Impact of a pharmacy-led screening service for group A beta-haemolytic streptococci, on general practitioner visits and antibiotic consumption: A non-randomized controlled study

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Impact of a pharmacy-led screening service for group A beta-haemolytic streptococci, on general practitioner visits and antibiotic consumption: A non-randomized controlled study

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Supervisors: Dr Gráinne Cousins, Professor Paul Gallagher

January 2018
Candidate Thesis Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree Masters by Research is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CAESAR</td>
<td>The Central Asian and Eastern European Surveillance of Antimicrobial Resistance</td>
</tr>
<tr>
<td>CDC</td>
<td>Centre for Disease Control (America)</td>
</tr>
<tr>
<td>CONSORT</td>
<td>Consolidate Standards of Reporting Trials</td>
</tr>
<tr>
<td>CPR</td>
<td>Clinical Prediction Rule</td>
</tr>
<tr>
<td>CRP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>DDD</td>
<td>Daily Defined Doses</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>E. coli</td>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td>FAO</td>
<td>Food and Agricultural Organization of the United Nations</td>
</tr>
<tr>
<td>GABHS</td>
<td>Group A Beta Haemolytic Streptococci</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>HSE</td>
<td>Health Service Executive</td>
</tr>
<tr>
<td>ICGP</td>
<td>Irish College of General Practitioners</td>
</tr>
<tr>
<td>IIOP</td>
<td>Irish Institute of Pharmacy</td>
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<tr>
<td>MDR</td>
<td>Multi drug resistance</td>
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<tr>
<td>MRSA</td>
<td>Methicillin Resistant <em>Staphylococcus Aureus</em></td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
</tr>
<tr>
<td>OIE</td>
<td>The World Organisation for Animal Health</td>
</tr>
<tr>
<td>OSCE</td>
<td>Objective Structured Clinical Examination</td>
</tr>
<tr>
<td>OTC</td>
<td>Over The Counter</td>
</tr>
<tr>
<td>PGD</td>
<td>Patient Group Directive</td>
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<tr>
<td>POCT</td>
<td>Point of Care Testing</td>
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<tr>
<td>PSI</td>
<td>Pharmaceutical Society of Ireland</td>
</tr>
<tr>
<td>RADT</td>
<td>Rapid Antigen Detection Testing</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>TREND</td>
<td>Transparent Reporting of Evaluations with Nonrandomized Designs</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Summary

Background
Up to 75% of cases of pharyngitis are inappropriately prescribed antibiotics. In those with a bacterial infection, one strain could be treated with antibiotics, *Group A β-Haemolytic Streptococci* (GABHS), to minimise complications. The Centor Criteria, a clinical prediction rule, is recommended by UK and Irish General Practitioner guidelines for use in primary care. The Infectious Diseases Society of America recommends the use of RADT in combination with the Centor Criteria, to improve antibiotic prescribing. The aim of this study was to evaluate the effectiveness of a community pharmacy intervention, involving the Centor Criteria and Rapid Antigen Detection Testing (RADT) on General Practitioner (GP) visits and antibiotic prescribing.

Method
A non-randomised controlled, parallel trial of adults aged ≥ 18 years, presenting to one of 20 community pharmacies in Ireland with an uncomplicated sore throat. Patients presenting to pharmacy with a sore throat lasting between 3 and 10 days, with no reported symptom improvement were invited to participate in the study. Those in the intervention group were evaluated using the Centor Criteria and if necessary RADT, by the pharmacist. Those in the control group received usual care from their pharmacy team. Those with a Centor score of 1 or more were included in the study. All patients were followed up at 7 days to determine GP visits and antibiotic consumption. Secondary outcomes included; appropriateness of antibiotic (based on Centor score, RADT results and type of antibiotic prescribed), self reported antibiotic adherence, time to recovery and patient satisfaction.

Results
Five intervention pharmacies and nine control pharmacies recruited patients. At baseline patient groups were similar with 35 patients participating in the intervention and 79 patients in the control. Results of the study show that the
intervention in combination with the pharmacist advice could reduce GP visits by approximately one-third.

At follow up there were 29 patients in the intervention group and 66 patients in the control group. There were no significant differences across treatment groups for attendance at GP with 24.14% attending in the intervention group and 21.12% in the control (OR = 1.24, 95% CI = 0.42, 3.63, p = 0.7).

Antibiotic prescription was similar across treatment groups with 20.69% of those in the intervention group prescribed antibiotics and 19.7% in the control group prescribed antibiotics. Inappropriate prescription of antibiotics was found to be high in both treatment groups, based on the clinical presentation of patients at day one. Patient satisfaction was high with 94.12% of patients stated that they would use the service again in the future.

Conclusion

Patients are open to community pharmacists providing such point of care testing services, with many stating they would like to have more of these services on offer through the pharmacy. From the data presented it the intervention does not have a significant impact on GP visits or antibiotic prescribing. While further study is required on this intervention in the community pharmacy setting in Ireland, the study shows that pharmacists in combination with the intervention presented, have the potential to reduce GP visits and improve the rational use of medicines.
Acknowledgements

I would like to thank the support and efforts of the pharmacists, interns, pharmacy staff and patients of Boots Ireland for taking part in this study.

My supervisors - Dr Gráinne Cousins, who always steered me in the right direction, kept me motivated throughout the process and answered my many questions. Professor Paul Gallagher, Head of School of Pharmacy, who shared his wisdom and always kept his door open.

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Finally, I must express my very profound gratitude to my parents, Seán, my brothers, my sister and friends for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.
1 Introduction

1.1 History of Antibiotics

Antibiotics are chemotherapeutic agents, which are defined as agents toxic to the cause of a disease such as bacteria, viruses or other microorganisms\(^1\). Before the discovery and development of antibiotics the global mortality rates from infectious diseases were high\(^1\). For example, in 1924, the maternal mortality rate in the United States due to sepsis was 275 deaths per 100,000 live births. Following the discovery of sulphonamides, mortality rates dropped significantly to 55 deaths per 100,000 live births in 1955\(^2\). The US maternal mortality rate was lowest in 1987 with 7.2 deaths per 100,000 live births, having been approximately 600 per 100,000, prior to the discovery of antibiotics\(^3\).

The top three leading causes of death in the United States of America in 1900 were, pneumonia, tuberculosis and diarrhoea and enteritis, all which have a bacterial pathophysiology\(^4\). US statistics at that time were similar to Ireland\(^4,5\). Pneumonia and tuberculosis accounted for over 20% of deaths. Today tuberculosis and diarrhoea and enteritis, are no longer in the top ten causes of death, while, pneumonia and influenza account for less than 5% of deaths today\(^4\). Antibiotics, in combination with other techniques, have been used to treat these infections and reduce mortality rates. They also have been, and are used to treat life threatening infections such as streptococcal, staphylococcal, gonorrhoea, syphilis and many more infections\(^4\).

Today in the US and Ireland, the leading causes of death are heart disease, cancer, stroke and chronic lung disease\(^4,5\). Life expectancy is much greater now and most deaths are in older people unlike the early 1900s, in which, the burden was evenly spread across all age groups. In 1916, over 10% of all children under the age of one year died\(^5\). This is not the case today due to improvements in living conditions, hygiene practices, vaccination programmes, public health initiatives, medical improvements and the development of antibiotics\(^6\).
The development of antibiotics has also greatly reduced the number of deaths following surgery due to surgical site infections\textsuperscript{7}. The use of antibiotics prophylactically, allows for hip replacements, anastomosis of the colon, knee replacements, heart, respiratory, genitourinary tract, cancer, appendicectomy surgery, caesarean section, abortion, amputation, and surgery due to trauma resulting in a contaminated injury site\textsuperscript{7}. Without the prophylactic use of antibiotics during these surgeries the risk of death greatly increases and the benefit risk ratio is heavily weighted towards the risk, thereby reducing the number of people eligible for surgery\textsuperscript{7}.

In the late 19\textsuperscript{th} century, microorganisms were first discovered to be the cause of numerous infectious diseases\textsuperscript{8}. The antibiotic era began with the use of living cultures from bacteria such as Pseudomonas aeruginosa and Penicillium\textsuperscript{1}. The use of these bacteria led to the discovery of certain antibiotics such as tyrothrycin\textsuperscript{1}.

Ehrlich first postulated a “magic bullet” which did not target the host but could selectively aim and inhibit a disease causing agent\textsuperscript{9}. In 1904, he began research which resulted in a drug to treat syphilis, a disease which at the time was incurable\textsuperscript{9}. The drug salvasaran, was discovered after 5 years of research and was found to cure infected rabbits. This treatment was only replaced when penicillin was brought to the market\textsuperscript{9}.

In 1928, Alexander Fleming discovered penicillin\textsuperscript{1,8,9}. He found that \emph{Staphylococcus Aureus} was unable to grow when surrounded by a blue mould of a fungus of the Penicillium genus. Penicillin was first administered in clinical settings in the 1940s\textsuperscript{8}. This discovery was invaluable throughout World War II. Ehrlich and Fleming's discoveries began what we now know as the antibiotic era\textsuperscript{8,9}.

