outbreaks, the size, severity and overall impact on public health were minimal and therefore the social and economical cost to the local community was low. This was not unexpected given most primary care cases of acute infective conjunctivitis in children are mild and resolve within several days even without treatment (Rose et al. 2005). However, infection control measures and preventative advice disseminated at the time probably also played a role in containing the size and the spread of the outbreak, such as excluding the children from school, practice of good hand hygiene and prescribing of ophthalmic antibiotics by clinicians.

The current study monitored the sales of OTC ophthalmic chloramphenicol to indicate the presence of a conjunctivitis outbreak in small areas. This was the first study in the UK that has utilised pharmacy sales data for ophthalmic chloramphenicol for such purpose. Consequently, comparison of the current findings with other UK studies has not been possible. Outside the UK, experience in using medicines sales data to identify outbreaks of other infectious diseases exist (Edge et al. 2006; Hogan et al. 2003; Magruder 2003;

Vaergu et al. 2006) but none has investigated infective conjunctivitis or any other ocular infection.

Although infective conjunctivitis has not been studied previously as part of a syndromic surveillance programme, comparison with more successful programmes identified a number of notable differences. These differences might serve as an indication as to why the present study was unsuccessful in identifying the two small conjunctivitis outbreaks.

Firstly, disease outbreaks that have been successfully identified through the sale of non-prescription medicines usually involve a substantially greater number of affected individual than that in the current study (Andersson et al. 2013; Edge et al. 2006; Hogan et al. 2003; Magruder 2003; Vaergu et al. 2006). Secondly, medicine sales data utilised in these investigations were all available on a more frequent basis, such as weekly if not daily. Thirdly, sales data were often obtained from a more extensive coverage of pharmacies or retail outlets in the area of the outbreak than that in the current study. It has been suggested that in order to detect a local outbreak, a near complete coverage of data would be required for a syndromic surveillance system to achieve a successful detection (van den Wijngaard et al. 2011). Perhaps it is because of these more stringent requirements for robust, high quality data and an outbreak of a substantial size, syndromic surveillance systems have been reported to be less useful for small outbreak detection (Buehler et al. 2008).

It has been suggested that one of the advantages of using medicines sales data for disease surveillance is its ability to provide an earlier warning about an outbreak than is possible with a traditional surveillance system (Dailey et al. 2007). This suggestion was based on the knowledge that some people, instead of seeking medical attention in the first instance of experiencing disease symptoms, would attempt to manage their illnesses first using non-prescription medicines (Proprietary Association of Great Britain [PAGB] 2005a, 2009). Whilst this is clearly a possible scenario for OTC ophthalmic chloramphenicol in the treatment of acute infective conjunctivitis, no data has been published to demonstrate this is the case. The present study was unable to investigate

whether an earlier warning for a conjunctivitis outbreak was possible with sales data of ophthalmic chloramphenicol because the data obtained was unable to identify the outbreak in both of the areas studied.

5.4.4 Implications of findings

The potential value of pharmaceutical sales data for public health has been recognised as part of 'Our Healthy Future', the public health strategic framework for Wales (Jones 2009; Welsh Government 2009a). In particular, medicine sales data has a role in realising the goal to improve health information and intelligence to help local authorities focus on the health and wellbeing challenge of local populations and communities. In the present study, an infective conjunctivitis outbreak served as an example of an acute public health problem occurring in the community that could be identified using medicine sales data from pharmacies. Over time, as more medicines, covering a wider range of therapeutic areas, become reclassified from POM to P and from P to GSL status, medicine sales data as a tool to identify health needs may extend beyond acute illnesses to include chronic conditions.

The literature on surveillance and outbreak detection of infective conjunctivitis using medicine sales data is very limited in the UK. Recently published studies on the subject of infective conjunctivitis have mainly focused on developing effective diagnostic tools (Jefferis et al. 2011), understanding changes in the level of ophthalmic chloramphenicol prescribing (Davis et al. 2009) and devising the best management strategy for the illness in the primary care (Everitt et al. 2006; Rose et al. 2005; Rietveld et al. 2005). In part, the lack of attention in the area of surveillance is probably because occurrences of major outbreaks of infective conjunctivitis are few and far between in the UK, thus providing little initiative for research. However, despite most cases of acute infective conjunctivitis are not life-threatening and would not cause any permanent damage to individual health, the impact of a large scale outbreak on any local health care services could be substantial because of the combined number of people that could be affected. Early warnings about the presence of a local outbreak would be particularly beneficial for vulnerable groups in

settings such as hospitals, care homes or schools to allow for extra vigilance and preventative actions in these facilities.

Currently in Wales the detection of a conjunctivitis outbreak relies on passive reporting of unusual events by individual healthcare professionals or people who work with vulnerable groups, such as school teachers or nurses working in care homes. This means the occurrence of a potential local outbreak may not always be apparent because of a lack of awareness of what is happening in the surrounding area. Furthermore, notification of an outbreak to public health agencies could be delayed by the time needed for a person to contact or access the healthcare system. The current method of surveillance is also unable to capture individuals who have not accessed local healthcare services, therefore the spread and impact of an outbreak could be underestimated. The use of pharmacy sales data for ophthalmic chloramphenicol could potentially address these surveillance gaps and serve to be a useful tool for public health agencies in responding to conjunctivitis outbreaks. However, experience from the present study suggests for this to be feasible, a good coverage of pharmacy sale data would be needed and such data is currently unavailable to public health agencies in Wales.

To further explore the potential of pharmacy sales data for the detection of conjunctivitis outbreak, sales data should be obtained from rest of the community pharmacies that were located in the outbreak area. If possible, sales for other ocular anti-infectives beside ophthalmic chloramphenicol should also be obtained and examined to see if there was a change in their sale that could signal the outbreak. Period of study could be extended to allow additional comparison of sales between outbreak and non-outbreak periods.

5.5 Summary

During the period of a conjunctivitis outbreak in Pontypool, Wales, OTC sales and primary care prescription of ophthalmic chloramphenicol were both significantly greater than the quantities supplied in the corresponding non-outbreak periods of previous years. In contrast, no significant change in the

supply of OTC and prescribed ophthalmic chloramphenicol was observed during a conjunctivitis outbreak that took place in Aberdare.

Whilst the findings from one of the outbreaks suggest the sales of OTC ophthalmic chloramphenicol may be a sensitive indicator for the presence of a conjunctivitis outbreak in the community, the increase in sales observed was small due to the low numbers of data-providing pharmacy in the study area. Furthermore, the quantity of ophthalmic chloramphenicol prescribed or sold was not consistently higher than that supplied during their corresponding non-outbreak periods in previous years. Consequently, the current study was unable to determine whether pharmacy sales data for ophthalmic chloramphenicol was sufficiently sensitive to detect outbreaks of local conjunctivitis.

Future work needs to ensure a better coverage of pharmacy sales data is obtained in the outbreak area and will require greater collaboration between PHW and the local community pharmacy businesses.

Chapter 6:

Monitoring of seasonal influenza and related symptoms in the community

Monitoring of seasonal Influenza and related symptoms in the community

6.1 Introduction

6.1.1 Influenza

Influenza, also known as the 'flu', is a common, usually self-limiting, acute infection that primarily affects the upper respiratory tract (Wilks et al. 2003). It can also lead to illnesses that are more serious such as secondary bacterial pneumonia in vulnerable patients, including elderly and people who are immunocompromised (Torok et al. 2009). Of the three distinct types of viruses that cause influenza; type A, B and C, the first two are responsible for most clinical presentations and are capable of causing wide spread infection in humans (Wilks et al. 2003). The term 'epidemic' has been defined as "*the occurrence in community or region of cases of an illnesses in excess of normal expectancy*" (Porta 2008). Both the type A and the type B viruses are known to cause influenza epidemics. The term 'pandemic' has been defined as "*an epidemic occurring worldwide, or over a very wide area, crossing international boundaries, usually affecting a large number of people*" (Porta 2008). To date, all pandemics have so far been caused by the type A virus (Torok et al. 2009). The type C virus is the least common of the three and does not cause epidemics or pandemic (Torok et al. 2009).

In England and Wales, data derived from incidences of influenza-like illnesses (ILIs), a term used to describe a group of clinically diagnosed symptoms that indicates influenza infection, revealed influenza epidemic occurs almost every year (Fleming and Elliot 2008). In the United Kingdom (UK) and other countries in Northern Hemisphere, a higher number of incidents related to influenza is observed in the winter months, typically between November and April. For countries in the Southern Hemisphere, the peak incidence usually occurs between May and September (Treanor 2010). A number of theories have been put forward to explain the seasonality but the exact reasons are unclear (Eccles 2002; Lofgren et al. 2007; Lowen et al. 2007).

The influenza virus is primarily spread through dispersion of small-particle aerosols by the respiratory route (Torok et al. 2009) and it is traditionally thought to infect children more commonly than any other age group (Wilks et al. 2003). However, depending on the dominating strain of the circulating virus, each epidemic may affect a particular population more than the others and this has been documented for past epidemics in the UK (Fleming et al. 2003; Fleming and Elliot 2008).

For most encounters in primary care, a diagnosis of influenza is made solely based on clinical features that are suggestive of an infection (National Institute for Health and Care Excellence [NICE] 2009b). However, studies have found signs of common symptoms are not always an accurate indicator (Call et al. 2005). Diagnostic assessment is often aided by knowledge about the presence of influenza in the community, as positivity rates confirmed by virological analysis during seasonal epidemics have been shown to be as high as 80% to 90% (Boivin et al. 2000; Monto et al. 2000). Laboratory testing remains the only reliable method to confirm an influenza infection but it is not recommended as part of the routine management of seasonal influenza in the UK (NICE 2009b; Torok et al. 2009).

In uncomplicated influenza, symptom onset is usually rapid. Systemic symptoms, such as feverishness, chilliness, headache, myalgia, malaise and/or anorexia, are prominent. They occur one to two days post-exposure and lasting typically up to three days. Systemic symptoms could be presented at the same time with, or followed by, respiratory symptoms. The latter include cough, pharyngeal pain, nasal obstruction and discharge, and occasionally ocular symptoms, such as tearing and/or burning. These localised symptoms could last for more than two weeks (Eccles 2005; Torok et al. 2009; Treanor 2010).

The use of antiviral drugs in uncomplicated cases is not normally required for healthy individuals unless risk factor are present that could lead to complications (British National Formulary [BNF] 2013). The latest NICE guideline considers the following as high risk for developing complications from influenza: pregnancy, age over 65, chronic diseases (cardiac, pulmonary,

renal, hepatic or neurological), diabetes mellitus, immunosuppression and obesity (Health Protection Agency [HPA] 2012a). For the majority of patients, practising simple self-care measures such as ensuring an adequate fluid intake, bed rest and use of over-the-counter (OTC) medicines to relieve bothersome symptoms form the main management strategy (Blenkinsopp et al. 2009; NICE 2009b; Robb and Berrington 2012).

6.1.2 Common cold

Sometimes mistaken to be the same as an influenza infection, the term 'common cold' refers an array of symptoms that is the result of an upper respiratory tract infection (URTI) caused by a multitude of viruses other than influenza (Robb and Berrington 2012). The majority of URTIs is caused by the rhinovirus family but others such as coronavirus, parainfluenza virus and respiratory syncytial virus are also known to be causative agents (Treanor 2009). Like influenza, common colds exhibit a seasonal pattern in the Northern Hemisphere, with higher incidence in the autumn through to winter and lower in the spring through to summer (Heikkinen and Järvinen 2003). It has been estimated that, on average, adults experience two to four episodes of colds per year and higher in children who experience six to eight episodes per year (Treanor 2009).

The initial symptoms of a common cold include: sore throat, rhinorrhoea, nasal obstruction, sneezing and cough. Over the course of the infection a combination of sinusitis, hoarseness, headache, malaise, chilliness and/or feverishness with varying severity may also develop but occur less frequently (Heikkinen and Järvinen 2003; Treanor 2009, 2010; NICE 2011). The overlap in symptomatology of a common cold and a flu means it is difficult to determine the underlying causative agent based on symptoms alone. However, it has been suggested that if prominent macular pain or fever are present an influenza infection may be suspected (NICE 2011).

The diagnosis of a common cold (or a ‘cold’) is primarily symptom-based and patients can often recognise symptoms easily themselves (Arruda et al. 1997); no clinical examination or investigation is normally required for routine patient

care (NICE 2011). Given the benign and self-limiting nature of a common cold, with most severe symptoms lasting up to seven days and minor symptoms such as cough lasting up to several weeks (Eccles 2005), no specific treatment is normally needed in healthy individuals. Self-care measures such as maintaining an adequate fluid intake, a nutritious diet and plenty of rest is advisable (NICE 2009b). In the UK, a wide range of medicines indicated for the relief colds and flu symptoms are available OTC without the need of a prescription. Whilst the use of many of these products are not recommended by NICE due to the lack of efficacy (NICE 2011), OTC cough, cold and flu medicines are nonetheless extremely popular among the UK population (Boardman et al. 2005; McIntyre et al. 2003; Proprietary Association of Great Britain [PAGB] 2005a, 2005b, 2011a; Wazaify et al. 2005).

In the present study, 'URTI' is used to refer to infections that are caused by influenza as well as viruses that could rise to symptoms associated with a common cold.

6.1.3 Surveillance of influenza

Every year, influenza (Molinaria et al. 2007) and other viral respiratory tract infections (Fendrick et al. 2003) are associated with significant economical costs to the society and can place the National Health Service (NHS) under enormous pressure (Elliot et al. 2008; Fleming 2000, 2001; Meier et al. 2013; Pitman et al. 2007). The main reason for their substantial impact on healthcare demand is the ability to rapidly infect susceptible individuals and at times do so on a large scale causing epidemics or pandemics (Torok et al. 2009). Consequential to the high volume of people who might be affected and therefore requiring medical care, there has been an emphasis on surveillance of respiratory diseases in order to better manage healthcare resources, particularly during time of high healthcare demand (Davies and Finch 2003; Fleming 2001; Hanratty and Robinson 1999).

Other reasons for monitoring, particularly for influenza, are to gather information on when the flu season has started, which are the dominant strains circulating in the community, and to contribute knowledge towards the

decision on vaccine composition for the following season. Furthermore, surveillance information produce up to date reports on trends and spread in influenza activity, burden of disease, uptake and effectiveness of clinical countermeasures, for health professionals and the public (HPA 2012b). The emergence of the novel A/H1N1 (2009) influenza virus in the summer of 2009, which lead to the declaration of the first pandemic for 40 years (World Health Organization 2009), highlighted the need to strengthen influenza surveillance to better support the above goals to effectively manage an unexpected influenza outbreak (HPA 2010c).

In England and Wales, a variety of influenza surveillance systems are in place and they can be broadly divided into three categories as shown in Table 6.1.

Table 6.1 Sources of influenza surveillance data for England and Wales

Primary Care Surveillance
General practitioners surgeries
Telephone health helpline
GP Out-of-Hour consultation
Passive reporting of respiratory-related outbreaks
Flusurvey
Emergency department attendance (England only)
Medical Officers of School Association (South England only)
Community influenza telephone survey (England only)
Microbiological Surveillance
Virological Analysis
Sentinel virological surveillance scheme
Hospital Reports
Data Mart (England only)
Disease Severity and Mortality
Hospitalization
Mortality

Surveillance in primary care monitors unconfirmed cases of influenza in the general population and is based on data derived from clinical diagnosis by a doctor or from non-clinical surrogates that are known to resemble influenza activity (HPA 2013d; Public Health Wales [PHW] 2013a). The heterogeneity of the data ensures a good coverage of surveillance in the community. This potentially allows capturing of incidences in specific and vulnerable populations, such as school children, as well as individuals who may not be able or choose not to access healthcare services, such as users of telephone health helpline services.

Microbiological surveillance entails the collection and analysis of patient samples obtained through various networks of general practitioners (GP) surgeries, hospitals or private microbiology laboratories across the UK (HPA 2013d; PHW 2013a). Data collected via this route represents confirmed cases of true influenza infection, which enables the identification of circulating strains and provides statistics on positivity rates and guide the physician diagnosis of influenza.

Lastly, disease severity associated with influenza is estimated based on morbidity and mortality statistics derived from hospital admission for respiratory complications, such as pneumonia (HPA 2011), and all-cause death registration (Donaldson et al. 2009; HPA 2012b). Details about each of the schemes are documented elsewhere (HPA 2010c, 2012b; Public Health England [PHE] 2012).

6.1.4 Syndromic Surveillance

Outside of the UK, particularly in the US, the use of syndromic surveillance systems is becoming increasingly common in supporting the detection and management of influenza and respiratory disease outbreaks (Buehler et al. 2008; Paterson and Durrheim 2013). In comparison to traditional surveillance data described in the previous section, a syndromic surveillance system utilises novel, pre-diagnostic data that resembles the activity or onset of a particular disease, and adopts:

"*an investigational approach where health department staff, assisted by automated data acquisition and generation of statistical signals, monitor disease indicators in real time or near real time to detect outbreaks of diseases earlier and more completely than might otherwise be possible with traditional public health methods*" (Buehler et al. 2004).

A variety of disease indicators have been used as data input for syndromic surveillance systems to monitor influenza. Some examples include: emergency department visits (Bourgeois et al. 2006; Elliot et al. 2012; Josseran 2006), outpatient clinic visits (Harcourt et al. 2012), school absenteeism (Kara et al. 2011; van den Wijngaard et al. 2008), sales of prescription (Patwardhan and Bilkovski 2012; Sugawara et al. 2012) or OTC medicines (Anon. 2009e; Das et al. 2005; Hogan et al. 2003; Liu et al. 2013; Magruder 2003; Ohkusa et al. 2005; Vaergu et al. 2006; Villamarín et al. 2013), telephone triage or calls to health helpline services (Cooper et al. 2007; Espino et al. 2003) and data derived from web searches (Johnson et al. 2004) and social media (Culotta 2013). Many of these data sources have already demonstrated the potential to be a valuable tool for influenza surveillance (Buehler et al. 2008; Dailey et al. 2007).

Beside the ability to detect and track the spread of an influenza outbreak in a population (Smith et al. 2011; van den Wijngaard et al. 2011), several other advantages have been suggested to be associated with non-traditional compared to traditional influenza surveillance data. These include improved monitoring of disease burden (Liu et al. 2013), detecting a shift in antigenicity of influenza viruses (van den Wijngaard et al. 2011), providing an earlier warning for emerging influenza outbreaks (Dailey et al. 2007) and confirmation for the absence of unusual increase of disease cases (van den Wijngaard et al. 2011).

In England, the provision of syndromic surveillance for influenza and respiratory diseases currently consists of the routine monitoring of URTI symptom calls to NHS Direct (NHSD), which is a telephone health helpline service accessible to the general public living in England (Cooper et al. 2007).

Data on the number of respiratory-related admissions to emergency departments (Elliot et al. 2012) and GP out-of-hours consultations for ILI have also been utilised for influenza surveillance (Harcourt et al. 2012). At the time of writing, in Wales, the only example of syndromic surveillance is the use of cold and flu telephone call data from NHS Direct Wales (NHSDW) to monitor the activity ILI in community (PHW 2010b).

6.1.5 Over-The-Counter medicines sales data

As mentioned earlier, a syndromic surveillance system can utilise a myriad of data that are indicative of disease activity in a population. Among the data that have been tested, a number of studies explored using the sales of OTC cough, cold and flu medicines for the syndromic surveillance of influenza (Das et al. 2005; Hogan et al. 2003; Liu et al. 2013; Magruder 2003; Ohkusa et al. 2005; Villamarín et al. 2013). Some of these studies have been described in detail in Section 1.4.1. The rationale for using such sources is multifold and may apply to the UK population as described below.

Firstly, the symptoms of cold and flu are common in the UK population (McAteer et al. 2011; PAGB 2009) and they are frequently managed using a range of cold and flu medicines available without a prescription (PAGB 2005b). Secondly, the self-management of these cold and flu symptoms through the use OTC medicines often occurs prior to, or even instead of, seeking medical attention (Banks 2010; Willemsen and Harrington 2012). This, by implication, means sales of OTC cold and flu remedies could potentially be timelier in spotting an increase of influenza infection than healthcare service based surveillance.

Thirdly, in many community pharmacies automatic recording of sales information is already being undertaken through computers at the point of sale. A detail electronic record, including information on the type of medicine and location of the pharmacy, potentially could be made instantly available for transmission and subsequent analysis. This provides the opportunity for rapid detection of unusual increase in sales and initiation of public health measures.

Lastly, it has been suggested the cost of implementing a syndromic surveillance system using OTC medicines sales data would be lower than setting up a new, dedicated surveillance system (Wagner et al. 2003). This suggestion makes the assumption that the infrastructure and hardware required to enable data collection are already in place and maintained by the data suppliers. In addition, it assumes that the surveillance activity is embedded into the day-to-day operation of the data providers and imposes no additional burden.

At the time of writing this thesis, no syndromic surveillance system yet exists in the UK that utilises medicines sales data for of influenza surveillance. This is despite pharmacy businesses, medicine manufacturers and pharmaceutical marketing firms have already been, for many years, collecting and utilising these sales information for internal monitoring and sales forecasting. Syndromic surveillance studies conducted in non-UK populations indicated that sales of OTC cough, cold and flu remedies possess the potentials for detecting and monitoring influenza epidemics (Section 1.4.1). Whether or not the same could be applied to the UK population is unknown and no such study has been undertaken.

6.1.6 Aims and objectives

The aim of the current study was to explore whether the readily available medicine wholesale data for the sales of OTC cough, cold and flu medicines would be of value to the monitoring of seasonal influenza in Wales.

The specific objectives of the study were to:

- identify the pattern of sales for the selected OTC cough, cold and flu remedies
- determine the temporal relationship between sales of such medicines and influenza activity indicators
- determine which of those medicines studied are most sensitive to the activity indicators of influenza in the Welsh population

6.2 Method

6.2.1 Study design

The current study utilised historical pharmacy wholesale data for the sales of selected OTC cough, cold and flu medicines and compared the levels of sales, retrospectively, with two influenza activity indicators routinely used in Wales. Details about each of the datasets are described in the next section.

6.2.2 Medicines sales data

Pharmacy wholesale (herein referred to as pharmacy or medicines sales data) were obtained from the Regional Sales Analysis (RSA) database which was maintained by IMS Health. This was the same pharmacy sales database as utilised in Chapter 2 (Section 2.2.2.2), Chapter 3 (Section 3.2.2.2) and Chapter 4 (Section 4.2.2.2). Data obtained from the RSA database represented the purchase of medicines by pharmacies from wholesalers as a surrogate for pharmacy-to-patient sales which may occur at a later date.