Following the discovery of penicillin, numerous antibiotic discoveries occurred\textsuperscript{8}. In 1935, sulphonamides were identified, followed by aminoglycosides, chloramphenicol, tetracycline and macrolides in the 1950s\textsuperscript{8}. Vancomycin was then discovered in 1956. Synthesis of antibiotics such as methicillin and nalidixic acid was carried out in the early 1960s. Development of first, second and third cephalosporins occurred over the following years from 1967 to 1986\textsuperscript{8}. 
New quinolones were also created towards the end of the 1980s. Since then very few antibiotics have been developed\(^8\). The last class of antibiotic to be discovered and marketed was in 1987, twenty years ago\(^{10}\).

### 1.1.1 Types of antibiotics and how they work

Antibiotics can be grouped into classes according to how they work and where they work in the bacterial cell. There are many components to a living cell, including bacterial cells. All living cells are surrounded by a membrane, which in most cases is a phospholipid bilayer surrounding the cytoplasm. In bacteria this membrane is complex\(^{11}\). The purpose of the bacterial membrane is to protect the cell and to allow nutrients to enter the cell. There are two main groups which differ in their cell membrane structure, Gram-negative bacteria and Gram-positive bacteria\(^{11}\). Different bacteria fall into either group, however, within these groups the bacteria including their cell membrane structure may differ markedly depending on the environment in which the specific bacteria may need to survive\(^{11}\). Figure 1.1 depicts the main differences in the cell membranes of the two groups.

**Figure 1.1 Differences between Gram-negative and Gram-positive bacterium cell wall structure\(^{12}\).**

The Gram-negative bacteria consists of three main layers; the outer membrane, the peptidoglycan wall and the cytoplasmic or inner membrane\(^{11,12}\). The outer membrane is a lipid bilayer, unlike the inner membrane which is a
The phospholipid bilayer. Enzymes and porins can be found in this layer of the cell. The main defining feature in Gram-positive bacteria is the absence of the outer membrane\textsuperscript{11,12}. Gram-negative bacteria have surface appendages on the outer membrane, such as, flagella for motility, secretion systems for injecting toxins and efflux pumps, for removing waste materials\textsuperscript{11}.

The peptidoglycan layer is rigid and provides the cell with its shape. Gram-positive bacteria have a much thicker peptidoglycan layer to compensate for the absence of the outer membrane\textsuperscript{11}. This layer is formed through peptide cross linking of glycan strands. The shape of the cell varies from genus to genus of bacteria. In Gram-negative bacteria, the outer membrane attaches to the peptidoglycan layer via lipoproteins. This layer in Gram-positive bacteria contains surface proteins such as teichoic acids which allows the bacteria to interact with the surrounding environment, thereby, infecting the host\textsuperscript{11}.

A phospholipid bilayer makes up the inner cell membrane. The purpose of this is to protect the cell’s organelles to allow; the production of energy via mitochondria, synthesis of lipids and protein secretion\textsuperscript{11}. Antibiotics work via a variety of mechanisms which include:

- DNA replication inhibition: Quinolone antibiotics are engaged in this in both Gram-negative and Gram-positive bacteria. However, these antibiotics work on different enzymes during this process\textsuperscript{13}.
- Inhibition of RNA synthesis: Rifamycin binds to a RNA-polymerase enzyme which results in bactericidal activity against Gram-positive bacteria and bacteriostatic activity against Gram-negative bacteria\textsuperscript{13}.
- Inhibition of peptidoglycan cross linking of the cell wall: β-lactam antibiotics such as penicillin, cephalosporins, and glycopeptides are responsible for cell lysis through this method\textsuperscript{13}. This involves inhibition of an enzyme called β-lactamase, which is associated with the construction of the peptidoglycan wall\textsuperscript{13}.
- Inhibition of production of peptidoglycan strands, which make up the cell wall. This is the method by which the antibiotic vancomycin works\textsuperscript{13}. 


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• Prevention of protein synthesis: Tetracyclines, macrolides and lincosamide antibiotics are ribosome inhibitors which result in bacteriostatic activity, due to the inhibition of organelle production\(^\text{13}\).

Most antibiotics have a mechanism of action which falls into one of these groups.

Antibiotics can then be further classified according to the range of bacteria which they work against. They can be classed as broad spectrum or narrow spectrum antibiotics\(^\text{14}\). The main types of antibiotics which are used globally are broad spectrum antibiotics, i.e. those which can be used on a wide range of organisms, such as co-amoxiclav, which is a mixture of a penicillin antibiotic, amoxicillin and clavulanic acid, which is also a \(\beta\)-lactamase inhibitor\(^\text{14}\). Conversely narrow spectrum antibiotics act against a smaller number of bacteria, for example, erythromycin\(^\text{14}\). Broad spectrum antibiotics are the most commonly prescribed antibiotics globally\(^\text{15}\). Narrow spectrum antibiotics are the preferred treatment method where possible, however, even in the hospital setting when the infecting organism is identified broad spectrum antibiotics are frequently used\(^\text{15}\).

Since the discovery of antibiotics their use has steadily increased and they can be used for a number of reasons. The main use of antibiotics is to treat acute bacterial infections, in both human and animal populations\(^\text{15,16}\). They can also be used long-term for; primary or secondary prophylaxis, elimination of current infections and other non-antibacterial purposes such as immunomodulation, or prokinetic effects\(^\text{16}\).

Between 2000 and 2010, global antibiotic consumption increased by 30\%\(^\text{15}\). The US, China and India consume the largest quantities of antibiotics. These quantities also include agricultural use. India in 2010, had the highest consumption globally, at over 12 billion standard units of antibiotics, of which consumption had jumped considerably since 2000\(^\text{17}\). Among western countries, the US reported the highest use of antibiotics with over 6 billion standard units of antibiotics per annum, only slightly decreasing over the preceding ten years\(^\text{17}\).

Overall consumption of antibiotics in European countries reduced or remained stable between 2011 and 2015. Out of 29 European countries which
reported on their antibiotic consumption, there were several countries which reduced antibiotic consumption, such as Estonia, Spain, Finland and Denmark. However, there were also countries which reported an increase over this 5-year period, including Bulgaria, Belgium, Croatia, Greece and the Czech Republic.\textsuperscript{18,19}

Over the past 18 years there has been an increase in the number of countries reporting on the use of antibiotics, which accounts for the increase in the number of European countries included in figure 1.\textsuperscript{2} As shown, France reduced antibiotic consumption slightly over the 18-year period from over 35 Defined Daily Doses (DDD) per 1000 inhabitants per day in 1997 to over 30 DDD per 100 inhabitants per day.\textsuperscript{14} Finland has also reduced consumption of antibiotics reducing from approximately 25 DDD to 20 DDD per 1000 inhabitants per day over the 18-year period.\textsuperscript{14} Antibiotic use remains unchanged in the Netherlands however, it consistently reports the lowest figures over the 18-years, of 10 DDD per 1000 inhabitants per day. Ireland only began to report levels of antibiotics consumption in 1998 (figure 1.2).\textsuperscript{14}
Figure 1.2 Consumption of antibiotics For Systemic Use (ATC group J01) in the community and hospital sector in Europe 1997, and 2015. Defined Daily Dose (DDD)\textsuperscript{14}.

* Country provided only total care data.
In 2011, macrolides, penicillin and tetracyclines were the main antibiotics administered globally, both in humans and animals\textsuperscript{15}. In the United States, the top three antibiotics prescribed in 2013 were azithromycin, ciprofloxacin and amoxicillin, all broad-spectrum antibiotics. Ireland is similar to the rest of Europe, with most antibiotics prescribed being broad spectrum over the past decade. However, in Ireland, narrow-spectrum antibiotic use has seen an increase, as depicted in figure 1.3\textsuperscript{15}. Sweden and Norway are the only two countries to predominantly use narrow spectrum antibiotics, which did not change between 2000 and 2010\textsuperscript{15}. However, antibiotics are not just over used in the human population, the agricultural industry, which includes the food chain, consumes the highest volume of antibiotics globally\textsuperscript{15}.

**Figure 1.3** Antibiotic consumption per capita by class and country, 2000 and 2010\textsuperscript{15}.
The agricultural industry uses high volumes of antibiotics\textsuperscript{15}. As can be seen in figure 1.4, antibiotic consumption in the agricultural industry is high across the globe, with parts of western Europe administering high volumes of antibiotics to livestock\textsuperscript{15}. It is estimated that 63,200 tonnes of the total 100,000 tonnes of antibiotics produced globally were used in livestock. This number is expected to increase dramatically with 105,600 tons of antibiotics being used in livestock in 2030\textsuperscript{15}. The type and volume of antibiotics reported by low income countries are believed to be under reported, due to inaccurate records on antibiotic use\textsuperscript{15}.

There are three main agricultural uses of antibiotics; treatment of bacterial infections and acceleration of animal growth and prevention of disease\textsuperscript{15}. More antibiotics are used for the growth of animals and prevention of disease compared to those used in the human population\textsuperscript{15}.

Antibiotic use in animals continues to rise, due to increasing populations with growing incomes in low and middle income countries\textsuperscript{15}. Pigs and chickens consume the majority of antibiotics relative to other animals. Approximately 80% of antibiotics consumed in the US, are used in food animals. In the US, Brazil and Argentina, feedlots are used in intensive farming prior to the animals being slaughtered. Approximately 75% of US feedlots use at least one antibiotic in the animals to promote growth or to prevent disease\textsuperscript{15}.