In the present study, medicines sales data were expressed as the total number of unit packs sold on a monthly basis from May 2003 to April 2009 across Wales. One unit sale described the sale of one item, regardless of the volume or quantity contained in a pack.

The medicines included in the current analysis were any pharmacy (P) or General Sales List (GSL) medicine manually identified in the RSA database indicated for the relief of general cold and flu symptoms (e.g. all-in-one preparations), nasal congestion, sinusitis or coughs in adults. Products not available as oral dosage forms were excluded. In addition, generic products that were listed in the RSA database as a single-ingredient medicine, for example: paracetamol tablets/liquid, pseudoephedrine tablets/liquid or codeine phosphate linctus, were also excluded due to uncertainty as to whether they were sold OTC or used to dispense a prescription. Preparations that were considered suitable for the current study were grouped into three categories based on the classification used in the *Chemist and Druggist: Guide to OTC Medicines and Diagnostic* reference book (September 2008 issue). The three

categories were: (1) cold and flu, (2) cough and (3) sinusitis and nasal congestion medicines. Lists of all preparations in each of the category are shown in Appendix 18, Appendix 19 and Appendix 20, respectively.

6.2.3 Disease activity indicators

6.2.3.1 Influenza diagnostic data

Seasonal influenza data were provided by the PHW Communicable Disease Surveillance Centre (CDSC); an epidemiological investigation arm of PHW. The CDSC serves several public health functions concerning mainly infections from detecting and investigating infectious disease outbreaks to their monitoring and dissemination of relevant information within Wales (PHW 2011b). The influenza data were collected by a sentinel surveillance network that were comprised of 44 volunteer, GP practices across the whole of Wales, covering approximately 10% (355,000 patients) of the Welsh population (PHW 2011b). This network of GP practices is the routine data provider for the monitoring seasonal influenza in Wales (PHW 2011b). The participating GP practices recorded anonymised basic patient information and the date of influenza diagnosis based on the clinical case definition of: URTI symptoms, fever, chills, myalgia and cough.

Prior to 2010, influenza diagnostic data were manually recorded using notepads by the practitioner and reported to PHW using post, email or fax. This has subsequently been replaced by an automated system named 'Audit+ Data Quality System' which started operating in October 2010 (PHW 2011b). The new surveillance system include an improved coverage of 400 (80%) GP practices in Wales (Keramarou et al. 2011). The current study did not include data collected by the Audit+ Data Quality System as the new system was set up post the data collection period.

In the current study, the numbers of clinically diagnosed cases of influenza for each of the seven age bands (0-4, 5-14, 15-24, 25-34, 35-44, 45-64, 65+ years old) were obtained for Wales in a weekly format for a six-year period between May 2003 and April 2009. The weekly data were aggregated into their

corresponding month. Diagnosis of influenza in children under 15 years old were excluded from the study to reflect the range of cough, cold and flu products included in the pharmacy sales data which were primarily indicated for adults.

6.2.3.2 Telephone health data

NHSDW is a confidential, nurse-led, telephone health helpline service that was set up in 2000 for Wales and is similar to NHSD operating in England (Hanlon et al. 2009). The NHSDW service, managed by Welsh Ambulance Service NHS Trust, operates 24 hours a day and seven days a week. The goal of the service is to provide an open-to-all gateway to reliable and timely health information and advice for everyone in Wales. In addition to handling calls made to NHSDW via a dedicated telephone number NHSDW also provides out-of-hour call handling and clinical telephone triage for GP out-of-hour, emergency dental and medical care services and ensures unscheduled care resources are allocated appropriately according to the urgency of the call (Colman 2009). Calls to NHSDW are charged at the same rate as any local landline number.

When a call is made to NHSDW, a call handler will first take some basic personal details and determine the urgency of the call, for example, whether the call was for a request of health information or query regarding a medical condition. Depending on the nature of the call, it may then be transferred to a nurse, a health information advisor or a dental nurse advisor where the caller's symptoms are assessed in more detail and the best course of action determined.

The clinical assessment process is aided by Clinical Assessment System, a computer-based decision support software, whereby the nurse uses his or her own clinical judgement and chooses the most appropriate, symptom-based, clinical algorithms to respond to caller's symptoms (Jones 2008). There are around 200 clinical algorithms and each consists of a series of questions relating to the symptoms described, which eventually leads to a recommended outcome (Cooper 2008). The outcome may result in the caller receiving information about how to care for themselves at home, details of a local pharmacy to attend, or if the problem is more serious, they might be advised to

see their GP or go to a hospital. If needed, NHSDW can also arrange an ambulance to be sent to the caller (Cooper and Chinemana 2004; Colman 2009).

In the current study, NHSDW call data for clinical algorithms for cold and flu symptoms and symptoms affecting the nose, sinuses and throat were obtained directly from Welsh Ambulance Service NHS Trust. The specific clinical algorithms included in the study were: (1) cold and flu, (2) nasal congestion, (3) stuffy nose, (4) coughs and (5) sore throat. Call data for children 15 years old and below were excluded from the NHSDW analysis.

NHSDW call data were obtained for a three-year period from May 2006 to April 2009 (three years less data than both GP diagnostic data and OTC medicine sales data). The call data were provided in a daily format with the following details about each call: clinical algorithm used, caller's home location in 22 Local Health Board (LHB) geography and date of the call. Daily call data were aggregated into their corresponding month and the total monthly calls made to NHSDW for Wales were calculated. In addition to the call data obtained for the five selected clinical algorithms, daily data for the total number of calls to NHSDW, irrespective of the clinical algorithm used, were also obtained. The call volume for each of the selected clinical algorithm was expressed as a percentage of total calls each month.

6.2.4 Data processing

Each of the three datasets was obtained from a different source and they had to be processed into appropriate format before statistical analysis could be undertaken. All processed and reorganised data were manually screened for errors before transferring to the statistical software for analysis (PASW v18).

Influenza diagnostic data were provided by PHW in a weekly format in Microsoft Excel spreadsheet. The corresponding monthly aggregates of numbers of influenza diagnoses were computed using Microsoft Excel spreadsheet.

NHSDW call data were provided in Microsoft Excel spreadsheet in a list format and the calls were arranged in chronological order based on the date and time of each call. Two new variables were created in Microsoft Excel spreadsheet that corresponded to the month and the year of the call using the built-in date and time functions before importing into PASW v18 for further analysis.

Crosstabs function in PASW v18 was used to compute the count of the calls by clinical algorithm and LHB geography for each month of each year. The data were then exported into a Microsoft Excel spreadsheet and calls made in each of the 22 LHBs were combined to give the total number of calls for Wales. Finally, the volumes of cold and flu symptom calls as a percentage of total calls were calculated in Microsoft Excel spreadsheet.

Pharmacy sales data were extracted from the IMS Health Dataview and exported into Microsoft Excel spreadsheet as described in Appendix 9. The packs of OTC preparations sold in each of the 22 LHBs were combined to give the total figures for Wales using Microsoft Excel.

6.2.5 Analysis

6.2.5.1 Descriptive analysis

The times series for the sales of OTC (1) cold and flu, (2) cough and (3) nasal congestion and sinusitis medicines were each separately compared with the time series of (a) cold and flu symptom calls made to NHSDW and (b) numbers of influenza diagnosis and their patterns examined.

In order to present the time series of medicines sales data, NHSDW call data and influenza diagnostic data on the same time series chart their data values needed to be standardised. The standardised time series was computed by converting each data point for the sales of medicines, number of symptomatic calls and influenza diagnosis to number of standard deviations away from their respective data mean. The data mean was the mean of all available data points for the respective time series.

The times series for the sales of OTC medicines were compared with GP diagnostic time series for the period May 2003 to April 2009; and with NHSDW call data for the period May 2006 to April 2009.

6.2.5.2 Cross-correlation function

Cross-correlation function is a common method used to help to understand the temporal relationship between one signal relative to another (Dailey et al. 2007). It does so by calculating the correlation coefficient (r) between two time series, by moving one in time relative to the other, at different time latencies or time lag (t). This process identifies at what specific time latency the correlation between two time series would be at their maximum. This indicates the timeliness of one signal (e.g. sales of OTC medicines) in relation to another (e.g. cold and flu symptom calls or influenza diagnosis). In other words, if one time series demonstrated a significantly similar pattern to another time series but earlier, it may possess the capability for early detection. It has been suggested cross-correlation function is useful in the early phase of exploring the potential of a new disease surveillance data (Dailey et al. 2007; Edge et al. 2006; Espino et al. 2003; Hogan et al. 2003; Johnson et al. 2004; Magruder 2003).

In the current study, cross-correlation function was used to determine the maximum correlation between two time series at time latencies between t=-3 and t=3. A correlation of r=1 indicates the two time series are identical; r=0 means they share no correlation; r=-1 suggests the two time series are identical but showing the opposite trend. In terms of timeliness, a maximum and statistically significant correlation observed at a positive time latency (e.g. t=1, 2 or 3), this would suggest the medicine sales time series preceded the disease activity indicator time series and provided a timelier detection. Conversely, if it was observed at a negative time latency, this would suggest the medicines sales time series lagged behind the disease activity indicator time series and provided a delayed detection. If the maximum correlation is observed at a time latency of zero, this would suggest the medicines sales time series was no more or less timely than disease indicator time series.

An example of a cross-correlation chart is shown in Figure 6.1. A correlation exceeding the 95% confidence interval, as marked by the upper and lower confidence limits (two standard errors), was considered to be statistically significantly different from no correlation. In the example shown in Figure 6.1, upper and lower confidence limits mark the bounds of 95% confidence interval. The vertical bars indicate the maximum correlation of r=0.77 was observed at the time latency of 1 and exceeded the 95% upper confidence limit. These results suggest (a) there is a significant positive correlation between the two time series, and (b) this occurred when one time series preceded the other by one unit of time and therefore the former data source potentially possess an early detection capability for the latter.

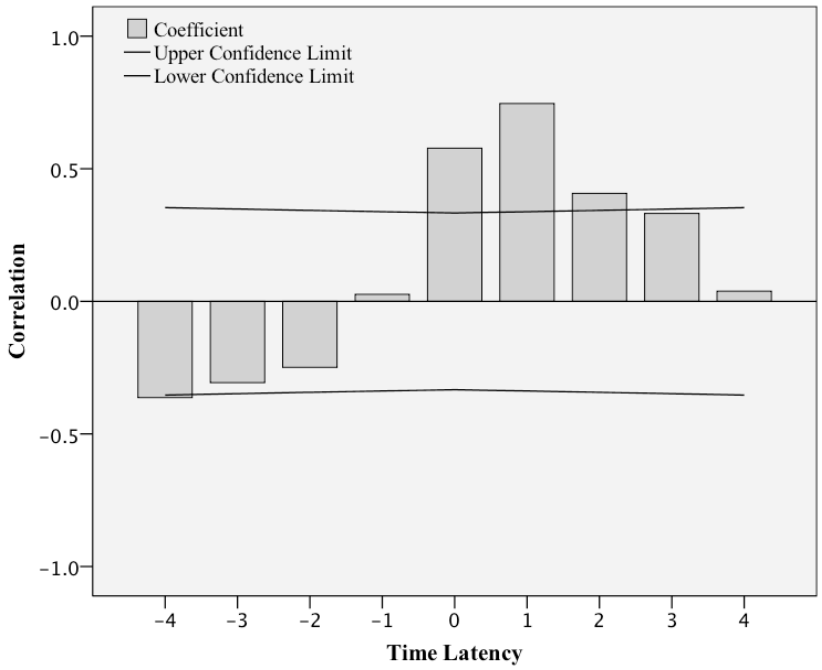


Figure 6.1 An example of a cross-correlation chart showing the correlations of two time series at a time latency between t=4 and t=-4. Upper and lower confidence limits mark the bounds of 95% confidence interval (± two standard errors)

All data analysis and statistics were performed using PASW version 18 (PASW Inc., Chicago, IL, USA).

6.3 Results

6.3.1 Descriptive analysis

6.3.1.1 Sales of Over-the-Counter medicines

A total of 117 preparations (cold and flu medicines [n=88], cough medicines [n=9], nasal congestion or sinusitis [n=20]) were identified and extracted successfully from the RSA database. As shown in Figures 6.2, 6.3 and 6.4, respectively, a marked seasonal pattern was associated with the sales of each of the three categories of medicines. Each year, peak sales generally occurred between September and January, corresponding to the winter months, and the nadirs between May and August, corresponding to the summer months.

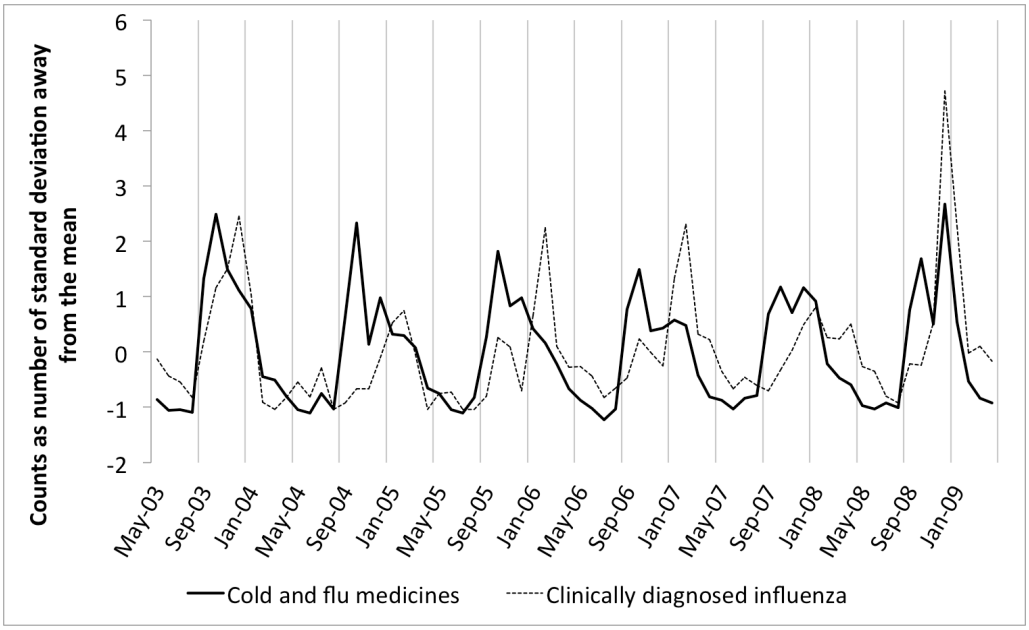


Figure 6.2 Sales of selected over-the-counter cold and flu medicines and number of general practitioner diagnosed influenza for Wales presented as the number of standard deviations away their respective mean

The increase in the sales of cold and flu medicines during the winter consisted of two distinctive peaks and could be characterised by the observation of one larger spike in October followed by a smaller spike in December (Figure 6.2). This pattern for the cold and flu category of medicines was observed every

winter during the study period with the exception of 2003/04 and 2006/07. During the former period, only one spike in sales was observed and in the latter the second smaller spike occurred in January instead of December.

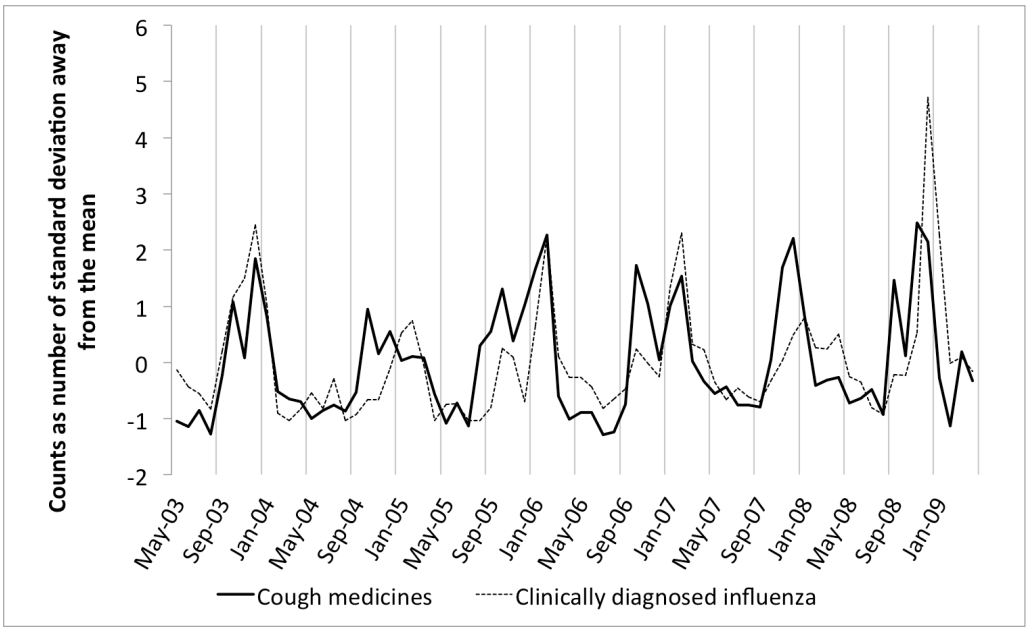


Figure 6.3 Sales of selected over-the-counter cough medicines and number of general practitioner diagnosed influenza for Wales presented as the number of standard deviations away their respective mean

Similar to cold and flu medicines, cough medicines saw the highest levels of sales between October and December but this was only observed for four out of the six winters that were monitored (2003/04, 2004/05, 2007/08, 2008/09). In the two winters that did not match this trend (2005/06 and 2006/07), the observation of the second sales spike was in February instead of December (Figure 6.3). Unlike cold and flu medicines, not every winter season during the study period demonstrated a two-peak sales pattern during the winter, nor was it the case that a large spike was always followed by a smaller spike. For example, only one spike was observed in the winters of 2007/08. In the winters of 2004/04, 2005/06 and 2008/09, whilst two peaks were present the second spike was larger than the first. Nadirs for the sales of cough medicines generally occurred between May and September each year.

Sales patterns for the nasal congestion and sinusitis category of medicines were similar to the pattern of cold and flu medicines (Figure 6.4). Their peak sales occurred between September and January each year and this was also characterised by the presence of two peaks with one large spike observed in October followed by a smaller, second spike in December. The only exception to this pattern was in the winter of 2007/08, during which the October peak was absent but the December peak was observed.

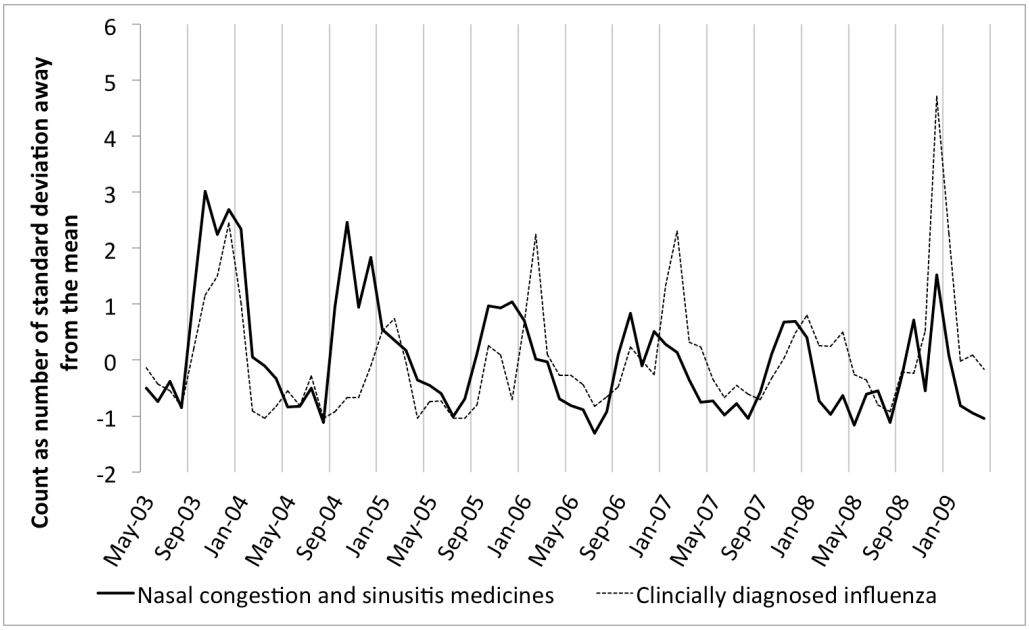


Figure 6.4 Sales of selected over-the-counter nasal congestion or sinusitis medicines and number of general practitioner diagnosed influenza for Wales presented as the number of standard deviations away their respective mean

6.3.1.2 Influenza diagnosis

The pattern of GP diagnosed influenza from May 2003 to April 2009 in relation to the sales of (1) cold and flu, (2) cough and (3) nasal congestion and sinusitis medicines are shown in Figure 6.2, Figure 6.3 and Figure 6.4, respectively. Over the six year study period, influenza diagnosis was the highest in either January or February for four out of six of the winters (2004/05, 2005/06, 2006/07, 2007/08). In two of the winters (2003/04 and 2008/09), the highest level of influenza diagnosis was observed in December.

The timing of peak sales for each of the three categories of medicines and peak influenza diagnosis were compared. For cold and flu medicines the occurrence of highest point of sales all preceded peak influenza diagnosis by two to four months except for 2008/09. During the winter of 2008/09, the second sales spike was observed in December and this coincided with peak influenza diagnosis.

Cough medicines saw the month of peak sales matched with peak influenza diagnosis for three out of the six winter seasons (2003/04, 2005/06, 2006/07). For two of the winter seasons the month of peak sales preceded peak influenza diagnosis by one month (2007/08, 2008/09).

Nasal congestions and sinusitis medicines saw matching peak sales and peak influenza diagnosis for two of the winter seasons only (2003/04, 2008/09). In all other winters the month of peak sales preceded the month of peak influenza diagnosis by three to four months.

6.3.1.3 Calls to NHS Direct Wales

Cough symptom and cold and flu symptom calls to NHSDW both demonstrated a strong seasonal trend during the three years between 2006 and 2009. The timing of peak call volume for cough symptoms and cold and flu symptoms calls was observed within the same month or within one month difference (Figure 6.5).