Many high income countries have banned the use of antibiotics for the purpose of growth promotion\textsuperscript{15}. Food producers with better sanitation and preventative measures in place such as vaccination have seen little impact on their livestock following the cessation of antibiotic use as growth promoters. Those with lower hygiene standards have seen their livestock deteriorate\textsuperscript{15}. The European Union in 2006, banned the use of all antibiotics as growth promoters, which resulted in a significant decrease in antibiotic consumption in the agricultural industry. In 2013, Canada and the US published guidelines to farmers on reducing antibiotic use as growth promoters in their livestock. These guidelines were voluntary and are currently not legally enforced. However, they have not been fully adopted by veterinarians and farmers across the US and Canada\textsuperscript{15}. Since the publication of these guidelines there has been a small amount of regulation introduced, this regulation, introduced in 2005, enforced elimination of antibiotics such as enrofloxacin in poultry and further regulation in
2012 banned off label uses of third and fourth generation cephalosporins in animals. Argentina and India, who produce high volumes of meat have not banned antibiotic growth promoters\textsuperscript{15}.

Use of antibiotics in aquaculture is also growing. This is mainly in China, parts of Asia and in Chile and South America\textsuperscript{15}. For example, it is reported that salmon in Chile, are administered at an estimated 12 antibiotics over their lifespan, including quinolones\textsuperscript{15}. This is thought to increase antibiotic resistance which can be spread to wild fish\textsuperscript{15}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{global_antibiotic_consumption.png}
\caption{Global antibiotic consumption in livestock (milligrams per 10km\textsuperscript{2} pixels)\textsuperscript{15}.}
\label{fig:global_antibiotic_consumption}
\end{figure}

Considerable levels of antibiotics which have been used in the human and animal populations appear in the surrounding environment such as soil and ground water\textsuperscript{15}. This occurs through human and animal waste. In fact up to 90\% of antibiotic doses are excreted through the animals urine and up to 75\% is excreted in the faeces which passes straight into the environment\textsuperscript{15}. The antibiotics could also seep directly from the animal feed into the soil. Once the antibiotic is in the soil it can end up in ground water, creating an environmental vector\textsuperscript{15}.

Antibiotics can also be found in the environment from manufacturing, through incorrect handling and disposal\textsuperscript{15}. Incorrect disposal of antibiotics includes antibiotics being flushed down toilets and septic systems leaking into soil and ground water. In some cases the antibiotic residue will degrade, however,
some can withstand water treatment plants and are then found in rivers and soils, which can then find their way into the food chain and the general population\textsuperscript{15}. This causes an unnecessary exposure to antibiotics resulting in an increased risk of antibiotic resistance developing.

1.2 Antibiotic Resistance

Antimicrobial is an umbrella term which includes antibiotic, antiprotozoal, antiviral and antifungal medicines\textsuperscript{20}. Antimicrobial resistance occurs when the microbes change in response to their exposure to an antimicrobial compound, such as an antiviral, antifungal or antibiotic\textsuperscript{21}. This can result in the microbe becoming resistant to the compound\textsuperscript{21}. While antimicrobial resistance is a global threat, for the purposes of this study, antibiotic resistance will be the focus.

Many antibiotics that are used in medicine and the agricultural industry are derived from Actinomycetes, bacteria which are soil dwelling\textsuperscript{22}. It is believed that many of the genes which are part of these Actinomycetes provided many bacteria with the antibiotic resistance genes which are found today\textsuperscript{22}. Bacteria change when exposed to antibiotics, resulting in the bacteria becoming resistant to the antibiotic\textsuperscript{23}. Bacteria can be intrinsically resistant to the antibiotic or they can acquire resistance\textsuperscript{24}.

Intrinsic resistance of a bacterium to an antibiotic is as a result of fundamental structural or functional aspects\textsuperscript{24}. For example, certain antibiotics may not be able to cross the cytoplasmic membrane of a Gram-negative bacteria, e.g. vancomycin inhibits peptidoglycan cross linking in the periplasm of the Gram-positive bacterial cell, however, vancomycin is unable to cross the membrane of Gram-negative bacteria, to allow this to occur\textsuperscript{24}. Figure 1.5 illustrates intrinsic resistant mechanisms. In this illustration, antibiotic A enters the cell through a porin protein, which spans the membrane, allowing it to reach its target and stop peptidoglycan synthesis. Antibiotic B enters through the porin also, however, it is removed by efflux. Finally, antibiotic C is unable to breach the outer membrane and therefore, cannot target the penicillin binding protein\textsuperscript{24}. 
Bacteria develop or acquire resistance to antibiotics through different mechanisms of which three main mechanisms have been identified and will be discussed\textsuperscript{24}:

1. Minimisation of intracellular antibiotic concentration
2. Modification of the antibiotic mark
3. Inactivation of the antibiotic through hydrolysis or alteration of the antibiotic\textsuperscript{24}.

### 1.2.1 Minimisation of intracellular antibiotic concentration

Bacteria can become resistant to antibiotics via this method by reducing the quantity of antibiotic which can cross the bacterial cell membrane or via removal of antibiotics from the cell\textsuperscript{24}.

The presence of the outer membrane in Gram-negative bacteria results in reduced permeability to many antibiotics\textsuperscript{24}. Antibiotics get around this problem by passing through the porins present in the membrane. However, bacteria can reduce the number present on the membrane through downregulation and inserting other transport channels which are more selective, only allowing certain molecules to pass through. The antibacterial activity of cephalosporins and carbapenems has been reduced as bacteria such as Enterobacteriaceae,
*Pseudomonas spp.* and *Acinetobacter spp.*, have increased resistance via this method\textsuperscript{24}.

Conversely, efflux pumps transport antibiotics out of the cell. There are different types of efflux pumps which can have narrow specificity or broader specificity. These pumps molecules out of the cell. Efflux pumps with broad specificity are deemed multidrug resistance (MDR) efflux pumps, as they can pump different types of antibiotics out of the bacterial cell\textsuperscript{24}. Overexpression of efflux pumps in the membrane results in resistance to antibiotics. Numerous MDR efflux pumps have been found in all types of bacteria\textsuperscript{24}.

There are multiple genes which encode MDR pumps on chromosomes which increase the expression of the efflux pumps. Overexpression is frequently due to mutations in the regulatory network which controls efflux-pump expression. These genes in some cases are able to transfer between bacteria\textsuperscript{24}. *Enterobacteriaceae, P. aeruginosa* and *S. Aureus* are bacteria in which this overexpression of efflux pumps is commonly found. Local environmental factors of the host in which the bacteria reside, can also increase efflux pump expression, such as the presence of bile\textsuperscript{24}.

**1.2.2 Modification of the antibiotic mark**

Antibiotics generally attach to their target with high affinity\textsuperscript{24}. There are two main ways in which the antibiotic mark can be modified; genetic modification or post translational modification of the mark.

Transformation is a process which can result in protein modification, by taking DNA from the environment and forming ‘mosaic’ genes\textsuperscript{24}. A single point mutation in the genetic code can alter the site to which the antibiotic binds, thereby reducing the affinity the antibiotic has for its target which reduces the efficacy of the antibiotic. This has been found in bacteria such as, *N. gonorrhoea*, where the penA gene, has resulted in resistance to cephalosporins, resulting in the treatment of this infection, clinically challenging\textsuperscript{24}.

To stop the antibiotic binding to the target in the bacteria, modification of the genetic code of the target site, as described above, is not always required\textsuperscript{24}.
Protection of the target has also been found to occur. One example which has been described is the erythromycin ribosome methylase family of genes, which, methylate a specific gene, altering the binding site of the drug in the bacteria. This prevents antibiotics such as macrolides, lincosamines and streptogramins binding to the target site.

1.2.3 Inactivation of the antibiotic through hydrolysis or alteration of the antibiotic

Bacteria may directly modify antibiotics or destroy them, thereby resisting their action. Hydrolysis of the antibiotic has been known to be carried out for years by β-lactamases. This prevents the antibiotic from binding to the target site in the bacteria. Varying forms of these β-lactamases have evolved and continue to evolve over the years, quite rapidly, which has an impact on clinically serious infections in settings such as hospitals. Antibiotics affected by this include; penicillin, cephalosporins, carbapenems, clavams and monobactams.

Steric hindrance involves modification of the structure of the bacteria which prevents the antibiotic from binding to its target. There are a wide range of enzymes which facilitate the addition of a chemical group to the antibiotic. Chemical groups which can be added to drugs include phosphates, nucleotidyl, ribitoyl and acyl groups. Aminoglycoside antibiotics are highly affected by these enzymes, of which include, acetyltransferases, phosphotransferases and nucleotidyltransferases.