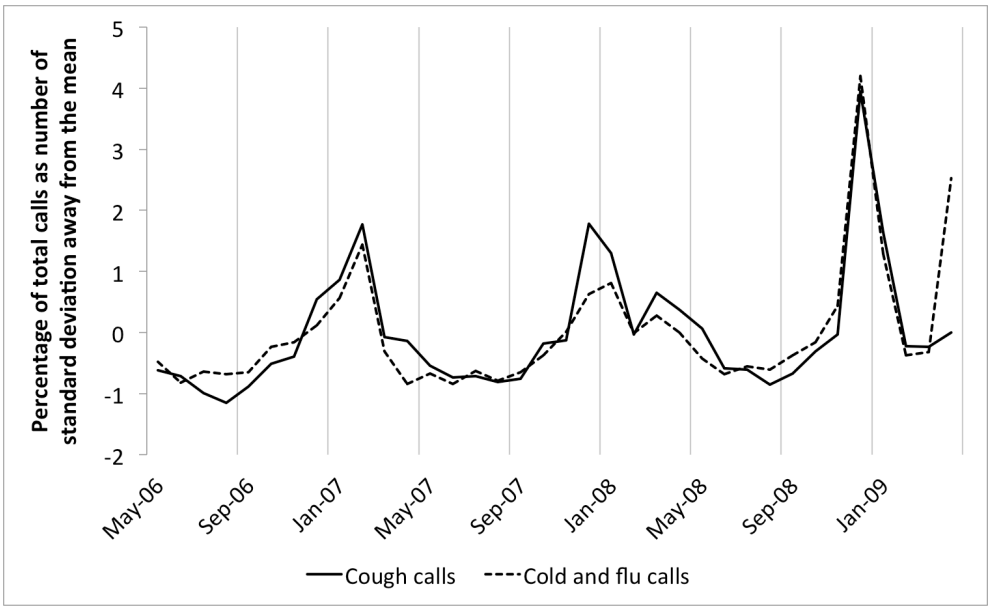


Figure 6.5 (1) Cough symptom and (2) cold and flu symptom calls as a percentage of total calls to NHS Direct Wales presented as the number of standard deviations away their respective mean

In contrast, sore throat calls showed no marked seasonal trend or any discernible pattern over the study period. However, a distinctive peak in December could be identified each year (Figure 6.6).

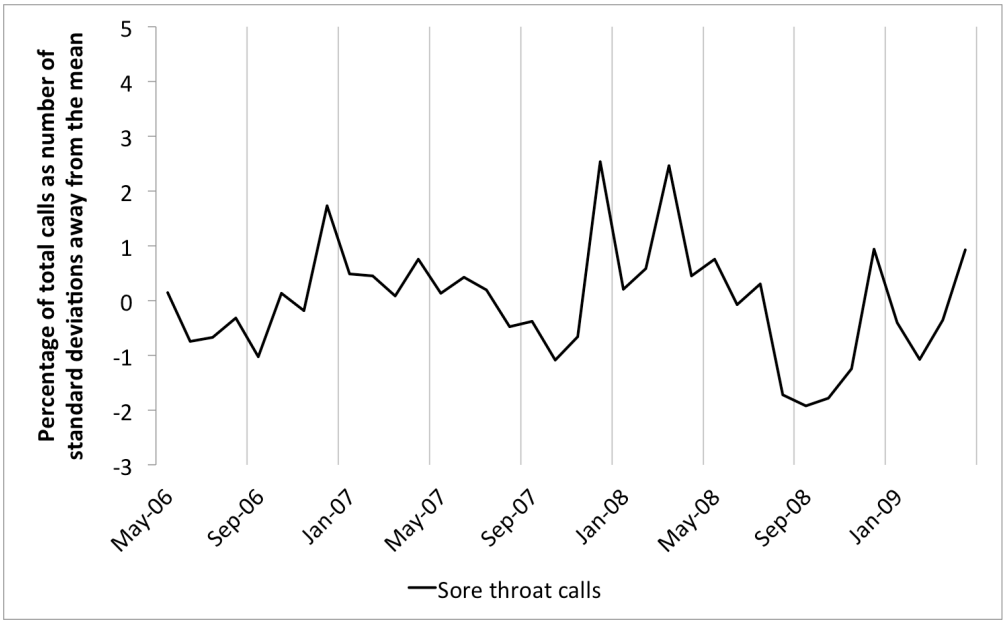


Figure 6.6 Sore throat symptom calls as a percentage of total calls to NHS Direct Wales presented as the number of standard deviations away their respective mean

Comparisons between the peak sales of medicines and calls to NHSDW revealed where there were two peaks in a winter season for the sale of medicine the timing of the first spike, in all cases, preceded the timing of peak calls to NHSDW by two to four month. By contrast, the timing of the second spike for the sales of medicine generally coincided with the timing of peak calls to NHSDW. These features were observed for (1) cold and flu, (2) cough, and (3) nasal congestion and sinusitis categories of medicines studied (Figure 6.7, Figure 6.8, Figure 6.9, respectively).

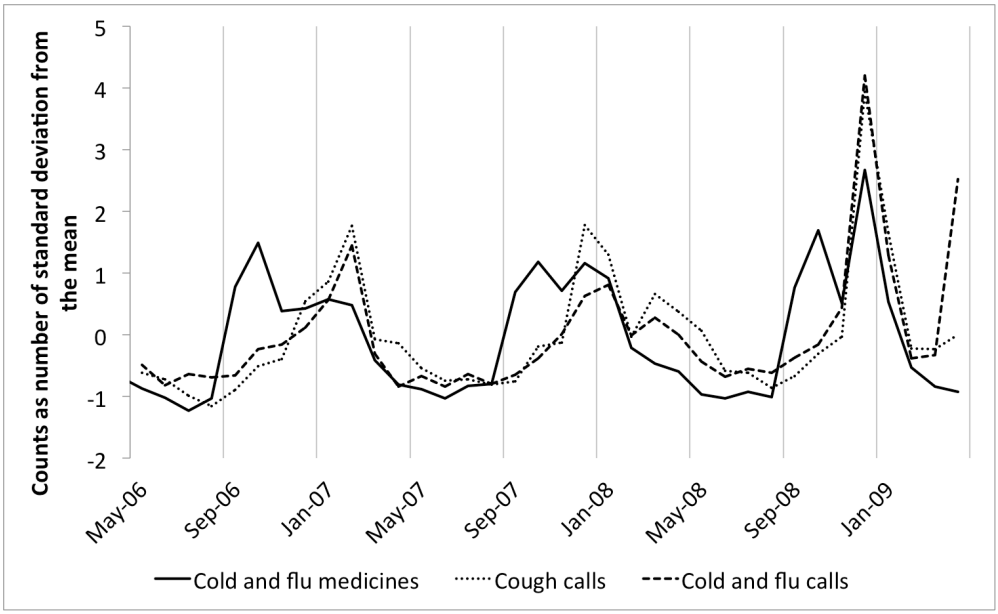


Figure 6.7: Sales of selected over-the-counter cold and flu medicines and calls made to NHS Direct Wales about cough or cold and flu symptoms presented as the number of standard deviations away from their respective mean

The analysis of NHSDW call data revealed calls reporting (1) nasal congestion and (2) stuffy nose symptoms were both low. During the period of available call data from 2006 to 2009, the cumulative numbers of calls in each 12 month period for nasal congestion symptoms were 47, 52, 80, 63, respectively. Stuffy nose symptoms were 15, 16, 2, 4, 2, respectively. In the 12 months to April 2009 calls reporting these two symptoms represented less than 0.05% of the total calls made to NHSDW. As a consequence of the low numbers these calls data were not analysed. The mean percentages of calls to NHSDW for (1) cold

and flu, (2) cough and (3) sore throat symptoms were 0.3%, 1% and 1.8%, respectively.

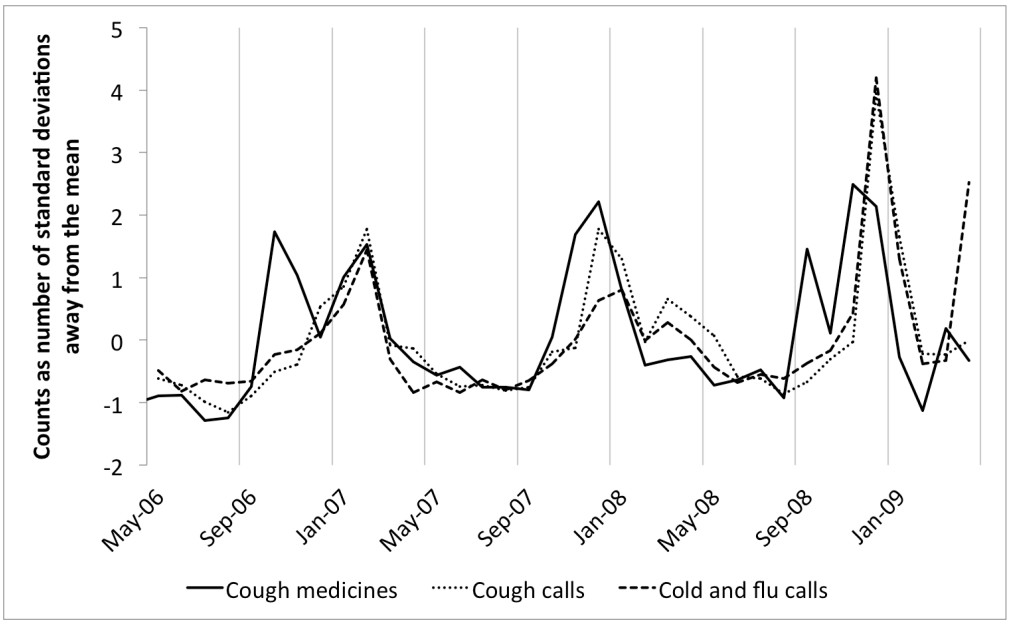


Figure 6.8: Sales of selected over-the-counter cough medicines and calls made to NHS Direct Wales about cough or cold and flu symptoms presented as the number of standard deviations away from their respective mean

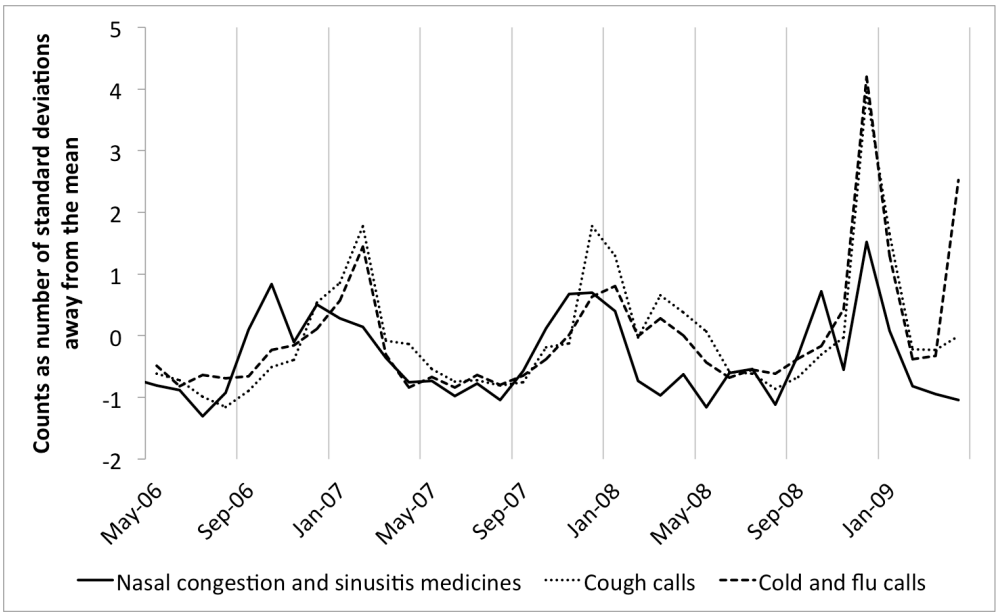


Figure 6.9: Sales of selected over-the-counter nasal congestion or sinusitis medicines and calls made to NHS Direct Wales about cough or cold and flu symptoms presented as the number of standard deviations away from their respective mean

6.3.2 Cross-correlation analysis

The results for the cross-correlation analysis are shown in Table 6.2. Out of the three categories of OTC medicines studied, cough medicines demonstrated a significant positive correlation with influenza diagnosis (r=0.61) and calls to NHSDW for cough (r=0.74), cold and flu (r=0.64) symptoms. The time latency in which these maximum correlations was observed were all t=1. This suggests sales of cough medicines provided a one month earlier signal for peak influenza activity than the disease activity indicators. A significant positive correlation (r=0.50) was also observed at a time latency of t=1 between the sales of cold and flu medicines and influenza diagnosis.

A significant positive correlation was observed between sales of nasal congestion and sinusitis medicines and influenza diagnosis (r=0.37), cough symptom calls (r=0.63), cold and flu symptom calls (r=0.52). The time latency in which these maximum correlations occurred were all observed at a time latency of t=0. This suggests sales of nasal congestion and sinusitis medicines was no different in timeliness for signalling influenza compared to the disease activity indicators. The maximum correlation between the sales of cold and flu medicines and cough symptom and cold and flu symptom calls to NHSDW were both significantly positive (r=0.53 and r=0.60, respectively). The time latency in which they were observed was at t=0 and t=2, respectively.

Contrary to the finding thus far, cross-correlation for the sales of the cold and flu, cough and nasal congestion or sinusitis medicines with sore throat symptom calls revealed a weak and significant negative correlation (r=−0.5, −0.39, −0.45) at a time latency of t=−3, t=−2, t=−2, respectively. The cross-correlation chart for the sales of cough medicines and sore throat calls to NHSDW is shown in Figure 6.10 to illustrate the observation of a negative correlation and at a negative time latency.

Table 6.2 Results of the cross-correlation analysis for the sales of over-the-counter (OTC) medicines, number of influenza diagnosis (May 2003 to April 2009) and calls to NHS Direct Wales for cold and flu symptoms (May 2006 to April 2009). The time latency (t) in which the maximum correlation (r) occurred between medication sales and disease activity indicator is reported (r, t [95% CI]). A positive t value indicates that change in the sales medicines preceded (i.e. more timely than) those of the disease activity indicator or vice versa. If a t=0 then neither data source is timelier or later than the other

	Cold and flu medicines	**Cough medicines**	**Nasal congestion or sinusitis medicines**
Influenza diagnosis	0.50, 1 -0.24, 0.24)	0.61, 1 (-0.24, 0.24)	0.37, 0 (-0.24, 0.24)
Cold and flu calls	0.53, 0 (-0.33, 0.33)	0.64, 1 (-0.34, 0.34)	0.52, 0 (-0.33, 0.33)
Cough calls	0.60, 2 (-0.34, 0.34)	0.74, 1 (-0.34, 0.34)	0.63, 0 (-0.33, 0.33)
Sore throat calls	-0.50, -3 (-0.35, 0.35)	-0.39, -2 (-0.34, 0.34)	-0.45, -2 (-0.34, 0.34)

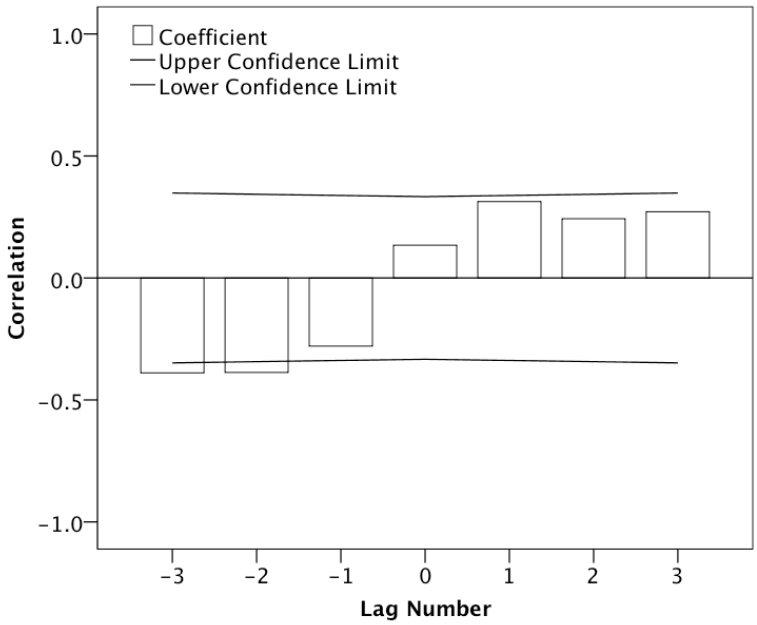


Figure 6.10 Cross-correlation chart for the sale of OTC cough medicines and calls to NHS Direct Wales for nasal congestion and sinusitis symptoms. Upper and lower confidence limits mark the bounds of 95% confidence interval

6.4 Discussion

6.4.1 Main findings

The results from the current study showed pharmacy wholesale data for (1) cold and flu, (2) cough and (3) nasal congestion or sinusitis categories of OTC medicines are well-correlated with clinically diagnosed influenza by GPs as well as with self-reported URTI symptoms to NHSDW, namely cough, cold and flu symptoms. These findings suggest (a) an increase in the sales of these products reflect the presence of some of the symptoms in the community and (b) a signal corresponding to seasonal influenza activity potentially exists in the pharmacy wholesales data. These observations are in agreement with the findings reported by others in non-UK populations (Das et al. 2005; Edge et al. 2006; Espino et al. 2003; Hogan et al. 2003; Johnson et al. 2004; Liu et al. 2013; Magruder 2003; Ohkusa et al. 2005; Pelat et al. 2010; Vergu et al. 2006) and lend support to further explore OTC medicines sales data as a potential source of surveillance information for seasonal influenza and upper respiratory diseases. An exception was the sales of OTC medicines and sore throat symptoms which revealed a significant negative correlation at negative time latency. The exact reason for this is unknown.

Of all the medicines studied, the cough medicine category correlated with influenza diagnosis the strongest and therefore warrants attention for further investigation. This is possibly because cough symptoms have been found to be one of the most predictive signs in differentiating patients with a true influenza infection from those with an influenza-like illness (Monto et al. 2000; Woolpert et al. 2012). The clinical case definition used by GPs in making a clinical diagnosis of influenza also included cough as a criterion and may have contributed to the high correlation between the time series. In line with this finding, a study by Liu et al. (2013) conducted in the US also showed sales of cough medicines were, among others, the group of medicines most strongly associated with hospital volumes of patients with influenza-like illnesses.

The variation observed in correlation between the different categories of medicines and respiratory disease indicators could be attributed to a number

factors. This may include the local availability of OTC products, usage pattern and accessibility to local healthcare services. Furthermore, depending on the dominating strain of influenza virus circulating at the time, symptoms experienced by the general population may differ between seasons. In addition, symptoms may also vary by age group, such as in the case of H1N1 influenza A virus as cough has been reported to be more prevalent in adults but not in children (Kuo et al. 2011). Consequently, cough may not always be a universal early symptom for influenza and the predictability of other therapeutic class of OTC medicines should be explored (e.g. sore throat medicines).

A two-peak pattern was identified for the sales of OTC medicines between the month of September and January. This feature was particularly prominent, although not exclusively observed, for cold and flu medicines. In nearly all of the winter seasons monitored the first of the two spikes almost all appeared in October and was followed by a second spike at around January or February time. One possible explanation for this is that the early October peak represented community pharmacy making advance purchases of stock in anticipation for the upcoming winter season. By contrast, the onset of the second sales peak corresponded well with the onset of peak influenza activity in some of the winters during the study. This potentially suggests the second sales peaks were associated with actual disease incidents taking place in the community. The presence of these two different signals in the pharmacy sales data could have reduced the correlations between the sales of medicines and influenza activity indicators.

The temporal relationship between sales of medicines and diseases activity indicators was examined using cross-correlation function. This was a simple procedure and utilised all of the data points in the statistical analysis. Cross-correlation has been used by many studies, either alone or in combination with another signal detection method, for evaluating the potential of a new type of syndromic surveillance data (Das et al. 2005; Edge et al. 2006; Espino et al. 2003; Hogan et al. 2003; Johnson et al. 2004; Kirian and Weintraub 2010; Liu et al. 2013; Magruder 2003; Pelat et al. 2010; Vergu et al. 2006).

The results from the cross-correlation analysis showed the medicines sales data appeared to have provided at least an equal or earlier indicator for influenza and URTI symptoms than the GP surveillance system and calls data collected by NHSDW. However, a difference in the early detection capability between the three categories of medicines was observed. For examples, sales of nasal congestion or sinusitis medicines provided no early signal for influenza diagnosis and URTI symptoms. In contrast, cough medicines consistently provided a one-month earlier signal for influenza diagnosis and URTI symptoms. Sales of cold and flu medicines provided between no early signal to two months earlier signal for influenza diagnosis and URTI symptoms. These variations were not unexpected as they probably reflected the different symptoms that are experienced at different stages of an infection (Eccles 2005; Heikkinen and Järvinen 2003) and has been reported by other also (Liu et al. 2013). However, the buy-in nature of the wholesale data could have confounded these results (discussed in Section 6.4.3.1) and therefore they need to be interpreted with caution.

A number of studies conducted outside the UK has demonstrated the early detection capability of medicine sales data for influenza and respiratory infections (Das et al. 2005; Hogan et al. 2003; Liu 2013; Magruder 2003; Vaergu et al. 2006). In these studies the earliness of detection has been reported to be ranged between 2 days and up to three weeks. Results from the present study indicate the current pharmacy sales data preceded GP diagnosed influenza and self-reported URTI symptoms by up to two month. This level of early detection outperformed that reported by any of the previous studies. This may have been associated with the buy-in nature of the current pharmacy sales data and should be interpreted with caution.

6.4.2 Strengths of the study

The current study utilised readily available surveillance data which have been collected via a consistent method over a seven-year period. The large amount of historical data was useful for identifying patterns and trends to allow comparison between the different winter seasons.

The collection of medicine sales data was facilitated by an existing and extensive network of community pharmacy in Wales. It was an inexpensive and convenient way of collating surveillance data compare to other kinds of influenza surveillance systems, such as the sentinel GP surveillance network. Since many community pharmacies, particularly large multiple chains, already operate and maintain electronic systems of their own for recording sales of medicines for commercial purposes, the technical effort and time required for obtaining such data was low. Although there were some limitations about the pharmacy sales data used (Section 6.4.3.1), they were considered suitable for generating preliminary results that may inform future research direction.