1.3 Burden of antibiotic resistance

While antibiotic resistance can occur naturally, inappropriate use and over prescribing of antibiotics facilitates antibiotic resistance. Antibiotic resistance is a serious threat to the global population. The development of antibiotic resistance is unpredictable. In the US, at least, 23,000 deaths annually are associated with antibiotic resistant infections, while in Europe there is a minimum estimate of 25,000 annual deaths caused by resistant bacteria. Multidrug Resistant and Extremely Drug Resistant Tuberculosis kills 200,000 people annually. There are 60,000 neonatal deaths in India due to antibiotic
resistant infections\textsuperscript{26}. Globally, the number is much higher at 700,000 deaths per year\textsuperscript{26}. If antibiotic resistance is to continue to develop it has been estimated that ten million deaths attributable to antimicrobial resistance could be reached by 2050\textsuperscript{29}.

The annual cost to society of antimicrobial resistance is approximately €1.5 billion due to illness and productivity loss\textsuperscript{30}. In the US, 2 million infections due to resistant bacteria costs $20 billion annually\textsuperscript{26}. It is reported that the cost of healthcare acquired infections in 2009 was greater than $45 billion. Within this the number of antimicrobial resistant infections resulted in significantly higher mortality rates than those without antimicrobial resistance, leading to more intensive care unit stays, more antimicrobial therapy and medical care\textsuperscript{31}. By 2050, the cost of drug resistance is estimated to cost $100 trillion annually\textsuperscript{26}.

The full burden of antibiotic resistance is still unknown, with significant under reporting of death, cost to society, related illness, disability adjusted life years, and length of stay in hospital\textsuperscript{10,32}. According to the World Health Organization (WHO) there are huge gaps in surveillance and poor standards in data sharing and coordination\textsuperscript{10}. Data gathered by WHO, has shown that there is a need for greater surveillance of antimicrobial resistance. In 2013, the WHO requested information for nine bacteria and antibiotic combinations from WHO member states, only 66\% of members were able to provide information on at least one bacteria\textsuperscript{10}. Of the 129 WHO member states 114 countries were able to provide some information on one or more of the nine combinations. The nine bacteria and antibiotic combinations included:

- \textit{Escherichia coli} and third generation cephalosporins
- \textit{Escherichia coli} and fluoroquinolones,
- \textit{Klebsiella pneumoniae} and third generation cephalosporins
- \textit{Klebsiella pneumoniae} and third generation carbapenems,
- \textit{Staphylococcus Aureus} and methicillin,
- \textit{Streptococcus pneumoniae} resistant to penicillin,
- \textit{Nontyphoidal Salmonella} and fluoroquinolones,
- \textit{Shigella species} and fluoroquinolones and
- \textit{Neisseria gonorrhoeal} and third generation cephalosporins\textsuperscript{10}. 
This information, included those found mainly in the community setting. The first five combinations listed also cause infections in the hospital setting\textsuperscript{10}. The information gathered came from various sources which included national country databases, however, this type of information was only found to be recorded at national level across Europe and America\textsuperscript{10}. Other information came from individual sites and where precision of measurement was questionable. The result is that those tackling antimicrobial resistance are facing an unknown, unable to determine the extent of the problem and struggling to determine the best strategy forward.

This study focuses on the treatment of bacterial pharyngitis. As has already been stated there are numerous strains of bacteria which are resistant to antibiotics\textsuperscript{21}. Those which are most threatening to the general population, and which are also used to treat streptococcal infection will now be discussed.

### 1.3.1 Methicillin Resistant Streptococcus Aureus (MRSA)

One of the most publicised resistant bacteria is \textit{Methicillin Resistant Streptococcus Aureus} (MRSA). MRSA first emerged in the 1960s and was typically seen in hospital acquired infections, however in the last ten years there has been quite an increase in community acquired MRSA\textsuperscript{10}. \textit{Staphylococcus Aureus} is common in wound and post-operative infections, and may result in food poisoning and toxic shock syndrome\textsuperscript{10}. High proportions of resistance increase the need for second line antibiotic treatment, which results in greater side effects for patients and could possibly produce further resistance in staphylococci and or other species\textsuperscript{10}. The WHO reported that the proportion of MRSA in WHO regions ranged from 20% to 80%. However, a 2012, report by the European Centre for Disease Control reported a stabilisation in MRSA\textsuperscript{33}. Figure 1.6 below, shows the percentage of isolates of \textit{Staphylococcus Aureus} which are resistant to methicillin over a 15-year period, per country. As of 2014, Scandinavian countries had the lowest, with less than 20\%\textsuperscript{15}. Since 2010, the number of percentage isolates in Ireland, has reduced from 24.4\% to 14.7\% in 2016\textsuperscript{34}. 


1.3.2 E. coli

E. coli has developed resistance to third generation cephalosporins, resulting in patients being treated with broader spectrum and more expensive antibiotics such as Carbapenems. However, strains of E. coli are also showing resistance to carbapenems\textsuperscript{10}. Other antibiotics for which certain infections such as urinary tract infections are caused by E. coli, have very little data gathered on them regarding resistance and therefore, it is unknown what other treatments could be used in other types of infections\textsuperscript{10}.

According to a surveillance report carried out by the European Centre for Disease Prevention and Control, the countries with the highest reported resistance for E. coli to third generation cephalosporins, fluoroquinolones and aminoglycosides include Italy and Greece with 10-25% of these isolates found. There is an 11.1% presence of E. coli producing extended spectrum beta-lactamase infections in Ireland, which has increased from 6.1% since 2010\textsuperscript{34}. In Ireland of those E. coli which are resistant there is 14.3% of isolates found to be multi-drug resistant\textsuperscript{34}. 

\textbf{Figure 1.6} Percentage of methicillin resistant Staphylococcus Aureus isolates in countries from 2011 to 2014\textsuperscript{15}. 

[Map showing percentage of methicillin resistant Staphylococcus Aureus isolates in countries from 2011 to 2014.]
1.3.3 *Klebsiella pneumoniae*

The Gram-negative bacteria, *Klebsiella pneumoniae*, have developed resistance to third generation cephalosporins. However, when this occurs practitioners often prescribe carbapenems, which are more expensive\textsuperscript{10,35}. This results in the development of resistance to this class also\textsuperscript{35}. *Klebsiella pneumoniae* strains have been shown to be resistant to carbapenems, which was first reported in 1982\textsuperscript{10,35,36}. There are some molecules which are currently in development for these infections\textsuperscript{36}.

Greece has over 50% of resistant *K. pneumoniae* isolates to third generation cephalosporins, aminoglycosides and fluoroquinolones, with Italy closely following with isolates found in 25-50% of cases\textsuperscript{35}. The highest number of invasive infections of this infection in Ireland were reported in 2016. Following a rise in multidrug resistance of *K. pneumoniae* in Ireland up to its highest of 12.3%, in 2012, however this figure reduced to 7.1% in 2016\textsuperscript{34}.

1.3.4 *Acinetobacter species*

*Acinetobacter spp.* has also developed resistance to Carbapenems. These infections are being treated using various combinations of drugs which include polymyxin and colistin\textsuperscript{35}. However, there are very few alternative treatment options to carbapenems once resistance develops to this group\textsuperscript{10}.

Spain, Italy and Greece has over 50% of isolates of *Acinetobacter spp.* which are resistant to fluoroquinolones, aminoglycosides and carbapenems, illustrated in figure 1.7\textsuperscript{35}. Countries further away from the Mediterranean Sea have approximately 1-5% of isolates of *Acinetobacter spp.* resistant to these antibiotics\textsuperscript{35}. In Ireland, 2016, 69 isolates were reported, which was a reduction from 87 isolates the previous year. In 2015, only 3% of isolates were found to be multidrug resistant\textsuperscript{34}. 

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1.3.5 Other types of resistant bacteria

*Streptococcus Pneumoniae* is problematic for children and the elderly and predominantly causes pneumonia, otitis media and meningitis\(^10\). *S. pneumoniae* can be resistant or have reduced susceptibility to penicillin. Before the discovery of penicillin, the survival rate from a *S. pneumoniae* infection was less than 20%. Treatment with penicillin resulted in this increasing to 90%\(^10\). In Ireland the number of infections due to *S. pneumoniae* has increased since 2010, from 314 infections to 365 infections in 2016, however, the proportion of high level resistant infections has decreased from 20 in 2011 to 0 in 2016\(^34\).

*Neisseria gonorrhoeal*, the bacteria responsible for gonorrhoea infections have developed resistance to third generation cephalosporins\(^10\). This class of antibiotics is used as a last line of resort in the treatment of this infection\(^10\). Currently Ireland has no information on this infection.

As discussed the WHO has gathered global data on different strains of bacteria which have developed resistance to penicillin\(^10\). However, data gathered by the World Health Organization and the European Centre for Disease Control and Prevention is not complete and further work needs to be
done to ensure that surveillance systems are running effectively in all countries.10

It appears from the reported data that resistance patterns vary across the
globe and Europe. In general, Northern European countries such as
Scandinavian countries and the United Kingdom have a lower prevalence of
resistant bacteria to certain groups of antibiotics35. However, this could change
should prevention strategies, not be put in place, in Southern European
countries.

1.4 Strategies for tackling resistance
All recent policy or strategies have highlighted the importance of addressing
inappropriate antibiotic use. There is a global consensus at national and
stakeholder levels that antibiotic resistance must be tackled37-39. The World
Organisation for Animal Health (OIE), the Food and Agricultural Organization of
the United Nations (FAO), and the WHO are all taking responsibility for their
part in dealing with antimicrobial resistance37.

The OIE has implemented intergovernmental standards for the
responsible use of antimicrobials in animals. Governments must have sufficient
legislation over the use of antimicrobials and veterinarians must be adequately
resourced to deliver the necessary services38.

The FAO has published their four-year strategy for 2016-2020, which
focuses on four main pillars over the four years. These pillars include
awareness, practices, evidence and all three will link in with the fourth,
governance39.

In 2015, the WHO published a global strategy for tackling antimicrobial
resistance. The strategy clearly lays out the responsibilities for each
stakeholder, both global and national20. The 5 main objectives are:

1. Improve communication, education and training on antimicrobial
resistance,
2. Improve surveillance systems and research to create a solid knowledge
base
3. Reduce infection through effective infection prevention measures
4. Optimise the use of antimicrobial medicines
5. Provide sustainable investment in new medicines, and alternatives\textsuperscript{20,39}.

The WHO proposes that these objectives are met through inclusion of antimicrobial resistance awareness programmes in schools curriculum from an early age\textsuperscript{20}. Creating national reporting systems which include information on prevalence and geographical patterns, which will feed into global systems, is also suggested. Prevention and improved diagnostic strategies such as; improving food and water safety, increasing vaccination and the use of relatively cheap rapid diagnostic tools are listed as necessary by the WHO for tackling antimicrobial resistance. Sustainable investment is required in order to ensure the longevity of the strategy and therefore, economic impact assessments are necessary for determining this\textsuperscript{20}.

The 2011-2016 European Union strategy for tackling antimicrobial resistance was evaluated in October 2016\textsuperscript{18}. Following on from this a 2017 action plan has been published which consists of three main aims, with action points attached to each. These aims are as follows:

1. “Supporting Member States and making the EU a best-practice region on AMR
2. Boosting research, development and innovation against AMR
3. Shaping the global agenda on AMR\textsuperscript{40}"

These aims will be met through those listed by the WHO and also greater stakeholder relationships to allow for; streamlined approval of new antimicrobials, greater understanding of resistance and offering assistance to nations to implement the WHO strategy\textsuperscript{40}.

National strategies have adopted the World Health Organization’s strategy. In 2001, a strategy for tackling antimicrobial resistance was published in Ireland\textsuperscript{41}. Since then, the National Clinical Programme for the Prevention of Healthcare-associated infection and Antimicrobial Resistance was established in 2011, in Ireland\textsuperscript{42}. The aim of this programme is to minimise the procurement of preventable healthcare acquired infections, reduce the spread of multidrug resistant microbes and reduce inappropriate antibiotic use. The programme
focuses on correct hand hygiene techniques, appropriate antimicrobial use and preventing the acquirement of infections through use of medical devices such as intravenous lines\textsuperscript{42}.

In 2014, following on from this programme, a national interdepartmental committee was established, which, consists of the Chief Veterinary Officer of the Department of Agriculture, Food and the Marine as well as the Veterinary officer, and the Chief Medical Officer of the Department of Health. In 2015, it was decided that a national strategy would be published by the end of 2016, however, to date nothing has been published\textsuperscript{43}.

Despite this numerous initiatives have been implemented and improved upon over the past number of years which have included improved control of reporting of infections and policing of inappropriate prescribing, implementation of infection control strategies and raising public and healthcare professional awareness through education\textsuperscript{43}.

The United Kingdom (UK) currently have a 5 year strategy in place which began in 2013 and will end in 2018\textsuperscript{44}. The three main aims of the strategy are to improve knowledge and understanding of the issue among the total population, conserve existing treatments and encourage the development of new antibiotics and therapies\textsuperscript{44}.

Prior to 2013, the UK carried out numerous programmes to address antimicrobial and especially antibiotic resistance. These included raising awareness, streamlining prescribing in primary and secondary care, improving prescribing in the veterinary industry and carrying out research in antimicrobial resistance\textsuperscript{44}. Seven areas in the 5-year strategy in the UK are changing and includes those aims which are listed by the new European Commission strategy 2017\textsuperscript{44}.

These public health strategies are developed using input from experts and data which is available on resistant pathogens. Missing data for bacteria and other pathogens is widespread and has major public health implications and threatens to derail these public health strategies\textsuperscript{10}. Improper collection and recording of information and under reporting of data is a global problem, especially in developing countries. In many cases it is unknown as to whether
countries have surveillance systems in place\textsuperscript{10}. The effect of this is the inability to track pathogens which negatively impacts the control efforts. For example, tuberculosis which is multidrug resistant is under reported\textsuperscript{10}.

The WHO report on antimicrobial resistance surveillance, highlights areas which need to be addressed by all member states. Health systems must be improved to capture the required data\textsuperscript{10}. Those struggling most to document this data were Africa, the Middle East and European countries outside the EU. The European Antimicrobial Resistance Surveillance Network (EARS-Net) is a surveillance network consisting of the 28 EU countries and Norway and Iceland\textsuperscript{10}. The Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) is a newer initiative to help develop countries outside of EARS-Net to develop antimicrobial resistant, national, surveillance systems\textsuperscript{10}. There are also European networks for antimicrobial resistant bacteria in food products. There are underutilised surveillance systems in place in other countries which have gaps in gathering data and under reporting is occurring\textsuperscript{10}. This has also been reported in high income countries which are considered to have good reporting systems for antimicrobial resistance, however, like any system for AMR reporting there is a need for review and improvement. Other collaborations such as the one created in the Western Pacific Region have collapsed due to other states of emergencies occurring in the member countries. This results in countries acting alone, reporting on the antimicrobial resistance with no support\textsuperscript{10}.

The WHO and European Commission aim to strengthen such collaborations to ensure accurate and timely reporting of resistant pathogens\textsuperscript{20,40}. With the data accurately recorded and reported, strategies can be streamlined and use of antibiotic medicines can be optimised.

1.4.1 Optimising the use of antibiotic medicines
The optimisation of antibiotics requires prevention strategies to be put in place, followed by increasing public awareness on the topic, decreasing inappropriate prescribing of antibiotics, discovering new treatments and creating new diagnostic tools\textsuperscript{20,44}.
1.4.1.1 Prevention strategies

Sufficient infection prevention strategies with acceptable standards are pivotal to reducing antibiotic resistance and preventing the spread of antibiotic resistant organisms\textsuperscript{44}.

Healthcare workers are a potential transmission portal for bacteria, when moving between patients. This is extremely important if they are carriers of antibiotic resistant bacteria\textsuperscript{45}. There is debate as to whether healthcare staff should be screened for specific bacteria such as MRSA and treated accordingly. However, improving hand washing technique has been the main focus for reducing the spread of resistant bacteria between patients\textsuperscript{45}. Improvements in hand hygiene and hand washing techniques over the past number of years in the UK have seen an obvious reduction in MRSA bloodstream infections\textsuperscript{44}. Studies have shown that educating healthcare workers, issuing regular reminders of hand washing technique and providing constant feedback on workers technique resulted in 40-50\% compliance rate\textsuperscript{45}.

Unfortunately, due to attitudes and beliefs, and despite studies showing that hand hygiene drastically reduces the spread of infections many healthcare workers globally do not adhere to the techniques\textsuperscript{46}. A top down approach has been found to improve the number of healthcare workers practicing hand hygiene, with, senior consultants and staff members adopting the practice, resulting in more junior staff carrying it out\textsuperscript{46}.

Other preventative practices which should be used include the use of protective equipment such as aprons, gloves and masks. Regular environmental cleaning, using the correct antiseptics, also result in the reduction of the number of resistant bacteria residing on surfaces. The Centre for Disease Control recommend the use of a 1:10 dilution of sodium hypochlorite to clean healthcare environments\textsuperscript{46}. However, while this will prevent and reduce the spread of infection it cannot eliminate it.
1.4.1.2 Novel treatments

Despite best efforts in tackling antibiotic resistance new treatments are and will be required. However, many pharmaceutical companies are no longer investing in the development of new antibiotics. The main reason for this is that any investment that has been put into this area in recent years has not seen a profitable return. Comparing sales of new products developed for chronic illnesses such as diabetes versus new antibiotics, Januvia sales were over $1,500 million dollars versus a new antibiotic of Teflaro over $50 million dollars over the first 2 years of launching on the market. Approximately eight new antibiotics have been launched in the last six years. Many of these are competing with already existing and cheaper antibiotics for the treatment of the same condition. While dosing schedules are easier in some of these new molecules, the higher price has deterred clinicians from prescribing them.

The Food and Drug Administration in the United States have issued new guidelines for new antibiotic clinical trials and have resulted in many new antibiotic developments being targeted for serious infections. New treatments for minor infections such as upper respiratory tract infection treatments have been side-lined, as, extremely large participant numbers would be required for clinical trials, to determine the superiority of the new drug versus the already existing treatments available.

It is reported that those antibiotics which are in development are for the most part intravenous and therefore, for hospital use. These new intravenous antibiotics are indicated for adults only, with the manufacturer intending the prescriber to use the drug in children, outside of the licensing, which presents numerous challenges to the prescriber.