Medicine sales data were compared with robust and routinely used datasets for the surveillance of seasonal influenza in Wales (PHW 2010b). Data from the two systems (NHSDW and GP sentinel network) are reliable and acted as a reference for disease activity in which new types of surveillance data could be evaluated against. Other surveillance data, such as results from microbiological surveillance, were also obtained from PHW at the time of the study but were not used due irregularity in patient sample submission between the months of perceived high and low risk of influenza infection by the GPs. Furthermore, no or low numbers of samples submitted during periods other than the winter months also prevented them from being useful for trend and pattern identification.

The comparison between sales of cough medicines and cough symptom calls yielded a stronger correlation than with (1) sore throat and (2) cold and flu symptom calls. This was a positive outcome as it provided some reassurance that the pharmacy sales data was correlating with the symptom of which the product is primarily indicated. The moderately-positive correlations observed between the sales of medicines and what appeared to be an unrelated disease indicator, such as cough symptom calls and sales of nasal congestion or sinusitis medicines, may have been a reflection of onset of multiple symptoms during the course of a cold or a flu infection (Eccles 2005; Heikkinen and Järvinen 2003).

6.4.3 Study limitations

This was the first study in Wales to examine the potential of pharmacy sales data as an alternative data source for the surveillance of seasonal influenza. A number of limitations have been identified and these are discussed in this section.

6.4.3.1 Medicines sales data

Range of products

The OTC medicines included in the present study were limited to preparations that were ready available for extraction in the RSA database. Consequently, data for less than a complete coverage of products were obtained for each of the medicine categories. For example, the cough medicine category contained the least number of preparations and was made up of mostly generic products. In contrast, the cold and flu medicine and nasal congestion or sinusitis medicine category consisted predominantly proprietary products. Whether a different sales trend would have been observed between the proprietary and generic product for each category of medicines is unknown. Future studies should include a greater range of products for each of the medicine categories and test if doing so would improve the sensitivity of medicine sales data to influenza activity or vice versa.

Grouping strategy

Medicines were placed into separate categories based on their main indication using a reference book for OTC medicines (Chemist and Druggist: Guide to OTC Medicines and Diagnostic reference book, September 2008 issue). This method of grouping assumes there was a universal usage pattern for these products across all geographical regions and is associated with two potential issues in disease surveillance. Firstly, differences in customers' perception of which product is most useful for a certain symptom can vary from population to population. Secondly, a grouping strategy based on clinical indication may not be the most effective way to discover medicinal products that are most sensitive to a particular disease.

To address these two issues, sophisticated statistical methods have been developed with the goal to identify medicinal products that are most sensitive to a disease in a population (Cami et al. 2009; Magruder 2004; Pelat et al. 2010; Wallstrom and Hogan 2007). However, these techniques have mainly been applied in studies where sales data are available for a large number of medicines. The present study included a total of 117 products which was a small number of products compared to studies that have utilised these specialised clustering techniques (n=768 unique products [Wallstrom and Hogan 2007], n=384 therapeutic classes [Pelat et al. 2010]). Nonetheless, adopting a specialist clustering method may become increasingly important as more complete and larger database of OTC medicine sales data becomes available over time.

Factors unrelated to disease activity

Sales of OTC cold and flu medicines are often accompanied by promotions and advertising campaigns particularly during the winter seasons. These activities could be targeted at pharmacies to encourage stock purchase or at the general public to raise product awareness. An increase in awareness about a product could potentially give rise to an unexpected increase in sales that may be misinterpreted as the emergence of an influenza outbreak. This could result in public health resources being wasted on subsequent investigations. Several studies approached this problem by obtaining marketing information relevant to the products monitored and interpreted suspicious increases in sales in conjunction with these information (Das et al. 2005; Kirian and Weintraub 2010; Liu 2013; Wagner et al. 2003; Welliver 1979). However, the current pharmacy sales data obtained from IMS Health was not accompanied by such data and thus the impact of promotion status on medication sales is not known.

As mentioned before (Section 6.4.1), one problem associated medicines wholesales data was that it could be affected by advance purchases of cold and flu medicines before the arrival of winter season each year. This provides a possible explanation for the two-peak sales pattern observed during the winter period. The onset of the first of the two peaks (October and January/February, respectively) could not be explained by either an increase in influenza

diagnoses or URTI symptoms experienced in the community during the same time. Having recognised that the early peak in sales may not have been due to the onset of actual respiratory infections in the community, the study attempted to control for this by creating a time series model that would eliminate this signal. However, this endeavour was unsuccessful and was not explored further.

As the study was unable to exclude the possibility that an increase in medicine sales may have been, in part, caused by the advance purchase of stock by pharmacies, the findings on medicines sales data as a potential early indicator for influenza and URTI symptoms need to be interpreted with caution. To overcome this challenge, actual pharmacy-to-patient sales data should be obtained instead of wholesale data.

Data reporting interval

The medicines sales data used in the current study were only available in a monthly format. Consequently, the earliness of medicines sales data in terms of identifying a change in influenza activity could only have been measured on a monthly scale. This reporting interval is substantially longer than weekly or daily sales data that have been used in other disease surveillance studies (Das et al. 2005; Edge et al. 2006; Kirian and Weintraub 2010). One drawback about the long data reporting interval is that an early detection of a disease signal by a few days could potentially be interpreted as having provided no early warning. Conversely, an early detection of a disease by a few weeks may be interpreted as having provided a one-month early warning. To overcome this, future studies should obtain daily or weekly sales data and verify the early detection ability of medicines sales data for influenza.

6.4.3.2 Disease activity indicators

Influenza diagnostic data

Data for clinically diagnosed influenza cases were collected through a volunteer sample of 44 GP practices which formed the Wales Sentinel Surveillance Scheme (PHW 2011b). This group of GP practices has been

collecting data since 1985 with no change in case definition and covers approximately 10% of the entire Welsh population (PHW 2011b). Although a 10% coverage of the population may appear low, an early review of the scheme indicated the proportions of patients in each age groups were comparable to the Welsh population (Palmer and Smith 1991).

The provision of the original Wales Sentinel Surveillance Scheme was superseded by the new 'Audit+ Data Quality System' introduced in 2010. The new system consisted of an improved coverage of 80% of all GP practice in Wales (PHW 2010b). It is now, at the time of writing, the main source of influenza surveillance data for Wales.

One of the changes introduced as part of the new system was the use of a Read Code based definition of influenza diagnosis instead of clinically diagnosed influenza based on symptoms (PHW 2010b). The Read code is a standardised coding system that classifies clinical terminologies used in the general medical practice, including codes for the diagnosis of a disease (Health and Social Care Information Centre 2013). Whether or not the new coding system would have an impact on influenza statistics and, by implication, influence the correlation between medication sales and influenza diagnosis observed in the current is not clear. A revalidation of the correlation between sales of the selected medicine and influenza diagnosis derived from Read codes may be necessary in the future once the Audit+ Data Quality System has accumulated sufficient data for historical comparison.

NSH Direct Wales call data

Unlike data for the sales of OTC medicines and clinically diagnosed influenza, which covered a total of six winter periods, NHSDW call data were only available for three winter periods. This was due to a system-wide change in how the NHSDW calls were recorded in 2006 and therefore data prior to 2006 could not be used. A longer period of study would have increased the confidence in the results.

6.4.3.3 Statistical analysis

Sales of selected OTC medicines were compared to influenza diagnosis and symptomatic calls to NHSDW by comparing the onset of their peak activity. As noted by Dailey et al. (2007), one weakness about the peak comparison method is that it only acknowledges data points that are of the highest value. Other features which might also be important about a peak, such as its size and width, are ignored. Whether or not these other features would provide additional information about an influenza epidemic was not explored in the present study.

Cross-correlation measures the association between two variables and does not imply a cause-and-effect relationship between medication sales and either URTI or infections of influenza. It was possible that some of the correlations observed between medication sales and the influenza indicators were attributed to the seasonal feature that was associated with the data used in the present study. Removing these seasonal features from the data would increase the confidence in the relationship between medication sales and the indicators of influenza activity. Other potential confounders, such as the beginning of school term, weather pattern and public holidays, could also influence the correlation between the time series (Magruder 2003). Future studies could consider constructing mathematical models to account for these variables and verify the correlations observed between medication sales and influenza activity. Such could not be undertaken in the current study due to time and resource constraints.

6.4.4 Implications of findings

Within the UK, experience in using OTC medicines sales data for the monitoring of seasonal influenza at any regional level is lacking despite it has been an area of public health interest in England (HPA 2010a), Scotland (Public Health Institute of Scotland 2003) and Wales (Jones 2009). The absence of a UK based study in this regard has been described in Chapter 1. This situation in the UK is in stark contrast to the US, where sales of non-prescription medicines have been found to be the third most frequently used information source for syndromic surveillance systems and their greatest

application has been for the monitoring of influenza (Buehler et al. 2008). The current study provided the first experience in using medicines sales data for the monitoring seasonal influenza in a UK population.

Subject to the limitations described in Section 6.4.3, the pharmacy sales data utilised in the present study for OTC cough, cold and flu medicines appear to contain a signal that corresponds to the activity of influenza and level of associated respiratory symptoms in Wales. Given that many people may not be able or indeed choose not to seek medical attention for a simple cold or flu, the ability of OTC medicine sales data to describe disease prevalence in this population addresses a surveillance gap that could not be achieved by the current, healthcare service based surveillance systems. Questions as to how such surveillance information can be integrated into existing public health protocol, in terms of outbreak detection, investigation of alerts, response to threats, and day-to-day workflow of local public health agencies remain to be examined.

A number of limitations has been identified for the medicines sales data currently available to PHW if they were to be utilised for influenza surveillance (Section 6.4.3.1). Among them the biggest challenge probably relates to the wholesale nature of the data. This ascertains the need to use medicine sales data that represent actual pharmacy and patient transactions for disease surveillance tasks. However, such data are not currently available to public health agencies in the UK and presents a major barrier for further research to be conducted in this field. As such, there may be a need to encourage collaboration between the public and the private sector to facilitate the sharing of these information for public health purposes.

The publication of the draft professional standards for public health practice for pharmacy (Royal Pharmaceutical Society [RPS] 2013) stressed that pharmacists should contribute to public health protection by being involved in the reporting of seasonal and pandemic influenza. As demonstrated in the current study, making use of medicines sales information may be a way to realise this public health goal for pharmacy.

6.5 Summary

Over the six-year study period, pharmacy wholesale data of OTC (1) cold and flu, (2) cough and (3) nasal congestion or sinusitis medicines demonstrated a significant positive correlation with GP diagnosis of influenza and cold and flu symptoms calls to NHSDW in Wales. In particular, cough medicines correlated with influenza indicators the highest and indicated the greatest potential for influenza surveillance. Although the sales of OTC cough, cold and flu medicines appeared to have provided up to two months advance warning for the onset of seasonal influenza, such could have been influenced by the wholesale nature of the pharmacy sales data used. Actual pharmacy-to-patient sales data should be obtained in future studies to verify the relationship between medication sales and influenza activity observed.

Chapter 7:

General Discussion

General Discussion and Conclusion

In 2013, the Royal Pharmaceutical Society (RPS) published its draft professional standards for public health practice for pharmacy (RPS 2013). In this document, a framework for the design, implementation, delivery and monitoring of public health services was proposed for pharmacy for the first time. The intention of the framework was to support pharmacists, the pharmacy team and commissioners in all pharmacy settings to develop new public health services and improve existing public health provisions.

Among the nine core areas of public health practice recognised by the draft framework, the use of over-the-counter medicines (OTC) sales data for public health as demonstrated in this thesis was particularly relevant to three areas of public health practice. These are summarised in Table 7.1.

The potential contribution of OTC medicines sales data to public health was investigated utilising two approaches. The first involved medicines that had undergone regulatory changes affecting their OTC availability and included (a) codeine and dihydrocodeine (DHC), (b) pseudoephedrine (PSE) and ephedrine and (c) ophthalmic chloramphenicol. OTC medicines sales data were used to investigate whether or not these changes had any impact on their supply either OTC or on prescription in Wales. The second approach explored whether or not OTC medicines sales data would be of any potential use for disease surveillance. This involved using sales data for OTC ophthalmic chloramphenicol to identify outbreaks of infective conjunctivitis and sales of OTC cough, cold and flu medicines to monitor seasonal influenza.

The current chapter discusses the main findings for each of these studies, considers the possible implications on policy and summarises the study limitations. Finally, future work is proposed followed by the overall conclusions.

Table 7.1 Draft professional standards for public health practice for pharmacy, their goals and possible contributions to each area by utilising over-the-counter (OTC) medicines sales information from community pharmacy (Adapted from source: Royal Pharmaceutical Society [2013])

Professional standards	Goal	Possible uses of OTC medicines sales data
Surveillance and assessment of the population health and wellbeing	Collect data from a variety of sources to support better understanding of the health and wellbeing needs of a population or community	• Understand local health needs • Identify population at risk of developing problems with OTC medicines (e.g. opioid containing analgesics) • Quantify effect of social deprivation on the health of population and self-care behavior
Public health intelligence	Information and analysis of the health and wellbeing needs of the population or community is used to inform development of pharmacy public health services	• Evaluate effectiveness and outcomes of pharmacy interventions (e.g. impact of medicine reclassification or pack size restriction on sales of OTC medicines) • Identify potential links between consumption of OTC medicines and morbidity data (e.g. OTC sales of paracetamol and statistics on deliberate self-poisoning)
Public health protection	Protect health by supporting the prevention and transmission of infectious diseases, screening for risk factors and disease, ensuring prudent use of antibiotics to mitigate the risks of antimicrobial resistance, protecting against pharmaceutical hazards and supporting the pharmacy response to an emergency	• Monitor supply of non-prescription antibiotics from pharmacies (e.g. ophthalmic chloramphenicol and azithromycin) • Contribute to the identification of emerging communicable disease epidemic or pandemic (e.g. elevated sales of OTC cough, cold and flu medicines and possible circulation of influenza)

7.1 Major findings

7.1.1 Impact of restrictions on Over-the-Counter availability

Due to concern over their potential of misuse and/or abuse (All-Party Parliamentary Drug Misuse Group [APPDMG] 2009; Medicines and Healthcare products Regulatory Agency [MHRA] 2005a), OTC sales of codeine and DHC containing analgesics became subject to various voluntary and legal restrictions between 2005 and 2009. To understand what the impact of these regulatory measures were on their supply in the primary care, medicines wholesale data for selected products were analysed. The results from Chapter 2 revealed there was a decline in sales of OTC codeine and DHC containing analgesics in Wales following the implementation of both voluntary and legal changes. Therefore, MHRA's intention to minimise the risk of addiction by restricting OTC availability of these medicines appeared to have been achieved (MHRA 2005a, 2009a). However, how much of reduction in sales had prevented users from developing problems with codeine and DHC containing products is unclear and was not examined. This was not one of the objectives for the current study but may be included in future work.

In Chapter 3, another example where sales of OTC medicines from pharmacy became subject to additional control involved oral and topical nasal decongestants containing PSE and ephedrine. In this particular case, legal changes regarding non-prescription supply were introduced because of their potential to be used as precursors in the illicit manufacture of the class A drug, methylamphetamine (MHRA 2007a). The actions taken by the MHRA included limiting the total weight of PSE and ephedrine that was allowed in an OTC pack and that could be sold to a customer in a single transaction (MHRA 2009c). Using medicines wholesale data, the study investigated the impact of these measures on OTC supply and the results revealed the sales of selected PSE containing products had significantly reduced in Wales. This finding was consistent with the sales trends reported for the UK as a whole (MHRA 2012b) and suggests the legal measures for PSE and ephedrine containing products had the required, desirable impact on OTC supply in Wales. However, it should be noted that in this study OTC sales data for ephedrine containing nasal

decongestants were unavailable and the impact of the policy change on these products could not be determined.

A potential concern about pack size restriction as a strategy to limit the availability of a medicine, or to deter deliberate misuse and/or abuse, was how easy individuals could bypass the regulatory effort, for example by making more frequent purchases of smaller packets. Such a change in consumer behaviour subsequent following a reduction in product pack size has been previously observed with paracetamol (Hawton et al. 2001). However, analyses of the medicines wholesale data revealed there was a simultaneous reduction in both the number of packs and total quantity of tablets/capsules sold in Chapter 2 (Figure 2.2). Similarly in Chapter 3, reduction in the number of packs and weight of active ingredient sold was observed (Figure 3.1). These observations suggest, overall, that consumers probably have not engaged in the practice of purchasing more packs.

Finally, another potential concern over restricting the OTC availability of a medicine is whether or not this encouraged individuals to obtain the same drug from their GP on prescription (Maguire 2010). This possibility was explored in both Chapter 2 and Chapter 3 by analysing GP prescribing data for Wales. The results from Chapter 2 indicate there was no significant increase in prescription supply of DHC following the pack size restriction; whilst prescription supply of codeine containing preparations increased year-on-year but followed the same trend as seen before the pack size restriction was introduced. In Chapter 3, there was no significant increase in the prescribing of either PSE or any other nasal decongestant on GP prescriptions. These findings provide reassurance that increased restriction on the OTC sale of these medicines did not result in an increase in patients seeking prescriptions for the same drug from their GPs.

7.1.2 Impact of increase Over-the-Counter availability

When a medicine is switched from POM to P status, its availability and accessibility to the general public is increased. For ophthalmic chloramphenicol, it had been reported that OTC supply in Wales increased in

the first three years following reclassification to a P medicine in 2005 (Walker and Hinchliffe 2009). The study in Chapter 4 monitored the supply of OTC ophthalmic chloramphenicol beyond the first three years and examined the long term impact following reclassification. Furthermore, additional medicines sales data were obtained for the present analysis from a multiple pharmacy company (Company A) in Wales for which OTC data was not available.

The results suggest that following the initial three-year growth, sales of OTC ophthalmic chloramphenicol declined and stabilised for the first time in 2008/2009. In the present study access was granted to previously unavailable sales data. It was not surprising, therefore, to find the total quantities of OTC ophthalmic chloramphenicol sold in Wales was more than previously calculated (Walker and Hinchliffe 2010). Despite the increase in use of OTC ophthalmic chloramphenicol, supply on prescription remained unaffected five years on. As a consequence there was no reduction in NHS drug spending and/or the burden on GPs in managing these patients. The exact reason why despite the additional quantity of ophthalmic chloramphenicol supplied OTC there was no impact on its prescription supply could not be determined from the present study and warrants further research.

When the temporal relationship between OTC sales of ophthalmic chloramphenicol and items dispensed on prescription was explored, it was found that there was a significant and positive correlation between the two variables. This may, in part, suggest that community pharmacists and GP prescribers were responding to similar presenting symptoms. However, whether or not prescribing and/or OTC sales of ophthalmic chloramphenicol were appropriate remains unknown. It has been reported that primary care practitioners commonly misdiagnose and mismanage infective conjunctivitis (Statham et al. 2008). In light of the high volume of ophthalmic chloramphenicol sold OTC, the question as to whether those supplied by pharmacists represent clinically appropriate decisions is an important question that needs to be answered. This was not explored in the present study but could be studied further.

7.1.3 Identification of local infective conjunctivitis outbreak

The study presented in Chapter 6 utilised sales data for OTC ophthalmic chloramphenicol to explore its sensitivity to identify known outbreaks of infective conjunctivitis in the local community.

Two separate outbreaks of infective conjunctivitis in South Wales were studied (Section 5.1.4). Sales of OTC ophthalmic chloramphenicol during one of the outbreaks (Pontypool) were found to be significantly higher than in corresponding non-outbreak period in one of two preceding years. Although the increase in sales of OTC ophthalmic chloramphenicol coincided with the period of the known outbreak, the number of additional packs sold was small (11 packs) and increase was not consistently higher than the supply during corresponding non-outbreak periods. As a consequence, how robust this would be to detect further outbreaks is unclear.

The low volume of OTC ophthalmic chloramphenicol sold in this particular study was, in part, due to the low coverage of medicines sales data in the study areas. The study could not exclude the possibility that sales of OTC ophthalmic chloramphenicol might have increased in pharmacies outside the area of those monitored. Investigating an outbreak in a larger area and involving more pharmacies may have improved the sensitivity to detect an outbreak.

Public Health Wales (PHW) currently possesses medicines wholesale data for OTC ophthalmic chloramphenicol, which includes data from pharmacies other than those owned by Company A. However, these data are not available down to individual pharmacy level and could not be analysed on a weekly basis. As such, unless these shortcomings can be resolved the value of OTC medicines sales data for local outbreak detection may be limited.

7.1.4 Influenza monitoring

In Chapter 5, the potential of medicines wholesale data to detect outbreaks of seasonal influenza and upper respiratory tract infections (URTI) was explored. This was undertaken by examining the temporal relationship between the sales

of selected OTC medicines and indicators of community-level influenza and upper respiratory tract infection (URTI) symptoms.

Over the six-year study period, wholesale data for selected preparations to treat (a) cough, (b) cold and flu and (c) nasal congestion medicines all demonstrated seasonal, year-on-year patterns. During the winter months each year (November to January), sales of all three categories of medicines could be characterised by a two-peak model. The first of the two peaks persistently occurred 2 to 4 months before the peak influenza diagnosis reported by GPs and peak calls to NHS Direct Wales (NHSDW) for URTI symptoms. On the other hand, the occurrence of the second sales peak was found to match with the month of peak influenza diagnosis and calls about URTI symptoms. The temporal mismatch between the first sales spike and peak influenza/URTI activity suggests there were other unknown factors influencing the sales of the selected medicines. Their exact nature could not be determined and require further investigation.

Results from cross-correlation analysis revealed the supply of (a) cough, (b) cold and flu and (c) nasal congestion medicines all demonstrated a significant and positive correlation with cases of GP diagnosed influenza and symptomatic calls to NHSDW at various time latencies. This suggests two possible properties about the medicines wholesale data in terms of disease surveillance. First, changes in the sales of the selected medicines are sensitive to changes in the activity of influenza and related symptoms in the community. Second, the different time latencies for which maximum correlation was observed suggest the three categories of medicines vary in their early detection capability.

Of the three categories of medicines studied, cough medicines sales demonstrated the highest correlation with each of the disease indicators. In addition, they consistently provided up to one month early warning to changes in influenza activity. Therefore, cough medicines as a group could be studied further for their application in disease surveillance. A longer study period and wider range of cough products could provide more confidence for the relationship observed between medicine sales and influenza activity.

The association between sales of OTC medicine and respiratory diseases found in the current study are consistent with that reported in the US population (Das et al. 2005; Liu et al. 2013; Magruder et al. 2004). However, the medicines wholesale data currently available to PHW is has a number of disadvantages and its usefulness for influenza surveillance may be limited (Section 6.4.3.1). Most notable of its drawback is that the buy-in nature of the data makes it vulnerable to factors unrelated to actual diseases activity in the community. This highlights the requirement for actual pharmacy-to-patient sales data if surveillance of communicable diseases, based on OTC medicines sales data, is to be an area of development for community pharmacy in the future (Jones 2009).

7.2 Implication of research findings

7.2.1 Widened availability of ophthalmic chloramphenicol

Removing the prescription barrier of a medicine through reclassification improves patient access to treatment and presents opportunities for self-care. This was exemplified with the reclassification of ophthalmic chloramphenicol as discussed in Chapter 4.

The availability of OTC ophthalmic chloramphenicol prompted self-management of infective conjunctivitis in individuals who previously may have left it untreated. This outcome could be considered a success from a reclassification perspective. Supplies of ophthalmic chloramphenicol on prescription, on the other hand, remained unaffected five years on. It would appear that people who previously visited their GP for an eye infection continued to do so even though ophthalmic chloramphenicol could be obtained without a prescription. In this regard, the reclassification policy may be considered to have been less successful as it failed to shift the burden of managing infective conjunctivitis from GP surgeries to community pharmacies or deliver any cost saving to the NHS.

For the policy makers, there may be a need to further promote patients to engage in self-care such as through events like the 'Self-Care Week' campaign (Welsh Government 2012a). Raising the awareness about specific conditions where effective treatment can be purchased from a pharmacy may help to focus public awareness. Making patients aware of the importance of choosing the right kind of service proportional to the seriousness of a health problem may also help to address this issue. The 'Choose Well' health campaign in Wales would be an example of such an endeavour (Anon. 2011).

Though the study was not designed to investigate the abolition of the NHS prescription charge in Wales in 2007 this may have prevented patients from practicing self-care. This was demonstrated by the year-on-year reduction in prescription supply of ophthalmic chloramphenicol up to 2007, followed by a sudden increase in prescribing when the prescription charge was removed (Table 4.11). This observation is in agreement with the findings reported by Grove et al. (2010) as participants in a before-and-after survey study showed there was a reduction in the purchase of non-prescription medicines and increase in prescription medicine utilisation after the abolition of the prescription charge in Wales.

The cost associated with purchase of OTC medicines may be a barrier to self-care and is well documented (Hanna and Hughes 2010; Paudyal et al. 2012c; Weidmann et al. 2011). This may have been one of the reasons why some individuals continued to obtain ophthalmic chloramphenicol on prescription. The to be established Common Ailments Service (CAS) in Wales (Welsh Government 2012b) may help lessen the burden of minor ailments on GPs, whereby eligible patients will be provided with free treatment for minor conditions under the NHS from community pharmacies. At the time of writing, ophthalmic chloramphenicol is considered to be one of the medicines that will be supplied under CAS (All Wales Medicines Strategy Group [AWMSG] 2013). Whether this approach will encourage patients to visit a community pharmacy instead of their GP remains to be studied.

7.2.2 Inappropriate use of Over-the-Counter medicines

Issues surrounding the misuse and abuse of OTC medicines, particularly addiction to analgesics that contain codeine and DHC, have attracted attention in recent years from healthcare professionals (Mackridge et al. 2013; Royal College of General Practitioners 2013), public health agencies (Reed et al. 2011; Public Health England [PHE] 2013b) and the medicine regulator (MHRA 2011b) in the UK. The need for more detailed information on the individuals who are affected, the type of medicines being misused/abused to guide the development and delivery of treatment services has been recognised (National Treatment Agency for Substance Misuse [NTA] 2011; Reed et al. 2011; PHE 2013; Welsh Government 2013a). It is an area of active research (Cooper 2013a, 2013b, 2013c).

As illustrated in Chapter 2 and Chapter 3, information generated from the sales of OTC medicines can provide trend data and quantify the volume of OTC medicines supplied. They may serve to be the first signs to indicate the scale of the problem associated with the inappropriate use of OTC medicines. The flexibility to analyse medicine sales data at a local level means identification of areas with higher than normal volume of sales is possible. This enables the population more at risk of developing problems to be spotted.

Using medicine sales data has lead to the identification of one particular Local Health Board (LHB) that showed unusually high volume of sales and prescription for non-soluble codeine (Section 2.3.3). This information may help to guide public health interventions, such as a review of local medicine sales or prescribing protocol. This was an example that shows how OTC medicine sales data could support the harm reduction objectives outlined in Welsh Government's national substance misuse strategy (Welsh Government 2013b). Objectives could include greater attention on the inappropriate use of OTC medicines and improving the monitoring of usage.

Findings presented in Chapter 2 demonstrated there has been a decline in the sales of OTC codeine and DHC containing products following the change in legislation regarding their supply. On-going monitoring of the supply situation

is essential to evaluate whether this has been sustained. Interpretation of medicines sales data should be supplemented by primary care prescribing data to determine if there was a switch from OTC purchases to obtain supplies from GPs. This does not appear to have been the case in Wales but could have changed given the study only examined data up to 12 months after the legal changes were introduced.

It has been reported that the regulatory changes for OTC codeine and DHC containing analgesics were ineffective in stopping supplies for non-medical purposes (Cooper 2013c). Methods adopted by users to circumvent detection included making purchases from more than one pharmacy and rehearsing answers to questions from staff (Cooper 2011, 2013c; Nielsen et al. 2012). Therefore, despite the fact that there has been a decline in the sales of OTC codeine and DHC containing products, it would appear the indicators relied upon by pharmacy staff to identify improper OTC requests may be unreliable (Cooper 2013b). More effective strategies to detect inappropriate OTC requests for codeine and DHC may be necessary. To this end, a pharmacist training package has recently been developed by the Centre for Pharmacy Postgraduate Education (CPPE) on the subject of addiction to OTC medicines (CPPE 2013). The learning programme considers what can be done to recognise the key risk factors, patient identifiers and triggers that may prevent OTC medicines from being misused. However, this training material is not currently available to pharmacists in Wales.

7.2.3 Self-selection of Pharmacy medicines

In 2012, the General Pharmaceutical Council (GPhC) launched a public consultation on the draft standards for registered pharmacies (GPhC 2012). Among the items that were raised include the proposal to allow pharmacy owners to selectively display P medicines for self-selection by customers. It has been argued that the move would allow a wider access to medicines and benefits the patient (Connelly 2012). However, many pharmacists and pharmacy professional bodies have opposed the decision on the grounds of patient safety (Anon. 2012d, 2013a; Sukkar 2013). Concerns over the lack of

monitoring for the sales of selected high risk OTC medicines, such as nasal decongestants, have been raised (Anon. 2012e).

At the time of writing this thesis, details as to how self-selection of P medicines will be implemented in practice have not been finalised. However, should it become a reality it could impact on how P medicines are consumed (Pharmacists' Defence Association 2013). It is not improbable that once a P medicine becomes more patient-accessible through self-selection, an increase in its non-prescription supply may ensue (Sukkar 2013). This holds two potential implications for OTC medicines sales data and these are discussed below.

First, the impact of the self-selection arrangement on the purchase of medicines with high misuse and/or abuse potential would be of interest to the medicine regulator (Sukkar 2013). OTC medicines sales data could serve as a tool to monitor non-prescription supply and used to support policy decisions regarding OTC availability. Secondly, OTC medicines sales data could facilitate robust pharmacoepidemiological studies (Bond and Hannaford 2003). Such studies could also be useful to identify unusual trends with adverse drug events in the community related to the use of OTC medicines. By way of an example, the MHRA has recently issued a new warning over the use OTC diclofenac in patients with cardiovascular disease (MHRA 2013c). Reverting its legal status from P to POM is currently being considered (Anon. 2013b). In this example, OTC medicine sales data could be used to help quantify and interpret the trends of related adverse events in the community and provide evidence to inform the reclassification decision.

Given the limited OTC medicines sales data that is currently available to government agencies, there may be a need to strengthen collection to support the self-selection initiative in the interest of patient safety. The GPhC could consider making the collection and sharing of sales data for self-selectable products a requirement for pharmacy businesses. This may have the added benefit of encouraging pharmacy owners to adopt a more responsible approach towards implementing self-selection of P medicines.

7.2.4 Antibiotic stewardship

The increased supply of ophthalmic chloramphenicol in primary care continues to cause concern eight years on (Price 2013). To date, no study has yet been carried out to investigate the clinical appropriateness of each supply. Therefore, how much of the supply reported in this study represents inappropriate sales remains unanswered. Even if bacterial conjunctivitis could be diagnosed accurately, the high level of ophthalmic chloramphenicol use could increase bacterial resistance (Price 2013).

Pharmacy staff need to demonstrate they are aware of the latest recommended treatment for acute infective conjunctivitis by promoting the practice of 'delayed' or 'no antibiotic' use. To this end, it is likely that sales data for OTC ophthalmic chloramphenicol will continue to be monitored. The applications to reclassify trimethoprim and nitrofurantoin to P status were both withdrawn in 2010 over concerns of antibiotic resistance (Anon. 2010b). These unsuccessful reclassifications should serve as a reminder for the pharmacy profession to act cautiously and responsibly when faced with requests for OTC ophthalmic chloramphenicol.

The launch of OTC ophthalmic chloramphenicol in 2005 was supported by a range of training and educational materials for pharmacists and medicine counter assistants (MCAs) (Anon. 2005; Elton 2005; Royal Pharmaceutical Society [RPSGB] 2005). Many of these resources were provided by medicine manufacturers as it is a common requirement for the application of a POM-to-P switch (MHRA 2012a). Understandably, much of the training effort focused on the initial phase of the product launch when the training needs of pharmacy staff were at their highest. However, in contrast, there is a much weaker emphasis on on-going training to keep up with the latest evidence. For ophthalmic chloramphenicol, the updated advice for their OTC supply were communicated in a single practice document produced by the Royal Pharmaceutical Society (RPS) in 2011 (RPS 2011c). Access to this document, however, was limited only to registered members of the pharmacy professional body. Whether this single document was sufficient to drive compliance among pharmacy staff to minimise antibiotic use remains to be studied. Further

collection of medicine sales data is recommended to monitor if the supply situation has changed.

One factor that may have contributed to the marked increase in use of ophthalmic chloramphenicol could have been patients' perception about infective conjunctivitis as a disease. A number of studies have examined this and found many patients believed an antibiotic is required to clear the infection (Everitt et al. 2003). As a consequence, a better awareness about the self-limiting nature of infective conjunctivitis may help reduce the use of ophthalmic chloramphenicol. Whilst a number of public health campaigns already exist to raise the awareness about the ineffectiveness of antibiotics in certain conditions, the target population has primarily been GP attendees suffering from colds or flu (RPS 2012; PHW 2013b). There may be a need for future campaigns to include information customised for pharmacy users, including information on infective conjunctivitis. The recent national public health campaign in Wales that focused on eye care was an opportunity where non-medicinal management of infective conjunctivitis could have been promoted (Community Pharmacy Wales [CPW] 2013; PHW 2013c)

In summary, the results from the current study support the recommendation that further reclassifications of antibiotics to OTC status should not be allowed (Anekwe 2010, Dryden et al. 2009). The risks of increased bacterial resistance, lack of comprehensive post-marketing surveillance data and mechanism to support long term training needs are some of the obstacles faced by the pharmacy profession.

7.2.5 Wales Common Ailments Service

In March 2012, the Welsh Government announced its plan to establish the CAS that will be delivered by all NHS contracted community pharmacies in Wales (CPW 2012a, Welsh Government 2012b). At the time of writing thesis, some of the conditions planned to be treated under the scheme include indigestion, scabies, sore throats, bacterial conjunctivitis, athlete's foot, thrush, head lice, diarrhoea, verrucas and threadworms (AWMSG 2013). As the service will be provided free of charge for eligible NHS patients, it is hoped

that individuals who previously chose to visit a GP for a free prescription would instead visit a pharmacy. As for individuals who already self-manage minor conditions by purchasing OTC medicines, it is anticipated they will continue to do so without the help from the NHS (Welsh Government 2013c).

The results from Chapter 4 indicate a large proportion of the Welsh population chose to manage infective conjunctivitis by purchasing OTC ophthalmic chloramphenicol. For some individuals, it was probably because the benefits of being able to purchase the treatment when and where desire outweighed the inconvenience associated with visiting a GP. Whether they will be just as motivated to continue to do so after CAS becomes available is unclear. It has been suggested the CAS initiative will encourage patients to over rely on the NHS for even minor conditions (Bro Taf Local Medical Committee 2013). Consequently, it would be pertinent that sales data for OTC ophthalmic chloramphenicol are monitored further to ensure CAS is not used as a means by which patients can shift drug acquisition costs on to the NHS. Likewise, sales data for other therapeutic classes of medicine that are to be supplied under CAS should also be monitored to allow the evaluation of the service on self-care behaviour.

The to-be-implemented CAS is envisaged to be supported by a centrally stored, electronic database that is accessible by every NHS contracted community pharmacy in Wales (Welsh Government 2013c). Under the proposed plan, users of CAS will have to be to registered with a pharmacy with basic personal information such as name, age, gender and address. Details about the product, quantity and date will also be recorded for each supply (Welsh Government 2013c). In comparison to the pharmacy sales data utilised in the current study, the availability of detailed patient record will be associated with several advantages. For example, local communities where health improvements are needed the most could be identified. Patient profiles could be generated to identify vulnerable patient groups. An interconnected and up-to-date patient record could allow pharmacists to identify individuals suffering from more frequent episodes of illness and initiate appropriate referral. These are some

unintended but possible uses of the data that are not available with the existing pharmacy wholesale data.

7.2.6 Disease surveillance

The capacity of the community pharmacy profession in rising up to the challenge of a major influenza outbreak has been demonstrated during the H1N1 (2009) influenza pandemic. In England, for example, community pharmacies played a key role in distributing health information to the public and supplied antivirals through pharmacy collection points during the pandemic (Richards 2009). In Wales, community pharmacists disseminated self-care and vaccination advice to the public (PHW 2009a, 2009b) and supported the care of vulnerable patient groups (Anon. 2009f). During seasonal influenza epidemics, community pharmacy has been the first port of call for the general public to seek advice and obtain OTC medicines for cold and flu symptoms. Recently, for the first time, community pharmacy in Wales were involved in the flu vaccination programme under NHS for the 2012/2013 winter season (CPW 2012b; Welsh Government 2012c). This was an encouraging development for community pharmacies in Wales and shows they are beginning to be recognised as a potential partner in the delivery of health protection strategy for seasonal influenza (UK Influenza Pandemic Preparedness Team 2011).

The first experience of using medicines sales data for disease surveillance in Wales was presented in Chapter 5 and 6. The two studies demonstrated how medicines sales data could contribute to "*new investigative techniques and non-traditional source of data to produce public health intelligence*" as identified in the public health strategy for Wales (Welsh Government 2009a). Recently published public health surveillance strategy in England has also highlighted the need to utilise novel sources of information and analytical approaches to support health protection and emergency preparedness (Department of Health [DH] Public Health England Transition Team 2012). The community pharmacy profession should capitalise on these opportunities for a greater involvement in public health and infectious disease prevention.

Offers to collaborate with the public sector would not only support these public health endeavours but could also raise the profile of community pharmacy.

Progress in understanding the use OTC medicines sales data for diseases surveillance is hampered by a number of barriers. Firstly, actual sales data as opposed to wholesale data, is required if timely detection of a disease outbreak is to be achieved. However, sales data are difficult to obtain due to the concerns of individual companies' over confidentiality and security. The research opportunity is therefore limited. Secondly, there is a need for regular and on-going supply of sales data to establish a baseline level of sales. This means the additional work involved may be unattractive to pharmacy owners. Thirdly, nearly 40% of all community pharmacies in Wales are independent pharmacies (Welsh Government 2012d) and they may not have a monitoring system in place that records the sales of OTC medicines. Lastly, the required IT infrastructure to facilitate downloading and sharing of medicine sales data and surveillance information between the data providers and public health agencies is at present lacking in Wales.

A variety of strategies could be considered to overcome the barriers outlined above. These may include public health agencies forming an agreement with private companies on issues surrounding data confidentiality and how data may be used for research and public health purposes. Furthermore, sales figures could be anonymised. To encourage as many pharmacies to participate as possible, experience from the US suggest personal invitations written by respected government or public health officials was key to promote private sector participation (Wagner et al. 2003). Offering a financial reward for the work involved may also encourage collaboration. To maximise sales data coverage, partnerships with large pharmacy multiples could be given priority in exchange for better data coverage earlier on. The need for a better data linkage between community pharmacy and other healthcare services has recently been recognised in Wales (National Assembly for Wales Health and Social Care Committee 2012). The establishment of CAS in Wales, underpinned by an improved IT infrastructure, offers potential opportunity where information sharing functionality could be included in the system design.

In summary, the utilisation of OTC medicines sales data for disease surveillance is an area of potential public health development in both England and Wales. It is in the best of interest of the community pharmacy profession to seize the opportunity to ensure progress continues on this issue.

7.3 Limitations

It was intended that, where possible, the studies reported in the thesis would use available data sources. This would ensure the findings were relevant to the work of PHW who facilitated the supply of medicines sales data from IMS Health and Company A (Section 4.2.2.3). The studies presented in this thesis have investigated (a) the impact of increased medicine regulation and reclassification on the supply of selected medicines, and (b) the relationship between medicines sales data and known disease outbreaks. All were of an ecological nature and involved retrospective data analysis. In the following section general limitations associated with the methods and data used are discussed.

7.3.1 Internet pharmacy

The pharmacy sales data utilised in the current study represent sales of OTC medicines from traditional high street pharmacies. Whilst the majority of the medicines studied were P medicines and could only be obtained from a pharmacy, it should be noted they could also be obtained through other routes. One notable channel of supply is through internet pharmacies for which sales data were unavailable. The difficulty in regulating medicines supply by internet pharmacies has been acknowledged by medicine regulators (MHRA 2012c). Inappropriate sales of OTC medicines by some internet pharmacies have been reported (Cooper 2011, 2013c). It was possible the extent of impact of the regulatory changes studied in Chapters 2 and 3 were different for the internet pharmacy sector. Therefore, the interpretations of the findings presented in those chapters should be limited to the context of traditional high street pharmacy.

7.3.2 Generic and proprietary medicines

In Chapters 2, 3 and 4, the majority of the OTC medicines studied were proprietary products. The reasons for excluding generic medicines from the analysis have been described (Section 2.4.2.3, Section 3.4.1.3 and Section 4.4.2.7) and related to ease of identification of the relevant data. As a consequence, the impact of medicine reclassification and pack size restrictions on the sales of generic or non-brand medicines were unknown. One solution to this is to acquire actual pharmacy-to-patient sales data directly from pharmacies for generic or non-brand medicines sold OTC.

7.3.3 Attitude, views and experience of healthcare professionals

To further understand the impact of the quantitative results presented in this thesis it is important the attitude, views and experience of healthcare professionals and patients in Wales are obtained. For instance, how were pharmacists and MCAs managing inappropriate requests of OTC medicines following the pack size restriction? Who were conducting sales of OTC ophthalmic chloramphenicol in a pharmacy and what was their level of awareness of antibiotic resistance? What were patients' views on the increasing restriction to their access of certain non-prescription medicines? These are important questions but were not explored due to time and resource constraints.

7.3.4 Settings of a disease outbreak

Outbreaks of infectious diseases are naturally occurring and unpredictable. Therefore, given the time frame for which medicine sales data were available, only a small number of outbreak incidents could be investigated. Moreover, the kind of disease outbreak that could have been studied was limited by the OTC medicine sales data available. For example, pharmacy wholesale data for anti-diarrhoeal medications was initially obtained from IMS Health to investigate outbreaks of diarrhoea. However, the sales data available consisted of mainly generic products and these were not a reliable indicator of OTC sales. Other difficulties encountered during the study relating to medicines sales data and disease surveillance are described below.

In May 2011, a viral conjunctivitis outbreak involving at least 51 individuals was reported in Rhondda Cynon Taf, Wales (PHW 2011c). As this outbreak had affected more people than either of the conjunctivitis outbreaks described in Chapter 5, it was of particular interest to study. However, there were two issues about the medicines sales data which prevented this from being used. Firstly, wholesales data obtained for the time around the outbreak were only available in Local Health Board (LHB) geography. This was too large to identify a local outbreak. Secondly, pharmacy retail data obtained from Company A (Section 5.2.2) was limited to 2008 − 2010 and therefore did not include the period of the large outbreak. These issues highlight the difficulties in studying local disease outbreaks that occur infrequently, particularly when OTC medicines sales data are not routinely collected over time.

The H1N1 influenza (2009) pandemic that affected Wales in the summer of 2009 was also considered for study using the sale of OTC cough, cold and flu medicines from IMS Health. However, this was not undertaken as a preliminary analysis showed that the sales of these medicines during the year of the outbreak were not different to that observed during non-outbreak years (Du et al. 2010). This lack of change in sales may be the result of two confounding factors. The first was that, at the time, public health agencies and healthcare professionals actively encouraged individuals experiencing symptoms not to attend a pharmacy (PHW 2009a). Secondly, the general public were advised to manage their symptoms using non-medicinal measures or take single ingredient paracetamol or ibuprofen to reduce their fever (PHW 2009c). The absence of another major influenza outbreak in the UK during the period of the study meant it was not possible to test if medicine sales data was sensitive to an unexpected influenza outbreak. This example highlights the difficulty in having a suitable outbreak setting in which the disease surveillance capability of medicines sale data can be studied.