Combination products are also being developed. Clinical trials are currently ongoing to analyse the effectiveness of these combination products. In the United States, December 2014, a cephalosporin-β-lactamase inhibitor combination was approved for the market for the treatment of complicated urinary tract infections and complicated intra-abdominal infections. These new molecules have been shown to have activity against bacteria which produces beta-lactamase and carbapenemase.
New tetracyclines, aminoglycosides, macrolides and fluoroquinolones are in development\textsuperscript{36}. Other new molecules include a drug class called pleuromutilins. This class has been derived from a fungus called Pleurotus mutillus which inhibits bacterial protein synthesis. One of the molecules in this class was granted a market licence in 2006 in the United States for the treatment of impetigo and another molecule in this class is used in veterinary medicine\textsuperscript{36}.

The rate of development of these antibiotics is not matching the rate of emergence of antibiotic resistance, bringing ever nearer the post antibiotic era. Only with funding from governmental bodies can drug companies hope to continue development of badly needed novel antibiotics\textsuperscript{36}. Therefore, today, prescribers must use the antibiotics available to them appropriately to ensure continuing availability of antibiotics required for infections.

1.4.1.3 Creating awareness of antibiotic resistance
It is widely accepted that cultural differences between countries are responsible for the widely different prescribing patterns of antibiotics among European countries\textsuperscript{47}.

An Italian study found that local appropriate antibiotic information programmes using healthcare professionals such as GPs and pharmacists, reduced antibiotic prescribing in the local community area by 11.9\%, when compared to the absence of the provision of information in a similar community. Methods used included posters, brochures and media advertising as well as a newsletter on antibiotic resistance for pharmacists and GPs. It found that the most effective method of recalling information from this educational campaign was through television. However, short term campaigns did not result in long term lasting knowledge among participants, showing that any campaign run must be viewed as longer term\textsuperscript{47}. Compared to the national reduction of 3.2\%, versus the same period in the preceding year, it shows that low cost campaigns are feasible and quite effective in reducing antibiotic prescribing\textsuperscript{47}.

Level of education has been shown to impact antibiotic use. Those with lower levels of education were found to consume higher quantities of
antibiotics\textsuperscript{48}. In France, between 2002 and 2007, a national campaign stating that “Antibiotics are not automatic” resulted in a 26.5\% decrease in antibiotics being consumed during the winter facilitated by fewer number of GP consultations\textsuperscript{49}.

These examples show that education is very important to effecting a cultural change in the use of antibiotics and should be a part of any strategy to reduce antimicrobial resistance.

\subsection{1.4.1.4 Reducing inappropriate antibiotic prescribing}

The World Health Organization defines medicine use as “rational (appropriate, proper, correct) when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community. Irrational (inappropriate, improper, incorrect) use of medicines is when one or more of these conditions is not met”\textsuperscript{50}.

Over use of antibiotics has driven antibiotic resistance\textsuperscript{15}. One of the main propellers of this over use is the high burden of infectious diseases in developing countries\textsuperscript{15}. As well as this, antibiotics are easily accessed\textsuperscript{15}. The development of resistance to these first line treatments has forced the use of last line antibiotic treatments for hard to treat infections such as MRSA, and bacteria are now showing resistance to these last line antibiotics\textsuperscript{15}.

A recent study carried out on antimicrobial resistance has shown that antibiotics which were prescribed in primary care can impact on bacterial resistance in a patient for up to 12 months. The same study also showed that the greater the number or duration of antibiotic courses prescribed during that period of time, the greater the chance that resistant bacteria would be found in that patient\textsuperscript{51}.

Healthcare facilities including hospitals, in the majority of countries, use approximately 20\% of the total quantity of antibiotics\textsuperscript{15}. Heavy use of antibiotics is common in hospital settings which has resulted in difficult to treat or resistant infections\textsuperscript{15}. The remaining 80\% of antibiotics are prescribed by primary healthcare facilities, in community settings, such as general practitioners, or they
are bought from healthcare outlets with no prescription. However, the antibiotics available without prescriptions are outside the US and Europe in low to middle income countries\textsuperscript{15}. Of those prescribed in community it is estimated that 50% are prescribed inappropriately for self-limiting viral infections\textsuperscript{15}. The volume of antibiotics which are bought outside the US and Europe, without prescription varies from country to country\textsuperscript{15}. Their use across the globe corresponds with seasonal fluctuations with infections such as influenza\textsuperscript{15}.

It has been shown that antibiotics are overprescribed for sore throats in Ireland, UK, Australia, US and Netherlands\textsuperscript{52,53}. Despite international implementation of standardised methods the Health Protection Surveillance Centre in Ireland has found that across Ireland there is a high degree of variation in prescribing and has called for standardisation of prescribing\textsuperscript{54}.

The WHO advocate the use of national and local stewardship programmes to ensure the appropriate use of antibiotics\textsuperscript{20}. Antimicrobial, encompassing antibiotic stewardship programmes have been developed over the last decade. These programmes aim to ensure the prudent use of antibiotics, thereby reducing treatment costs and improving clinical patient safety and patient outcomes, resulting in the preservation of antibiotic function\textsuperscript{46}. These stewardship programmes are in both primary and secondary care facilities and are multifaceted. They encompass a range of different arms including:

- developing treatment guidelines according to the situation,
- educating prescribers,
- susceptibility testing of antimicrobials,
- organism identification,
- deciphering pharmacokinetic and pharmacodynamic properties of drugs thereby dictating correct dosing and duration of antibiotics, and,
- formulary restriction and preauthorization\textsuperscript{46}.

Nonetheless, antimicrobial stewardship programmes face several challenges due to lack of devoted staff and funding\textsuperscript{55}. As well as this, a collaborative approach with many areas working in harmony must be adopted\textsuperscript{55}. It has been highlighted that these programmes do not reach all areas where antimicrobials
are in use and that interventions at the point of prescribing are necessary as well as centralised interventions which result in a top down approach\textsuperscript{55}.

Broad spectrum antibiotics are commonly used in healthcare settings where susceptibility patterns for microorganisms are not routinely analysed\textsuperscript{45}. This results in unnecessary use of these antibiotics and antibiotic resistance then occurs. Compounding this, are poor infection control practices, resulting in the spread of these resistant bacteria\textsuperscript{45}. Multidrug resistance is prevalent, with bacteria, in some cases, resistant to up to eight different antibiotics\textsuperscript{22}.

Formulary restriction and preauthorisation has been quite successful in reducing antibiotic prescribing. In the hospital setting, it has been found that 25-50\% of patients are prescribed antibiotics of which a third to half are inappropriate\textsuperscript{56}.

1.4.1.5 Hospital antimicrobial stewardship programmes

The Centre for Disease Control and Prevention, in the US has issued core prescribing practices which all prescribers should adhere to when prescribing antibiotics\textsuperscript{55}. Among these are; ensuring speedy prescribing based on national prescribing guidelines at the appropriate dose and duration, microbiological testing, documenting all aspects of the prescription and reviewing the prescription at appropriate intervals\textsuperscript{55}. The input upon which prescribing practices should be guided, should come from experts in pharmacy, microbiology and infectious diseases\textsuperscript{55}. However, implementation of these practices should involve multidisciplinary teams including nursing and physicians well as those already listed\textsuperscript{55}.

Programme interventions in hospitals have included; prescribers inputting clinical indications when ordering antibiotics, closed loop antimicrobial prescribing systems and educational campaigns for prescribers in hospital care\textsuperscript{55}. The reduction in antibiotic prescribing in these interventions ranged from 5\% up to 34\% and cost savings in some cases was as high as €150,000 in annual costs\textsuperscript{55}. Other studies, from 2000 to 2010, have shown that a 90\% drop in ciprofloxacin use resulted in a 10-25\% reduction in carbapenem resistant aeruginosa\textsuperscript{46}.  

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In Ireland, in 2010, a national clinical programme entitled, Antimicrobial Resistance Clinical Programme, was launched. The foundation on which this was developed was “every patient/resident/client should receive high quality healthcare in a healthcare system with a visible institutional safety culture”\textsuperscript{57}. The aim of the programme is to ensure that every healthcare worker observes the importance of infection prevention strategies, thereby reducing; inappropriate antibiotic use, the spread of multidrug resistant organisms and preventable healthcare acquired infections in healthcare settings\textsuperscript{57}.

Nurses are frequently and rightly recognised as essential in reducing antimicrobial resistance. They must be aware of it and act to reduce resistance through; their practice, education, research and policy. They are ideally positioned to change the prescribing patterns of doctors, reduce the consumption of antibiotics and ensure optimal use of antibiotics\textsuperscript{17}.

Pharmacists, like nurses, are well poised to influence antibiotic prescribing in hospital antimicrobial stewardship programmes\textsuperscript{58}. Studies have shown that antimicrobial stewardship programmes led by pharmacists in hospitals can be effective\textsuperscript{59}. However, it is frequently reported that pharmacists are implementing programmes in hospitals with no support from prescribers or infectious disease specialists and that more effective collaboration between physicians and pharmacists is essential\textsuperscript{58-60}.

1.4.1.6 Community antibiotic stewardship programmes
Antibiotic stewardship programmes in the community setting are vital\textsuperscript{49}. The majority of antibiotics dispensed are prescribed in primary care. General practitioners account for 70% of antibiotic prescriptions in primary care\textsuperscript{49}.