7.4 Future work

There are a number of areas where further research would help to better understand the findings of the current study. This could be supported by on-going collection of OTC medicine sales data through existing public health

arrangements in Wales. Collaboration between public health agencies and retail pharmacy businesses for new data provisions need to be explored to improve on the quality of medicine sales data currently available. Furthermore, implementation of new pharmacy services and improvements to the IT infrastructure in community pharmacies creates opportunities for pharmaceutical data to be utilised for public health research. Suggestions for further study include:

- Extend the duration of study to examine the long term impact of regulatory changes and updated professional guidance on the supply of selected medicines
- Obtain actual medicine sales data to quantify the OTC supply of own-brand and generic medicines and examine the impact of regulatory changes on the generic medicine market
- Undertake a qualitative study to determine the factors that contribute to the changes in sale of OTC medicines
- Undertake a qualitative study to identify the determinants for the supply of OTC medicines, particularly those associated with misuse and/or abuse potential, to identify relevant training needs and the development of educational materials
- Investigate the factors driving the high level of prescribing and OTC sale of codeine containing analgesics in Blaenau Gwent Local Health Board
- Obtain pharmacy sales data that is of better data coverage, in daily or weekly format and available by postcode to explore its sensitivity and ability to detect local disease outbreaks
- Obtain pharmacy sales data in a daily or weekly format to verify the correlation observed between sales of OTC cough, cold and flu medicines and indicators for influenza
- Extend the therapeutic class of medicines and explore whether the OTC sales data would be of value for the monitoring of other kinds of infectious diseases in the community

7.5 Conclusion

An aspect of pharmacy practice that has considerable public health potential but has not been fully exploited in the UK is the knowledge and data community pharmacy have about the supply of OTC medicines. The present study utilised OTC medicine sales data and explored its contribution to public heath.

The study investigated the impact of regulatory changes on the OTC supply of two therapeutic classes of potentially misused and/or abused medicines in Wales. The findings revealed these regulatory measures reduced the OTC supply of these medicines from community pharmacies. This provided reassurance to policy makers that the actions taken had the intended impact in practice and demonstrated the role of medicine sales data in policy evaluation. Whether the supply situations could change after an extended period of time is unknown and should be monitored further.

The impact of the reclassification of ophthalmic chloramphenicol was explored using OTC medicine sales data. The results showed that OTC supply has grown substantially and contributed to an overall increase in primary care use in Wales. This was despite a growing body of evidence that advised against its routine use in infective conjunctivitis and warnings about the risks of bacterial resistance. There may be a need for further training of pharmacy staff and patient education to promote the latest treatment recommendations for infective conjunctivitis.

OTC medicine sales data were utilised for infective conjunctivitis outbreak detection. In addition, the potential for monitoring seasonal influenza was also explored. The findings suggest the value of medicines wholesale data for diseases surveillance is limited in its current form. The ideal dataset should cover all pharmacies in the study area, available on a daily or weekly basis and at a geographical level that corresponds to the size of the disease outbreak. Such data is currently not available to public health agencies in Wales and serves to highlight the challenge if OTC medicine sales data are to be utilised for disease surveillance purposes.

In summary, it is recommended that government and public health agencies continue to strengthen the collection of OTC medicines sales data by collaborating with retail pharmacy businesses, and make use of this information to support the delivery of wider public health goals in Wales.

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Appendices

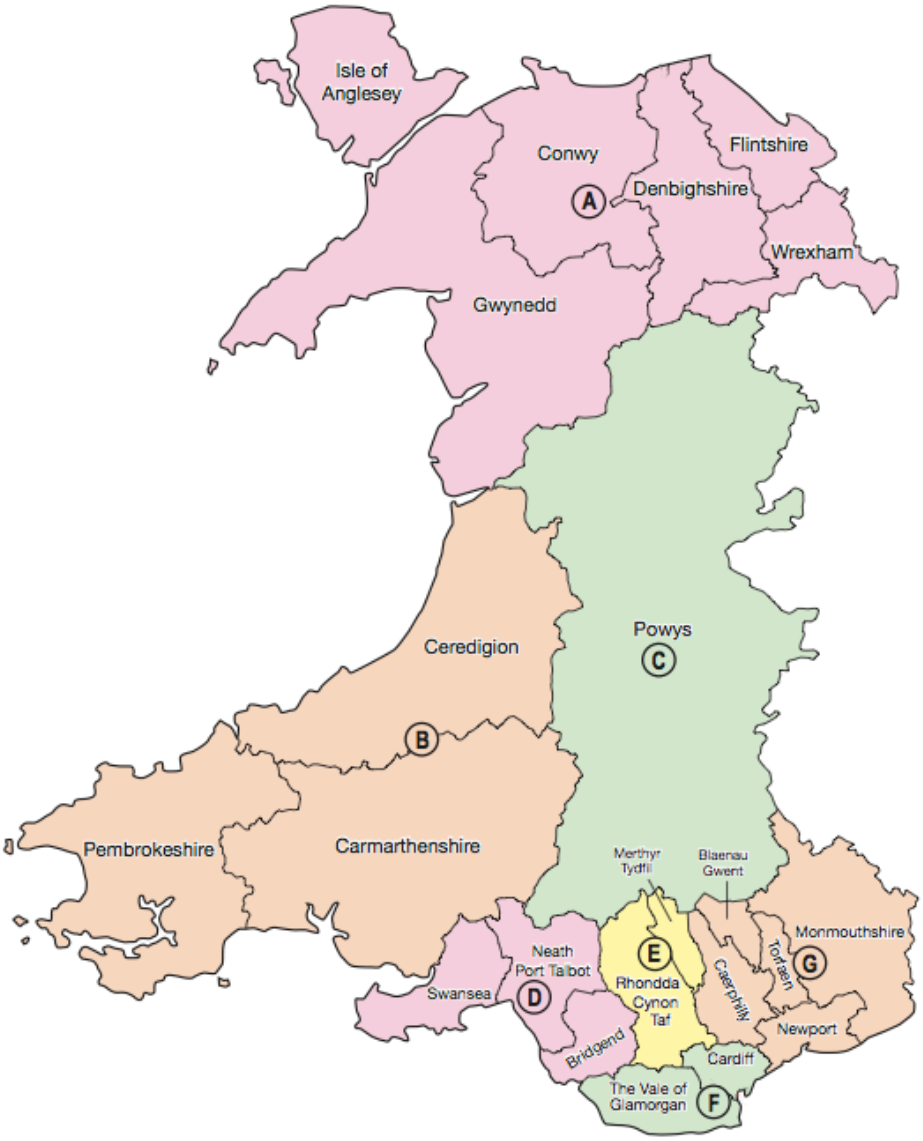
Appendix 1

Local Health Boards (LHBs) in Wales and their respective population size

Prior to October 2009	After October 2009	Population (Thousands)
Bridgend	Abertawe Bro Morgannwg	133.9
Neath Port Talbot		137.6
Swansea		230.1
Blaenau Gwent	Aneurin Bevan	68.8
Caerphilly		172.4
Monmouthshire		87.8
Newport		139.7
Torfaen		90.6
Anglesey	Betsi Cadwaladr	68.8
Conwy		111.4
Denbighshire		96.7
Flintshire		149.7
Gwynedd		118.6
Wrexham		132.7
Cardiff	Cardiff and Vale	330.5
Vale of Glamorgan		124.1
Merthyr Tydfil	Cwm Taf	55.6
Rhondda Cynon Taff		234.4
Carmarthenshire	Hywel Dda	180.7
Ceredigion		76.8
Pembrokeshire		117.6
Powys	Powys	131.7
	Total	2990.2

Appendix 2

Geographical representation of the Local Health Boards (LHBs) in Wales before (the 22 LHBs are indicated in words) and after the NHS Wales reorganisation in October 2009 (the seven new LHBs are color coded and indicated by letters A=Betsi Cadwaladr, B=Hywel Dda, C=Powys, D=Abertawe Bro Morgannwg, E=Cwm Taf, F=Cardiff and Vale, G=Aneurin Bevan)



Appendix 3

Deprivation indicators that are utilised to determine scores for each the deprivation component in Welsh Index of Multiple Deprivation 2008 (Welsh Government 2008)

Income

- Adult and children in income support households
- Adult and children in pension credit households
- Adult and children in income-based jobseekers allowance households
- Adult and children in tax credit (child tax credit and working tax credit) households below a low income threshold
- National Asylum Support Service supported asylum seekers in Wales in receipt of subsistence only and accommodation support

Employment

- Claimants of unemployment-related benefits
- Claimants of incapacity benefit / severe disablement allowance
- Participants on new deal for young people and intensity activity period (for new deal 25+) not included in unemployment-related benefits count
- Participants on new deal for lone parents

Health

- Limiting long-term illness
- Standardised all-cause death rate
- Standardised cancer incidence rate
- Singleton low birth weights

Education, skills and training

- Key Stage 2, average point scores
- Key Stage 3, average point scores
- Key Stage 4, average point scores
- Primary School all absence rate
- Secondary school all absence rate
- Proportion of people not entering Higher Education aged 18-19
- Proportion of adults aged 25 – 59 / 64 with no qualifications

Appendix 4

List of codeine containing preparations extracted from the NHS prescription database for Wales

Effervescent powders

Co-codamol 30mg/500mg
Co-codamol 60mg/1g
Kapake Insts 30mg/500mg
Kapake Insts 60mg/1g

Effervescent tablets

Aspirin/codeine 500/8mg
Co-codamol 30mg/500mg
Co-codamol 8mg/500mg
Co-Codaprin 8mg/400mg
Kapake 30mg/500mg
Medocodene 30mg/500mg
Solpadeine Plus
Solpadol 30mg/500mg
Tylex 30mg/500mg
Ultramol

Non-effervescent capsules

Boots Migraine Relief 8/500
Co-codamol 30/500
Co-codamol 8/500
Feminax Period Pain 8mg/500mg
Kapake 30mg/500mg
Medocodene 30mg/500mg
Paracodol 8mg/500mg
Solpadeine Plus
Solpadol 30mg/500mg
Tylex 30mg/500mg
Zapain 30mg/500mg

Non-effervescent tablets

Co-codamol 10/500
Co-codamol 12.8mg/500mg
Co-codamol 15mg/500mg
Co-codamol 30mg/500mg
Co-codamol 8mg/500mg
Co-Codaprin 8mg/400mg
Codafen Continus
Codagesic 8mg/500mg
Codanin 10mg/500mg
Codeine Phos 15mg
Codeine Phos 30mg
Codeine Phos 60mg
Codipar 15mg/500mg
Cuprofen Plus
Ibuprofen/codeine Phos 200mg/12.5mg
Kapake 30mg/500mg
Migraleve Complete
Migraleve Pink
Migraleve Yellow
Nurofen Plus
Painex
Panadol Ultra 12.8mg/500mg
Panerel Pain Relief 8.1mg/450mg
Parake
Propain
Propain Plus
Solpadeine Max 12.8mg/500mg
Solpadeine Mig Ibuprofen/codeine
Solpadeine Plus
Solpadol 30mg/500mg
Solpaflex
Tylex 30mg/500mg
Zapain 30mg/500mg
Ibuprofen/codeine Phos 200mg/12.8mg

Phos = Phosphate

Appendix 5

List of dihydrocodeine containing preparations extracted from the NHS prescription database for Wales

Effervescent tablets	Non-effervescent tablets
Paracetamol/Dihydrocodeine 500mg/7.46mg	Co-dydramol 10mg/500mg
Paramol 500mg/7.46mg	Codydragesic 10mg/500mg
Remedeine Forte	DF 118 Forte 40mg
Remedeine	DF 118 30mg
	DHC continus 120mg
	DHC continus 60mg
	DHC continus 90mg
	Dihydragesic 30mg
	Dihydrocodeine Tart 30mg
	Dihydrocodeine Tart 40mg
	Dihydrocodeine Tart 60mg M/R
	Dihydrocodeine Tart 90mg M/R
	Galake 10mg/500mg
	Paracetamol/dihydrocodeine 500mg/7.46mg
	Remedeine Forte
	Remedeine

M/R = Modified Release

Tart = Tartrate

Appendix 6

List of over-the-counter codeine containing analgesics and their respective pack sizes (number of tablets/capsules) extracted from the Regional Sales Analysis database for Wales

Effervescent tablets

Paracodol 8/500 (12)
Paracodol 8/500 (24)
Paracodol 8/500 (32)
Solpadeine Max 500/12.8 (16)
Solpadeine Max 500/12.8 (32)
Solpadeine Plus 500/8/30 (12)
Solpadeine Plus 500/8/30 (16)
Solpadeine Plus 500/8/30 (24)
Solpadeine Plus 500/8/30 (32)
Solpadeine Plus 500/8/30 (60)
Ultramol (12)
Ultramol (24)
Ultramol (32)
Ultramol (60)

Non-Effervescent capsules

Paracodol 8/500 (10)
Paracodol 8/500 (20)
Paracodol 8/500 (32)
Phensic Dual Action (24)
Solpadeine Plus 500/8/30 (12)
Solpadeine Plus 500/8/30 (16)
Solpadeine Plus 500/8/30 (24)
Solpadeine Plus 500/8/30 (32)
Ultramol (24)

Non-Effervescent tablets

Cuprofen Plus (12)
Cuprofen Plus (24)
Feminax (20)
Migraleve Complete (12)

Non-Effervescent tablets (continued)

Migraleve Pink (12)
Migraleve Pink (24)
Migraleve Pink PI (24)
Migraleve, Yellow (12)
Migraleve, Yellow (24)
Nurofen Plus (12)
Nurofen Plus (16)
Nurofen Plus (24)
Nurofen Plus (32)
Painex (32)
Panadol Ultra (20)
Propain (16)
Propain (32)
Propain Plus (16)
Propain Plus (32)
Solpadeine Max 500/12.8 (20)
Solpadeine Max 500/12.8 (30)
Solpadeine Plus 500/8/30 (12)
Solpadeine Plus 500/8/30 (16)
Solpadeine Plus 500/8/30 (24)
Solpadeine Plus 500/8/30 (32)
Solpaflex (12)
Solpaflex (24)
Syndol Easy Swallow (10)
Syndol Easy Swallow (20)
Syndol Easy Swallow (30)
Syndol (20)
Ultramol (32)
Veganin (10)
Veganin (30)

PI = Parallel Import

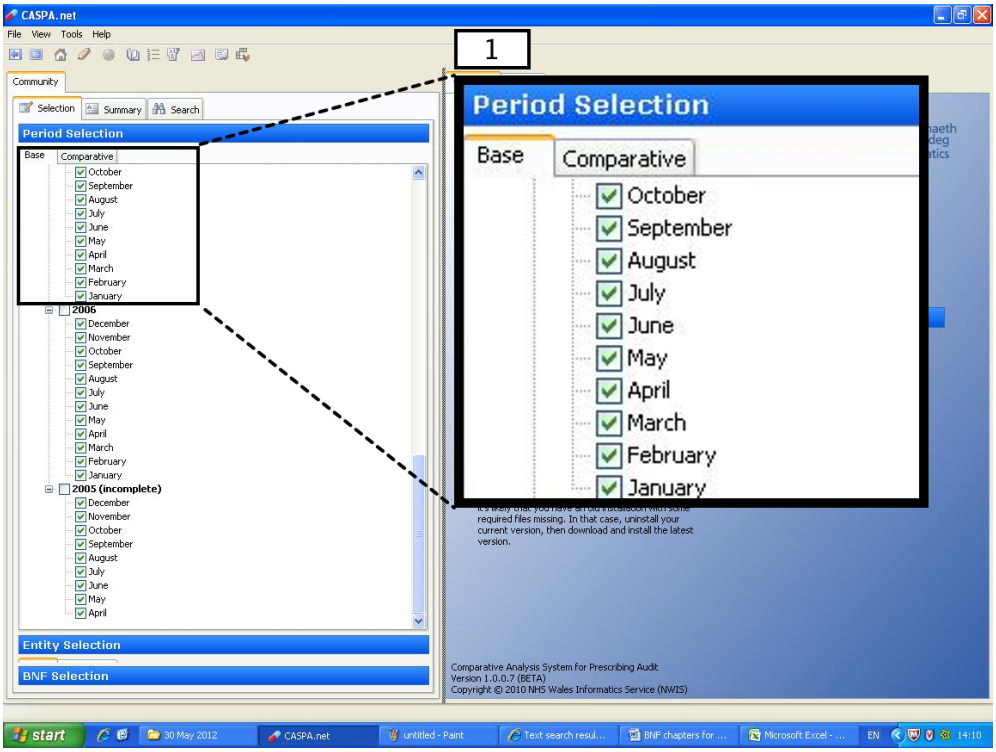
Appendix 7

List of over-the-counter dihydrocodeine containing analgesics and their respective pack size (number of tablets/capsules) extracted from the Regional Sales Analysis database for Wales

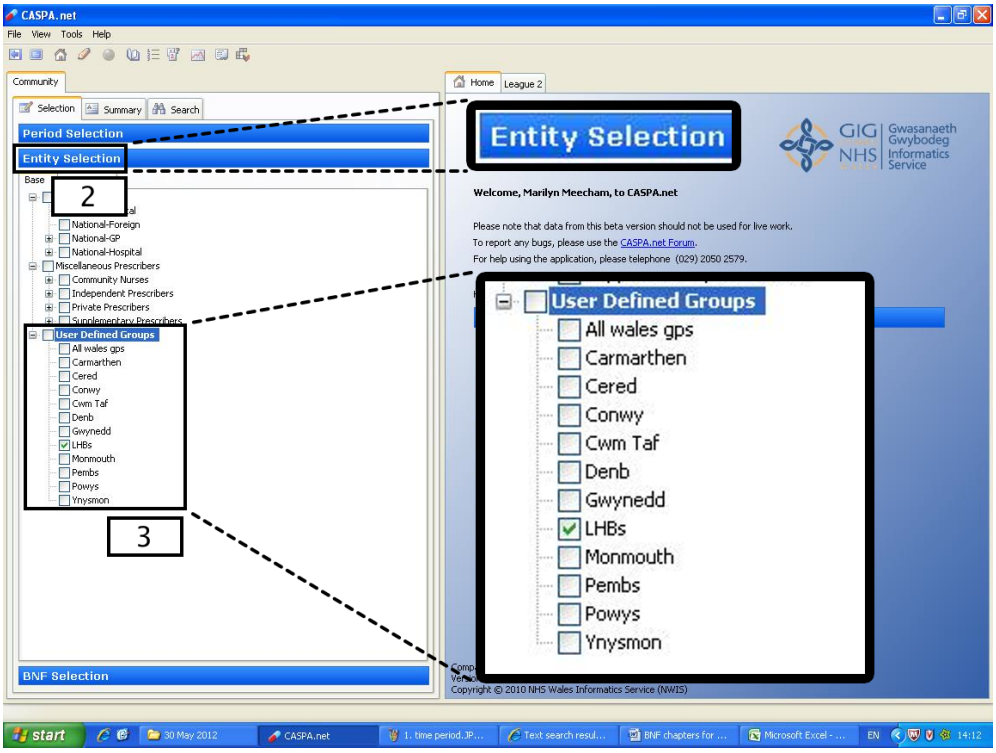
Soluble	Non-soluble
Paramol (12)	Paramol (12)
Paramol (24)	Paramol (24)
	Paramol (32)
	Paramol Swallow (12)
	Paramol Swallow (24)
	Paramol Swallow (32)

Appendix 8

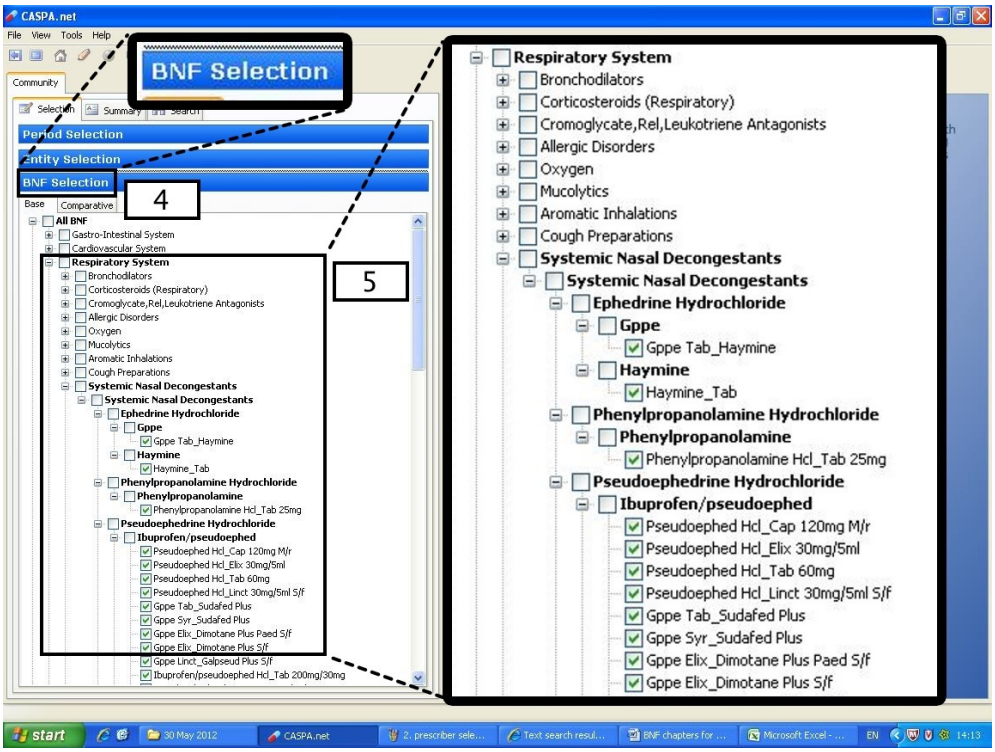
The extraction and transfer of NHS prescription data from CASPA.net into a Microsoft Excel spreadsheet



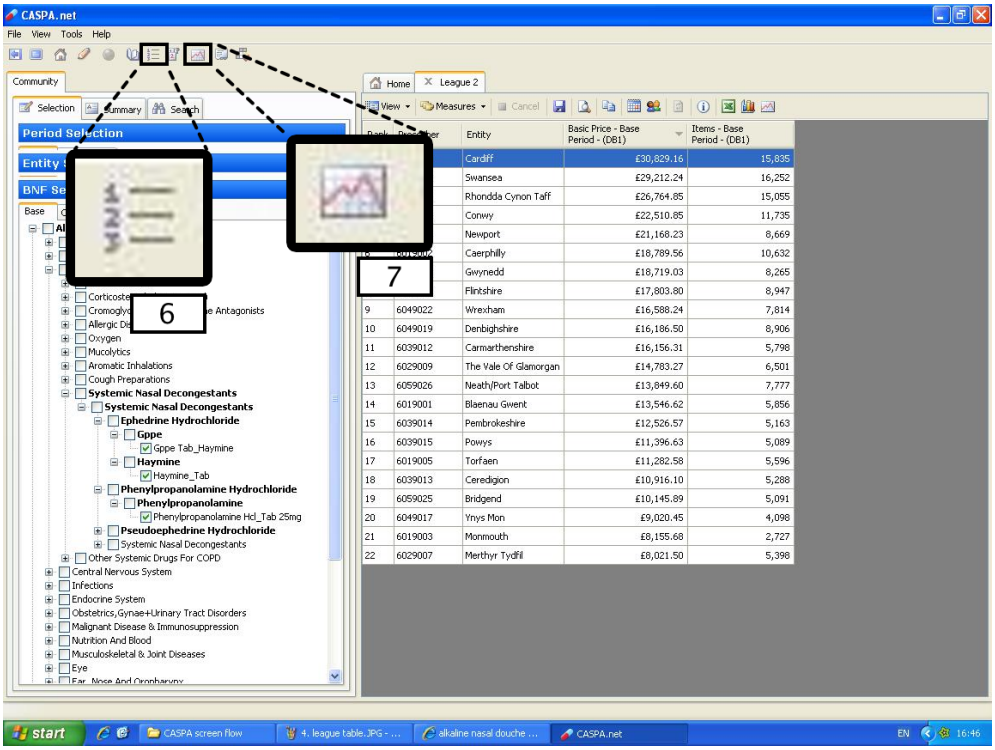
Step 1 Select (1) the desired time period



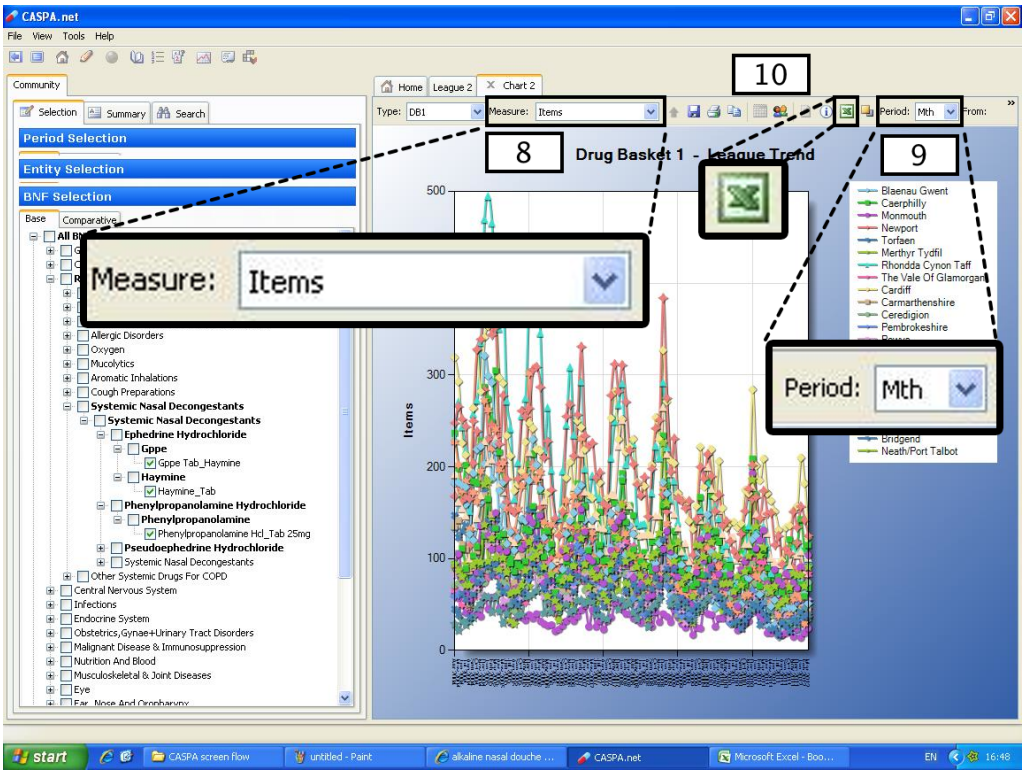
Step 2 (2) Select ‘Entity Selection’ and then select (3) the desired Local Health Boards



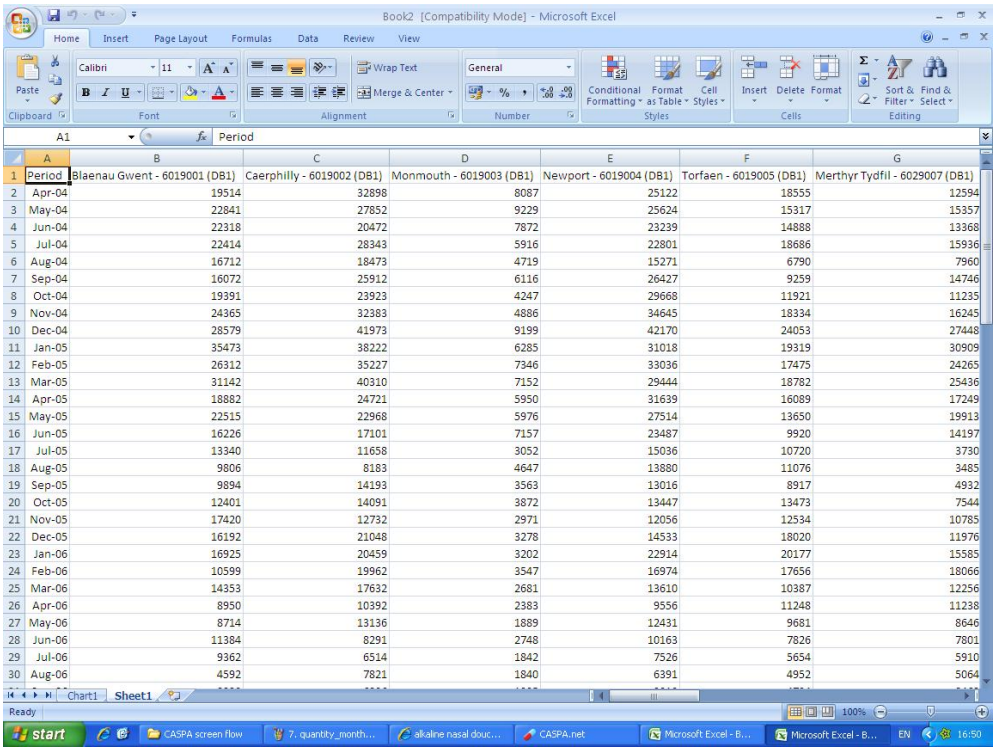
Step 3 Select (4) the 'BNF selection' tab and then select (5) the drug of interest



Step 4 Select (6) the 'League Table' button to generate a league table. After the league table has appeared select (7) the 'Trend Graph' button and a trend graph will appear



Step 5 Choose the desired output measure by selecting (8) ‘Measure’. Choose the desired data interval (monthly or quarterly) by selecting (9) ‘Period’. Lastly, export the data by clicking on (10) the Microsoft Excel button

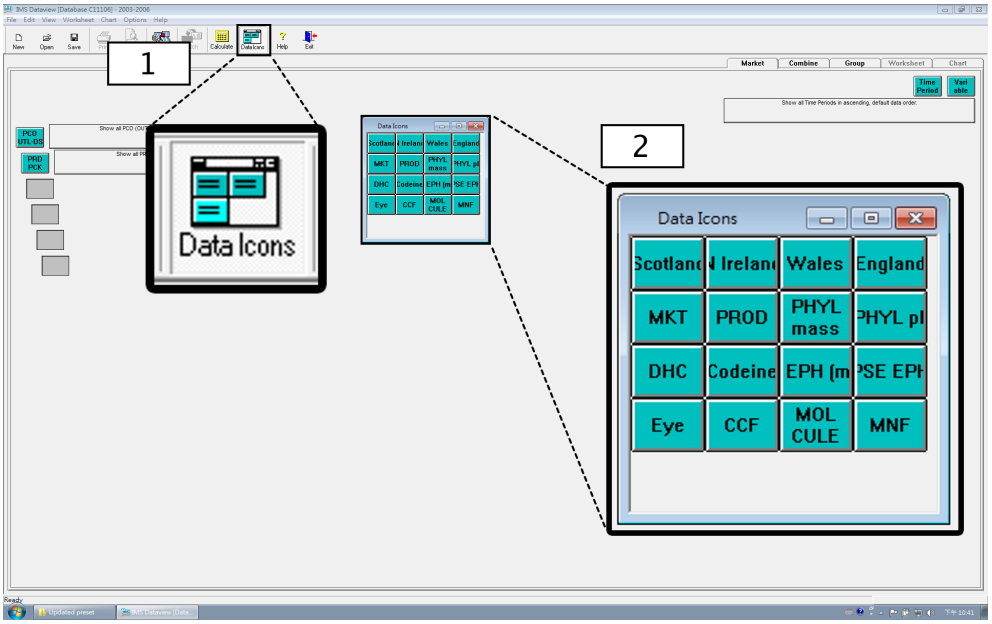


Period	Blaenau Gwent - 6019001 (DB1)	Caerphilly - 6019002 (DB1)	Monmouth - 6019003 (DB1)	Newport - 6019004 (DB1)	Torfaen - 6019005 (DB1)	Merthyr Tydfil - 6029007 (DB1)
Apr-04	19514	32898	8087	25122	18555	12594
May-04	22841	27852	9229	25624	15317	15357
Jun-04	22318	20472	7872	23239	14888	13368
Jul-04	22414	28343	5916	22801	18686	15936
Aug-04	16712	18473	4719	15271	6790	7960
Sep-04	16072	25912	6116	26427	9259	14746
Oct-04	19391	23923	4247	29668	11921	11235
Nov-04	24365	32383	4886	34645	18334	16245
Dec-04	28579	41973	9199	42170	24053	27448
Jan-05	35473	38222	6285	31018	19319	30909
Feb-05	26312	35227	7346	33036	17475	24265
Mar-05	31142	40310	7152	29444	18782	25436
Apr-05	18882	24721	5950	31639	16089	17249
May-05	22515	22968	5976	27514	13650	19913
Jun-05	16226	17101	7157	23487	9920	14197
Jul-05	13340	11658	3052	15036	10720	3730
Aug-05	9806	8183	4647	13880	11076	3485
Sep-05	9894	14193	3563	13016	8917	4932
Oct-05	12401	14091	3872	13447	13473	7544
Nov-05	17420	12732	2971	12056	12534	10785
Dec-05	16192	21048	3278	14533	18020	11976
Jan-06	16925	20459	3202	22914	20177	15585
Feb-06	10599	19962	3547	16974	17656	18066
Mar-06	14353	17632	2681	13610	10387	12256
Apr-06	8950	10392	2383	9556	11248	11238
May-06	8714	13136	1889	12431	9681	8646
Jun-06	11384	8291	2748	10163	7826	7801
Jul-06	9362	6514	1842	7526	5654	5910
Aug-06	4592	7821	1840	6391	4952	5064

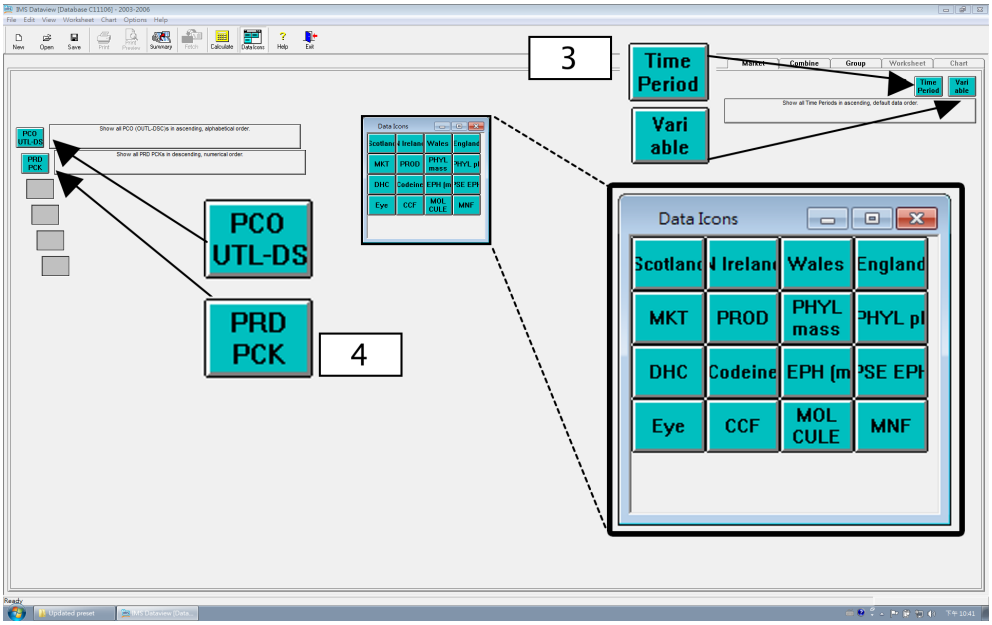
Step 6 Prescription data will appear in Excel spreadsheet

Appendix 9

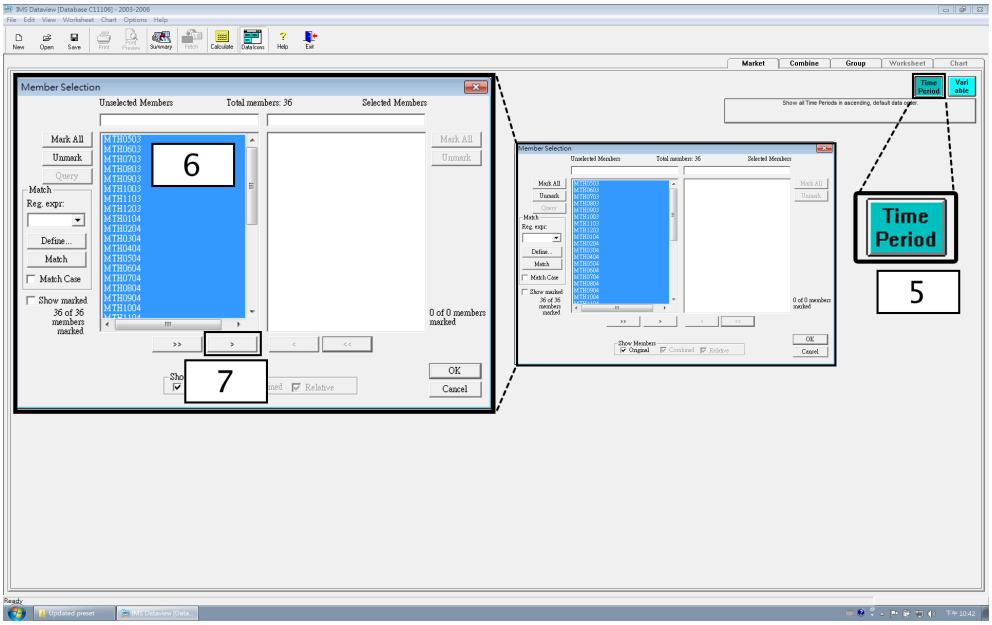
The extraction and transfer of pharmacy wholesale data from the Regional Sales Analysis database into a Microsoft Excel spreadsheet



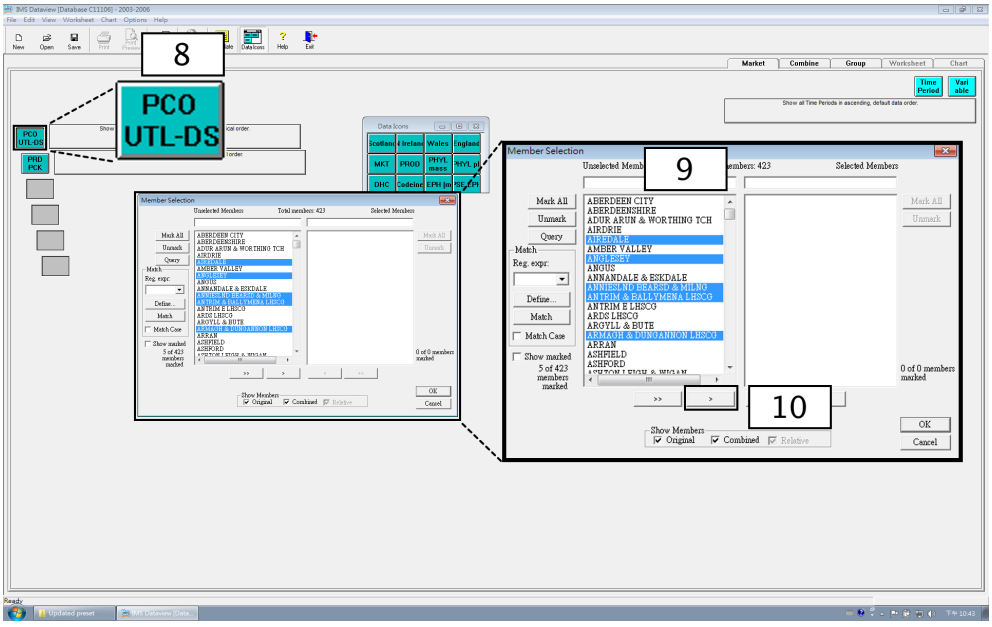
Step 1 Select (1) the 'Data Icons' button to bring up (2) the data element panel



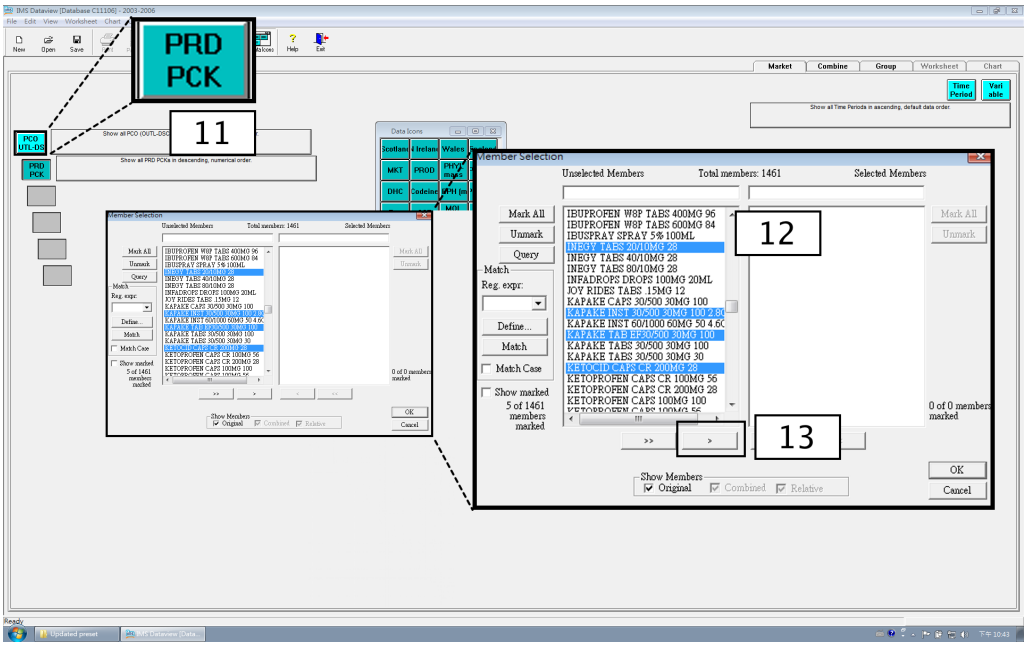
Step 2 Drag (3) the 'Time Period' and 'Variable' and (4) 'PCO ULT-DS' and 'PRD PCK' data elements box from the data element panel into pre-defined areas (as indicated by the arrows)



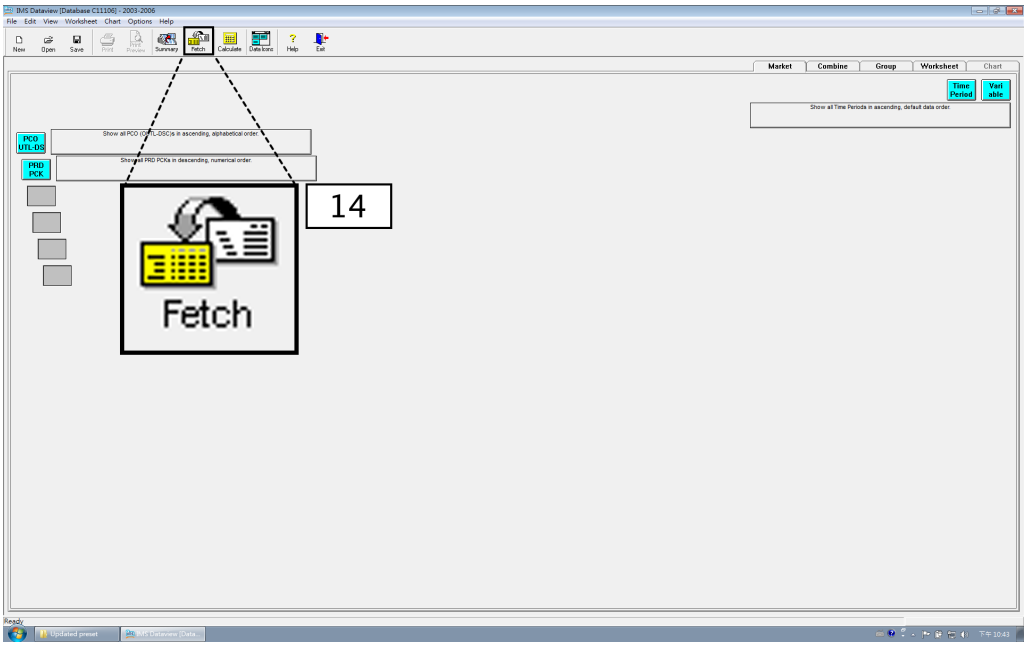
Step 3 Click on (5) ‘Time Period’ data element box and then select (6) the desired time period. Then (7) transfer them across to the empty column. Press OK.