Several factors influence prescribing of antibiotics. Prescribing patterns vary considerably across countries as well as within countries\textsuperscript{61}. Prescribing patterns between GPs vary due to several factors within which they work, which include cultural and structural differences\textsuperscript{61}. The expectation for GPs when prescribing is to follow objective criteria and have similar behaviours when they prescribe\textsuperscript{61}. A study which looked at determinants of between country differences in antibiotic use across Europe found surprisingly, that countries
which had prescribing guidelines, for example, for respiratory tract infections, had higher rates of antibiotic prescribing for these indications\textsuperscript{48}. This same study also showed that countries which enforced restrictions on the commercial conduct of pharmaceutical companies resulted in lower rates of antibiotic prescribing, and a lower number of antibiotics available on the market\textsuperscript{48}.

A recent study examined prescribing practices across six countries and found that, in some countries such as Russia and Lithuania, GPs regularly prescribed antibiotics to patients whereas in other countries, such as Denmark, GPs rarely prescribed antibiotics to patients\textsuperscript{61}. There were several factors which were found to influence these prescribing patterns. Among these were government leadership and an absence of antibiotic stewardship\textsuperscript{61}. However, even those countries which had low levels of antibiotic prescribing patterns there was inter-country variation. One factor which was found to influence this in Sweden, was sharing of knowledge. GPs who met with fellow GPs were found to adhere to prescribing guidelines more than those who did not meet and share knowledge with other GPs\textsuperscript{61}.

It has been shown that only 10\% of cases of pharyngitis should be treated with antibiotics, however, up to 75\% of adults suffering with pharyngitis have been prescribed antibiotics unnecessarily\textsuperscript{62}. In Spain, 38\% of patients presenting to their GP with a complaint of a sore throat were prescribed antibiotics, where as in Sweden the number prescribed antibiotics was 88\%\textsuperscript{61}. These Swedish GPs however, did not have national guidelines for the indication of an antibiotic in patients presenting with sore throats. This resulted in a heterogeneity across countries and was possibly related to a lack of policy-making factors in this subject area\textsuperscript{61}.

To combat this, international, national and regional programmes have been implemented by governments. These have had positive impacts across the board on antibiotic prescribing\textsuperscript{49}. Antibiotic committees and programmes have been set up at national level in numerous countries such as Belgium, Denmark, Norway, Germany, Switzerland, Sweden, Poland, Portugal and the UK\textsuperscript{49}. Some of these committees and programmes were established as early as 1995\textsuperscript{49}.
Materials have been produced for GPs to provide education to patients. Training has also been provided to educate GPs on good antibiotic prescribing practice and prescribing guidelines\textsuperscript{49}. Several European countries and the US have online resources for tackling antimicrobial resistance which are provided for GPs so that they can educate patients, at regional and national levels\textsuperscript{49}. In Ireland, there are online guidelines for antimicrobial prescribing in primary care\textsuperscript{49}. Ireland and Sweden provide online advice for patients around common ailments found in primary care, such as colds, flu and antibiotic use. Sweden’s online system is in various languages. Canada provides online recommendations and examples of delayed prescriptions for GPs\textsuperscript{49}.

Several countries provide feedback to prescribers on their patterns of antibiotic prescribing\textsuperscript{49}. European countries such as France, Luxembourg, Finland, Germany and Portugal have differing methods on how this feedback is provided. Feedback can be provided by the health insurers or local committees, in some countries it is as frequent as every three months. However, for other European countries there is no official feedback system\textsuperscript{49}.

There are restrictions in certain countries on prescribing of specific antibiotics in primary care. For example, in Denmark, GPs may only prescribe quinolones once biologic tests have been carried out\textsuperscript{49}. In Alberta, Canada, GPs may only prescribe the same antibiotics once they have received authorization from the appropriate authority. In Denver, United States, the GP cannot prescribe fosfomycin, this may only be authorised through an infectious diseases specialist\textsuperscript{49}.

Several European countries such as Belgium, Germany, Denmark, Norway, Portugal, Sweden, Switzerland and the United Kingdom provide support to GPs in the prescription of antibiotics. In one area in France where there is no specific support system for the prescription of antibiotics GPs can contact a hospital to speak to an infectious diseases specialist\textsuperscript{49}. Other areas in France have developed tools to avoid this, for example numerous teaching hospitals provide telephone services to GPs, supplying them with information from an infectious diseases specialist, some of these also provide training sessions to GPs\textsuperscript{49}.  

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Access to GPs also has an impact on antibiotic prescribing. It has been shown that those countries in which patients are registered to one GP, and only attend this GP, have lower rates of antibiotic prescribing\textsuperscript{48}. Conversely, those countries in which patients can attend any GP have higher antibiotic prescribing rates. Those healthcare systems which require patients to visit their GP prior to attending a consultant resulted in lower levels of antibiotic resistance\textsuperscript{48}. This study called for strengthening the ‘gate keeper’ role of the GP by restricting the number of GPs patients could attend\textsuperscript{48}.

A 2015 study, by Wang et al., suggests that community pharmacists should be more actively involved in the prescription of antibiotics\textsuperscript{49}. It was found that for two indications, otitis media and pharyngitis the prescribed duration of amoxicillin, was quite frequently, found to be too short. In these cases, the pharmacist can quite easily contact the GP to suggest the appropriate duration, thereby improving appropriate prescription of antibiotics\textsuperscript{49}. Another possibility for improving antibiotic consumption and compliance would be discussing the patient’s symptoms with them when they present with the prescription and determining if it is appropriate or not and suggesting to the prescriber if there is a more suitable alternative\textsuperscript{49}.

1.4.2 Improved diagnostics

The WHO has urged all members, as part of the antimicrobial strategy to invest in the development and implementation of new diagnostic tools\textsuperscript{20}. Many diagnostic tests such as laboratory cultures can take days to produce results\textsuperscript{63,64}. Speedier techniques are required and some have been developed. More investment in these and change in healthcare policies are needed to drive these new faster techniques\textsuperscript{64}.

Point of care testing and molecular diagnostics development have both seen an increase in the last five years. Half of molecular diagnostic tools, using for example DNA microarray analysis, focuses on infectious diseases\textsuperscript{64}. This type of tool was expected to grow by 15\% over the past four years. Point of care testing however, has seen much slower growth and infectious diseases testing accounts for 37\% of these tools currently available\textsuperscript{64}. Those developing
diagnostic tools face several barriers which include, regulatory differences especially between Europe and the US, lack of information regarding demand and prevalence of disease, the need for change in guidance and a lack of follow up to determine the cost effectiveness of the tools\textsuperscript{64}. The setting in which these diagnostic tests are being used contrasts greatly between developing versus developed worlds. In developing countries these tools are used mostly in clinical laboratories. In developed countries, they are used as home care kits, in GP surgeries and in response to a biomedical emergency\textsuperscript{65}.

Nanotechnology advances have resulted in numerous screening tools being developed in recent years\textsuperscript{65}. Point of care testing for CD4 in the diagnosis of HIV has been shown to result in a higher proportion of patients who are HIV positive initiating antiretroviral treatment\textsuperscript{66}. These diagnostic tools have allowed diagnosis to move away from the laboratory and into the community with diagnosis in less than 24 hours\textsuperscript{66}. In one South African study, it was shown that using a CD4 count diagnostic test, away from the laboratory, resulted in a lower loss-to-follow up for patients, and 1.7-3.1\% fewer HIV infections in the first year of diagnosis. This results in the test being 100\% cost-effective after 3 years\textsuperscript{66}. However, this is in the developing world.

Similarly, screening tools for bacteria such as the KlebSeq diagnostic tool, have been shown to be cost effective and reduce mortality rates in those patients infected with \textit{Klebsiella pneumoniae} \textsuperscript{31}. This tool specifically allows healthcare staff to identify patients with multidrug resistant bacteria and can also be used to prevent outbreaks in healthcare settings, thereby reducing mortality and healthcare costs\textsuperscript{31}.

Furthermore, the inclusion of rapid diagnostic testing in antimicrobial stewardship programmes results in better patient outcomes and reduced antibiotic use\textsuperscript{60}. Therefore, education for healthcare staff and patients and their families must be provided to allow rapid diagnostic testing to have the desired impact\textsuperscript{60}. Rapid diagnostic tests have been adopted in certain areas which has led to the supervision of prescriptions and antibiotic delivery in countries such as America, the UK and Ireland\textsuperscript{49}.
It is expected that the continued advancement of nanotechnology in the coming years will lead to affordable diagnostic tools being developed and allow for the use of these in areas with few resources\textsuperscript{65}.

1.5 Summary

Antibiotic resistance must be tackled. Antibiotics are essential for fighting infections, which are considered minor illnesses. However, were the antibiotics not present these minor illnesses would in fact be life threatening\textsuperscript{67}. As discussed there are many strategies in place to help reduce antibiotic resistance and the spread of infection. Education for patients, healthcare professionals and the general population including children is key for increasing awareness about antibiotic resistance\textsuperscript{37}. Unfortunately, there is still overprescribing of antibiotics by prescribers and inappropriate consumption of antibiotics by patients\textsuperscript{27,68,69}.