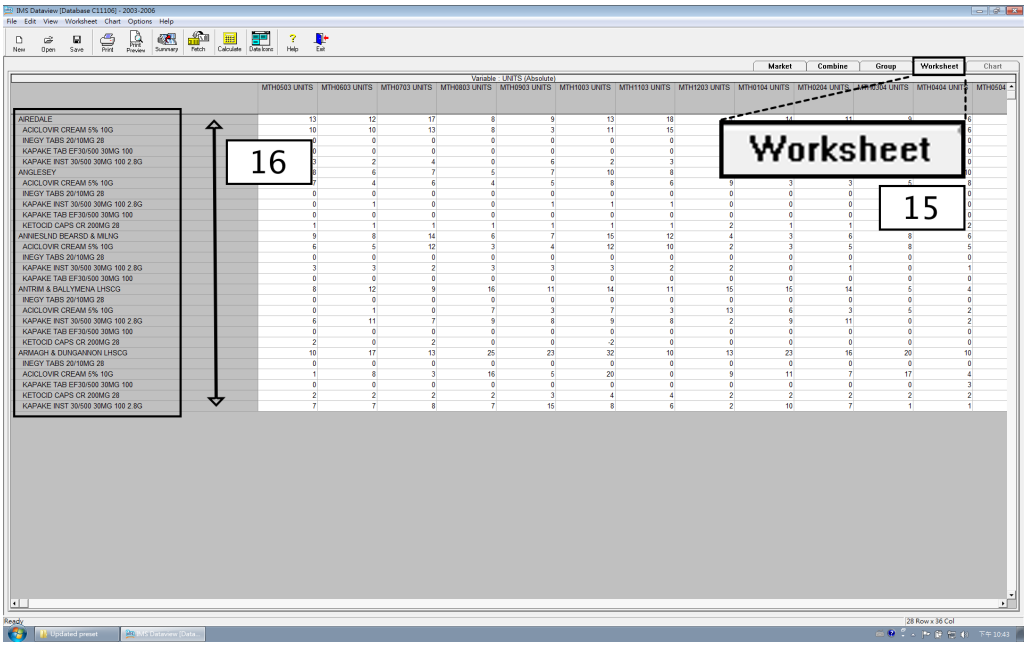
Step 4 Click on (8) ‘PCO UTL-DS’ data element box and then select (9) the desired Local Health Boards. Then (10) transfer them across to the empty column. Press OK.



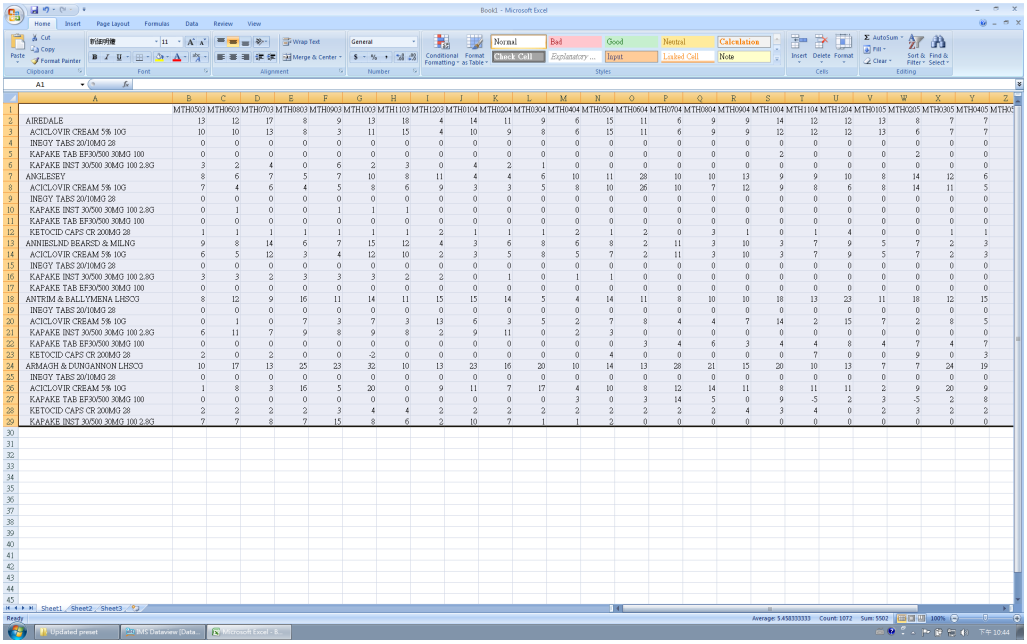
Step 5 Click on (11) 'PRD PCK' data element box and then select (12) the desired medicinal product. Then (13) transfer them across to the empty column. Press OK.



Step 6 Click on (14) 'Fetch' button will create a result worksheet containing the data



Step 7 Result worksheet appear automatically. If not, click on (15) the ‘Worksheet’ tab. Select (16) all of the rows containing the data and press [Control + C] to copy data



Step 8 Paste (Control + v) the copied data into Excel spreadsheet

Appendix 10

List of pseudoephedrine (PSE), phenylephrine (PE), ephedrine and inhalation based nasal decongestants prescribed and dispensed on NHS prescription that were extracted from the NHS Wales prescription database

PE Tablets or Capsules
Galpharm Max Strength Decongestant
Non-Drowsy Sudafed Congestion Relief
PE Hcl 12mg
Boots Decongestant 12mg

PSE Tablets or Capsules
Contac Non-Drowsy Dual Relief
Ibuprofen/PSE Hcl 200mg/30mg
Nurofen Cold & Flu
Paracetamol/PSE Hcl 500mg/30mg
Sinutab Non-Drowsy
Ibuprofen/PE Hcl 300mg/45mg
Actifed Multi Action
Boots Decongestant
Galpseud 60mg
Galsud 60mg
Non-Drowsy Sudafed Congestion
Otrivine Mu-Cron 500mg/60mg
Paracetamol/PSE Hcl 500mg/60mg
PSE Hcl 60mg
Sudafed 60mg
Contac Non-Drowsy 120mg
Sudafed Plus
PSE Hcl 120mg M/R

PSE Tablets or Capsules (cont)
Sudafed 12 Hour Relief 120mg M/R
Sudafed Plus
Sudafed-Sa 120mg
Haymine

PSE Liquids
Meltus Decongestant Oral Solution 30mg/5ml Sugar Free
Actifed Multi Action Syrup 30mg/1.25mg
Galpseud Plus Linctus Sugar Free
Galpseud Linctus 30mg/5ml Sugar Free
Galsud Linctus 30mg/5ml Sugar Free
Linctus Galpseud Plus Sugar Free
PSE Hcl Elixir 30mg/5ml
PSE Hcl Linctus 30mg/5ml Sugar Free
PSE HCl Liquid Spec 30mg/5ml
Sudafed Plus Syrup
Sudafed Elixir 30mg/5ml

Ephedrine Tablets
Haymine

Inhalation Therapy
Olbas For Child Oil
Benz Co Tincture
Benz Tincture BPC
Menthol & Eucalyptus Inhalator BP 1980
Menthol & Eucalyptus Ointment
Karvol Decongestant Inhalation Capsules
Karvol Family Decongestant Inhalation

Hcl = Hydrochloride

M/R = Modified Release

Appendix 11

List of topical nasal decongestants containing ephedrine, ipratropium, sodium chloride, phenylephrine or xylometazoline prescribed and dispensed on NHS prescription that were extracted from the NHS Wales prescription database

Topical Ephedrine

Nasal Drops 0.25%
Nasal Drops 0.5% BP
Nasal Drops 1% BP
Ephedrine in Normal Saline Nasal Drops 0.25%
Ephedrine in Normal Saline Nasal Drops 0.5%
Ephedrine In Normal Saline Nasal Drops 1%
Nasal Drops 0.1%
Nasal Drops 2%
Nasal Spray 2%

Topical Ipratropium

Aqueous Nasal Spray 21mcg
Rinatec Nasal Spray 20mcg
Rinatec Aqueous Nasal Spray 21mcg

Topical Sodium Chloride

Nasal Drops 0.5%, 0.9%, 5%
Solution 0.9% 2.5ml Unit Dose
Nasal Mist 0.9%
Nasal Solution 0.9%
Nebulizer Solution 7% 10ml Pre-filled
Nebulizer Solution 10% 10ml Vl
Nebulizer Solution 5% 20ml Vl
Nebulizer Solution 4.5% 10ml Vl
Nasal Douche Powder
Sterile Respiratory Solution 3%, 7%
Respiratory Solution 0.9% 20ml Unit Dose
Inhalation Solution 7% 5ml Unit Dose
Inhalation Solution 3%
Nasal Douche 0.9%
Inhalation Solution 1.8%, 7%
Inhalation Solution 0.9% 20ml Unit Dose
Nebulizer Solution 7% 5ml Vl

Topical Sodium Chloride (continued)

Nebulizer Solution 7% 10ml Ampules
Nebulizer Solution 7% 5ml Ampules
Nebulizer Solution 7%
Nebulizer Solution 3%
Nebulizer Solution 5% 10ml Vl
Nebulizer Solution 7% 4ml Vl
Nebulizer Solution 3% 10ml Unit Dose
Saline Steri-Neb Solution 0.9%/2.5ml Unit Dose
Nucare Sigma Normal Saline Nasal Drops 0.9%
Salex Saline Nasal Spray 0.72% 30ml
Select Pharma Normal Saline Nasal Drops 0.9%
Saline Steripoule Inhalation Solution 0.9% 20ml Unit Dose
Saline Steripoule Inhalation Solution 0.9% 2.5ml Unit Dose
Tubilux Nasal Drops 0.9%

Topical Phenylephrine

Nasal Drops 0.5%
Fenox Nasal Drops 0.5%

Topical Xylometazoline

Nasal Drops Pediatric 0.05%
Nasal Spray 0.1% 10ml, 15ml
Otrivine Nasal Pump Spray 0.1% 10ml
Otrivine Pediatric Nasal Solution 0.05%
Otrivine Nasal Solution 0.1%
Otrivine Menthol Nasal Spray 0.1% 10ml
Otrivine Sinusitis Spray 0.1% 10ml
Otrivine Adult Metered Nasal Pump Spray 0.1% 10ml
Otradrops Nasal Drops Pediatric 0.05%
Otradrops Nasal Drops Adult 0.1%
Otraspray Nasal Pump spray 0.1% 10ml
Tixycolds Cold & Allergy Nasal Drops 0.05%
Sudafed Non-Drowsy Decongest Nasal Spray 0.1% 15ml

Appendix 12

List of over-the-counter pseudoephedrine (PSE) containing products extracted from the Regional Sales Analysis database for Wales

PSE containing preparations (pack size in tablets/capsules/mls)
Benadryl Plus Capsules (12)
Benadryl Plus Capsules (24)
Benylin 4 Flu Liquid (200ml)
Benylin 4 Flu Tablets (24)
Benylin Day & Night Tablets (16)
Benylin Day & Night Tablets (20)
Day And Night Nurse Capsules (24)
Day Nurse Capsules (20)
Day Nurse Liquid (160ml)
Day Nurse Liquid (240ml)
Lemsip Caps Sinus 12hr (8)
Lemsip Max Flu Strength Sachet (10)
Lemsip Max Power Capsules (10)
Lemsip Max Sinus Cold & Flu 12 Hour Relief Capsules (8)
Mucron Tablets (12)
Nurofen Cold & Flu Tablets (12)
Nurofen Cold & Flu Tablets (24)
Nurofen Cold & Flu Tablets (36)
Sinutab Tablets (15)
Sinutab Tablets (30)
Sinutab Tablets Non-Drowsy (15)
Sinutab Tablets Non-Drowsy (30)
Sudafed Dual Relief Max Tablets Non-Drowsy (12)
Sudafed Dual Relief Max Tablets Non-Drowsy (24)
Vicks Medinite Liquid (180ml)

Appendix 13

List of over-the-counter phenylephrine containing products extracted from the Regional Sales Analysis database for Wales

Phenylephrine containing preparations (pack size in tablets/capsules/sachets/mls)
Anadin Cold Control Capsules (16)
Anadin Cold Control Sachets (5)
Beechams All In 1 Liquid (160ml)
Beechams All In 1 Liquid (240ml)
Beechams All In 1 Liquid Pocket Pack (2)
Beechams All In 1 Liquid Pocket Pack (6)
Beechams All In 1 Hot Lemon Sachet (10)
Beechams All In 1 Tablets (16)
Beechams All In 1 Tablets (8)
Beechams All In 1 Tablets Non-Drowsy (24)
Beechams All In 1 Ultra Capsules (16)
Beechams Decongestant Plus Capsules (16)
Beechams Flu Plus Berry Fruit Sachet (5)
Beechams Flu Plus Caplets (16)
Beechams Flu Plus Caplets (24)
Beechams Flu Plus Caplets (8)
Beechams Flu Plus Hot Berry Fruit Stick (10)
Beechams Flu Plus Hot Berry Fruit Stick (5)
Beechams Flu Plus Hot Berry Fruit Sachet (10)
Beechams Flu Plus Hot Lemon Sachet (10)
Beechams Flu Plus Hot Lemon Sachet (5)
Beechams Flu Plus Hot Lemon Stick (10)
Beechams Flu Plus Hot Lemon Stick (5)
Benylin Day & Night Cold & Flu Capsules (16)
Galpharm Flu Relief Decongestant Capsules (16)
Galpharm Flu Relief Flu Strength Liquid (160ml)
Galpharm Flu Relief Hot Lemon Sachet (10)
Lemsip Blackcurrant Sachet (10)
Lemsip Blackcurrant Sachet (5)
Lemsip Breathe Easy Sachet (10)
Lemsip Breathe Easy Sachet (5)
Lemsip Max All Night Cold & Flu Tablets (16)
Lemsip Max All in 1 Easy Breath Sachets (10)
Lemsip Max All in 1 Capsules (16)
Lemsip Max All in 1 Lemon Sachet (16)

Appendix 13 (continued)

List of over-the-counter phenylephrine containing products extracted from the Regional Sales Analysis database for Wales

Phenylephrine containing preparations (pack size in tablets/capsules/sachets)
Lemsip Max All In One Sachets (10)
Lemsip Max All In One Sachets (5)
Lemsip Max All In One Winter Berry & Orange Sachet (10)
Lemsip Max All In One (10)
Lemsip Max All In One (160ml)
Lemsip Max All In One (5)
Lemsip Max Breath Easy Sachet (10)
Lemsip Max Capsules (16)
Lemsip Max Capsules (8)
Lemsip Max Capsules Daytime (16)
Lemsip Max Cold & Flu Capsules (16)
Lemsip Max Day & Night Cold & Flu Capsules (16)
Lemsip Max Day & Night Capsules (16)
Lemsip Max Day & Night Capsules (8)
Lemsip Max Direct Blackcurrant Sachet (10)
Lemsip Max Direct Lemon Sachet (10)
Lemsip Max Sachet Blackcurrant (10)
Lemsip Max Sachet Blackcurrant (5)
Lemsip Max Lemon Sachets (10)
Lemsip Max Lemon Sachets (5)
Lemsip Max Sinus Max Strength Capsules (16)
Lemsip Max Sinus Sachet (10)
Lemsip Max Swallow Lemon Tablets (12)
Lemsip Original Lemon (10)
Lemsip Original Lemon (5)
Sudafed Dual Relief Non-Drowsy Capsules (16)
Sudafed Dual Relief Non-Drowsy Capsules (32)
Uniflu Gregovite C Tablets (12)
Uniflu Gregovite C Tablets (24)

Appendix 14

List of ophthalmic chloramphenicol preparations extracted from the NHS prescription database for Wales

Eye Drops	Eye Ointment
Chloramphenicol 0.5%	Chloramphenicol 0.5%
Chloramphenicol 1%	Chloramphenicol 1%
Chloramphenicol 0.5% Ud	Chloromycetin 1%
Chloramphenicol/Polyalc 0.5%	Optrex Infected Eyes 1%
Chloromycetin Redidrops 0.5%	Brochlor 1%
Minims Chloramphenicol 0.5% Ud p/f*	Golden Eye Antibiotic 1%
Sno Phenicol 0.5%	
Optrex Infected Eyes 0.5%	
Brochlor 0.5%	
Golden Eye Antibiotic 0.5%	

Ud = Unit dose, p/f = preservative free, Polyalc = Polyalcohol

Appendix 15

A list of proprietary ophthalmic chloramphenicol preparations sold in the UK, together with their respective retail price, pack size and availability

Eye drops 0.5% (10ml)	**Retail price (£)**	**UK availability**
Brochlor	4.85	October 2006
Galpharm Vision Chloramphenicol	4.38	October 2005
Golden Eye Antibiotic	5.10	June 2007
I-Care Chloramphenicol Antibiotic	4.48	N/A
Numark Chloramphenicol Antibiotic	4.05	September 2005
Optrex Infected Eyes	5.18	June 2005
Tubilux	4.34	September 2006
Eye Ointments 1% w/w (4g)		
Brochlor	5.06	July 2007
Galpharm Vision Antibiotic	4.96	July 2007
Golden Eye Antibiotic	5.50	March 2008
I-Care Chloramphenicol Antibiotic	4.69	N/A
Optrex Infected Eyes	5.72	July 2007

N/A: Information unavailable

Appendix 16

List of ophthalmic chloramphenicol preparations for which pharmacy wholesale data were extracted from the Regional Sales Analysis database for Wales

Eye Drops (10ml)	Eye Ointments (4g)
Brochlor 0.5%	Brochlor 1%
Golden Eye Antibiotic 0.5%	Golden Eye Antibiotic 1%
Galpharm Vision Antibiotic 0.5%	Galpharm Vision Antibiotic 1%
Optrex Infected Eyes 0.5%	Optrex Infected Eyes 1%
Tubilux Infected Eyes 0.5%	

Appendix 17

List of ophthalmic chloramphenicol preparations for which pharmacy retail data were obtained from Company A

Eye Drops (10ml)	Eye Ointment (4g)
Own-brand Antibiotic 0.5%	Golden Eye Antibiotic 1%
Golden Eye Antibiotic 0.5%	Optrex Infected Eyes 1%
Optrex Infected Eyes 0.5%	

Appendix 18

List of over-the-counter oral cold and flu medicines and their respective pack sizes extracted from the Regional Sales Analysis database which were monitored between May 2003 and April 2009

Liquid Preparations	**Product pack size(s)**
Beechams All In 1	160, 240ml
Beechams All In 1 Pocket Pack	2, 6 sachets
Benylin 4 Flu	200ml
Cold Relief Cold Flu	160, 200ml
Day Nurse	240ml
Galpharm Flu Relief Flu Strength	160ml
Lemsip Max All In One	160ml
Night Nurse	160ml
Vicks Medinite	180ml
Soluble Preparations	
Beechams All In 1 Hot Lemon	10 sachets
Beechams Flu Plus Berry Fruit	5, 10 sachets
Beechams Flu Plus Hot Berry Fruit	5, 10 sticks
Beechams Flu Plus Hot Lemon	5, 10 sachets
Beechams Flu Plus Hot Lemon	5, 10 sticks
Cold Relief All In 1 Powder	10 sachets
Cold Relief Hot Blackcurrant	5 sachets
Cold Relief Hot Lemon	5, 10 sachets
Cold Relief Maximum Flu Strength	10 sachets
Cold Relief Powder	8, 10 sachets
Galpharm Flu Relief Hot Lemon	10 sachets
Lemsip Blackcurrant	5, 10 sachets
Lemsip Breathe Easy	5, 10 sachets
Lemsip Max All In 1 Breath Easy	10 sachets
Lemsip Max All In 1 Lemon	16 sachets
Lemsip Max All In 1	5, 10 sachets
Lemsip Max All In 1 Winter Berry & Orange	10 sachets
Lemsip Max Easy Breath	10 sachets
Lemsip Max Direct Blackcurrant	10 sachets
Lemsip Max Direct Lemon	10 sachets
Lemsip Max Flu Strength	10 sachets
Lemsip Max Blackcurrant	5, 10 sachets
Lemsip Max Lemon	5, 10 sachets
Lemsip Original Lemon	5, 10 sachets

Appendix 18 (continued)

List of over-the-counter cold and flu medicines and their respective pack sizes extracted from the Regional Sales Analysis database which were monitored between May 2003 and April 2009

Solid Preparations	Product pack size(s)
Beechams All In 1	8, 16 tablets
Beechams All In 1 Non-Drowsy	24 tablets
Beechams All In 1 Ultra	16 capsules
Beechams Flu Plus	8, 16, 24 caplets
Benylin 4 Flu	24 tablets
Benylin Day &Night Cold & Flu	16 capsules
Benylin Day &Night	16, 20 tablets
Cold Relief All In 1	16 tablets
Cold Relief	16, 24, 32 capsules
Cold Relief Max Strength	16 capsules
Cold Relief Inhalant	10 capsules
Cold Relief	12, 16 tablets
Day And Night Nurse	24 capsules
Day Nurse	20 capsules
Galpharm Flu Relief Decongestant	16 capsules
Lemsip Max All Night Cold & Flu	16 tablets
Lemsip Max All In One	16 capsules
Lemsip Max All In One	5, 10 tablets
Lemsip Max	8, 16 capsules
Lemsip Max Daytime	16 capsules
Lemsip Max Cold & Flu	16 capsules
Lemsip Max Day & Night Cold & Flu	24 capsules
Lemsip Max Day & Night	8, 16 capsules
Lemsip Max Lemon	6 tablets
Lemsip Max Power	10 capsules
Lemsip Max Swallow / Dispersible Lemon	12 tablets
Night Nurse	10 capsules
Nurofen Cold & Flu	12, 24, 36 tablets

Appendix 19

List of over-the-counter cough medicines and their respective pack sizes extracted from the Regional Sales Analysis database which were monitored between May 2003 and April 2009

Cough preparations	**Product pack size(s)**
Cough Cold Unbranded Adult Chesty Non-Drowsy	200ml
Cough Cold Unbranded Chesty Adult	200ml
Cough Cold Unbranded Chesty Cough	150, 200ml
Cough Cold Unbranded Expectorant Adult + Decongestant	100, 150ml
Cough Cold Unbranded Adult Linctus	200ml
Lemsip Chesty Cough	100ml
Lemsip Dry Cough	100ml

Appendix 20

List of over-the-counter nasal congestion or sinusitis medicines and their respective pack sizes extracted from the Regional Sales Analysis database which were monitored between May 2003 and April 2009

Nasal Congestion or Sinusitis preparations	Product pack size(s)
Beechams Decongstant Plus	16 capsules
Cold Relief Decongestant Non-Drowsy	16 capsules
Cold Relief Decongestant	12 capsules
Cold Relief Decongestant	12, 24 tablets
Lemsip Sinus 12hr Relief	8 capsules
Lemsip Max Sinus Max Strength	16 capsules
Lemsip Max Sinus	10 sachets
Lemsip Max Sinus Cold & Flu 12h	8 capsules
Lemsip Non-Drowsy Decongestants	10 sachets
Sinutab	15, 30 tablets
Sudafed Congestion Non-Drowsy	12, 16 tablets
Sudafed Dual Relief Non-Drowsy	16, 32 capsules
Sudafed Dual Relief Max Non-Drowsy	12, 24 tablets