Numerous conditions have been associated with imprecise diagnostics and over prescribing of antibiotics, most notable of which is pharyngitis\textsuperscript{70}. 


2 Pharyngitis

2.1 Pharyngitis

Pharyngitis or sore throat, is characterised by pain or irritation which in most cases worsens when swallowing\textsuperscript{71}. Most people suffer between two to three sore throat episodes per year\textsuperscript{72}. In the UK recurrent sore throat has an estimated annual incidence of 100 per 1000 population\textsuperscript{73}.

Approximately 40\% of people experiencing a severe sore throat visit their General Practitioner\textsuperscript{74}. Each year in the US 12 million people visit a medical practitioner due to pharyngitis\textsuperscript{75}. There are 24 million visits to GPs in Ireland annually and sore throats account for 3.5\% or 840,000 of all GP visits\textsuperscript{76,77}. The majority of sore throats occur due to a viral infection (80\%), with 85\% of cases being fully resolved after 7 days\textsuperscript{72,78}. It is estimated that between 5-17\% of sore throats are caused by a bacterial infection, a strain of the many β-haemolytic streptococci\textsuperscript{63}. Antibiotic treatment is only recommended for one particular strain, \textit{Group A β-Haemolytic Streptococci} (GABHS)\textsuperscript{63}.

Pharyngitis can be acute or chronic\textsuperscript{79}. Chronic pharyngitis can be described as a state whereby a person suffers from three or more pharyngitis infections per year\textsuperscript{79}. Most cases of pharyngitis are acute, with only 1-2\% of cases progressing to chronic pharyngitis\textsuperscript{79}. The majority of pharyngitis cases are viral or bacterial in origin and in some small cases the origin could be non-infectious\textsuperscript{79}.

Viruses which are most commonly associated with acute pharyngitis include; \textit{Herpes simplex virus}, \textit{influenza sp. Rubeola}, \textit{Epstein-Barr virus}, \textit{cytomegalovirus} and \textit{human immunodeficiency virus type 1}\textsuperscript{79}. Herpes simplex virus infection should resolve within 7-10 days. If symptoms are present for longer, viruses such as Epstein-Barr virus may be suspected and treatment by a doctor is required\textsuperscript{79}.

Commensal bacteria are found to coat the pharynx and tonsils in all healthy individuals\textsuperscript{79}. This prevents viruses from binding to cells in the surrounding environment. A disruption to this bacterial barrier which results in an alteration of this environment allows virus particles to bind to pharyngeal
cells, resulting in a localised viral infection\textsuperscript{79}. Figure 2.1 illustrates the anatomy of the pharynx and tonsils\textsuperscript{80}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image1.png}
\caption{Diagram of the pharynx and tonsils\textsuperscript{80}.}
\end{figure}

Viral pharyngitis infections, as well as a painful throat, are frequently accompanied by rhinitis, cough, hoarseness and possibly conjunctivitis and diarrhoea\textsuperscript{79,81}. Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are recommended for the treatment of pharyngitis. NSAIDs have been shown to have a greater effect on pain when compared to paracetamol, however as a systemic treatment neither is recommended above the other, however, anti-inflammatory lozenges are available as topical treatment\textsuperscript{82}.

Bacterial pharyngitis can be caused by a variety of bacteria either non-streptococcal or streptococcal\textsuperscript{79}. Regardless of treatment with antibiotics 85\% of patients suffering from acute pharyngitis are symptomless within seven days\textsuperscript{83}.

Non-streptococcal infections include diphtheria and chlamydial infections which tend to be acute. However, chronic infections can be seen with mycoplasma infections when systemic illness is present. Certain non-streptococcal pharyngitis could be treated with antibiotics, however, inappropriate treatment is very likely due to failure to identify the particular bacteria\textsuperscript{79}. 

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Streptococcal pharyngitis can have different infecting pathogens such as *Group A, C, D or G β-haemolytic Streptococci* bacteria. The different strains can have similar symptoms\(^7^9\). As many as one-third of patients presenting with pharyngitis suffer from one of these strains of streptococci and at least 5% of patients with pharyngitis are infected with *Group C Beta-Haemolytic Streptococci*\(^7^3,^7^9,^8^4\). The severity of infection depends on the individual’s risk factors and bacterial factors\(^7^9\). As mentioned previously, *Group A β-Haemolytic Streptococci* (GABHS) is the only type of bacterial pharyngitis for which antibiotics are indicated\(^6^3,^7^1,^7^8,^7^9,^8^1,^8^3,^8^5\).

Non-infectious pharyngitis cases include gastroesophageal reflux disease (GORD) which frequently causes irritation and inflammation on the throat\(^7^9\). This is especially common in children. Presentation of this type of pharyngitis due to GORD may also include laryngitis, asthma and rhinosinusitis\(^7^9\). Lifestyle modification including diet, followed by treatment with a proton pump inhibitor generally resolves this type of pharyngitis\(^7^9\).

A syndrome characterised by periodic fever, aphthous ulcers and adenitis in combination with pharyngitis is another type of non-infectious pharyngitis. It occurs mainly in males aged 3-5 years\(^7^9\). Treatment with corticosteroids to manage symptoms is provided, however, they do not resolve symptoms\(^7^9\). Surgery involving removal of tonsils and adenoids has been shown to be an effective treatment. However, this is rarely carried out\(^7^9\).

### 2.1.1 *Group A β-Haemolytic Streptococci* (GABHS)

GABHS is a Gram-positive bacterium which causes a number of mild infections such as pharyngitis and impetigo\(^7^9,^8^6\). The World Health Organization, in 2005, estimated that globally there are 616 million new cases of Group A β-haemolytic Streptococcal (GABHS) pharyngitis each year\(^6^8\). Bacterial pharyngitis is most commonly caused by GABHS and up to 10% of adults in developed countries are likely to develop GABHS pharyngitis each year\(^8^6\).

GABHS is more prevalent in children with up to 15-37% of children suffering from sore throats infected with GABHS\(^7^9,^8^1,^8^7\). In comparison 5-15% of adults with a sore throat will have a GABHS infection. GABHS infection can
occur at any age, however it peaks between the ages of 5-15 years\textsuperscript{88}. From the ages of 4-10 years immunological activity in the lymphoid tissue of the pharynx is at its highest, resulting in intermittent pharyngeal symptoms\textsuperscript{79}. This is what determines the highest peak of prevalence across the 5-15 year age group\textsuperscript{79}.

GABHS most commonly resides on the mucosa of the throat and nasal passages. Up to 40\% of the population are asymptomatic carriers of GABHS for whom no antibiotic treatment is recommended\textsuperscript{78,86}. GABHS spreads through droplet transmission and incubation of the bacteria lasts up to 5 days\textsuperscript{79,81}. If patients are treated with antibiotics they are no longer contagious after 24 hours\textsuperscript{81}. GABHS pharyngitis usually resolves within 3-5 days, with treatment with antibiotics shortening the duration of infection by approximately 16 hours\textsuperscript{79}.

However, complications do arise and an estimated 517,000 deaths per annum occur globally due to complications of GABHS pharyngitis\textsuperscript{79}. The majority of these deaths are in developing countries due to restricted antibiotic and healthcare access and sanitation\textsuperscript{68}. Serious complications include glomerulonephritis, rheumatic fever and scarlet fever, with rheumatic fever the dominating cause of morbidity due to GABHS infection\textsuperscript{63,89}.

Post streptococcal glomerulonephritis (PSGN) is the most common complication of GABHS pharyngitis\textsuperscript{79,90}. It can also develop after a bacterial impetigo infection; however, it presents more rapidly in those with pharyngitis. Symptoms of PSGN include swelling in the face and or extremities, blood in the urine, hypertension, urinary sediment abnormalities and a slight fever, which resolve within weeks\textsuperscript{79,90}. Treatment of GABHS pharyngitis with antibiotics does not reduce the likelihood of developing PSGN\textsuperscript{79,90}. Symptom management is the main aim of treatment and in rare circumstances long-term kidney damage may occur. However, rare long-term damage such as kidney failure is more common in adults\textsuperscript{79,90}. Figures show that in developing countries the annual incidence of post streptococcal glomerulonephritis is as high as 28.5 per 100,000\textsuperscript{91}.

Acute rheumatic fever results from an autoimmune response to GABHS pharyngitis. Long-term damage to cardiac valves caused by acute rheumatic fever can result in rheumatic heart disease\textsuperscript{92}. Acute rheumatic fever complications associated with GABHS infection have been reduced through
appropriate therapy with antibiotics. The incidence of acute rheumatic fever globally has increased in the past number of years. In 1970 the incidence of acute rheumatic fever in America was 10 per 1,000 population and in 2008 it was reported to be approximately 30 per 1,000 population. In contrast across Europe acute rheumatic fever prevalence has curved upwards during this time but reduced in 2008 to similar levels seen in 1970 of 5 per 1,000 population. However, with the global incidence of GABHS complications increasing, vigilance must be maintained through prevention and treatment methods of GABHS.

Other complications of GABHS can occur. Scarlet fever and toxic shock syndrome are as a result of exotoxin production. Treatment with antibiotics for toxic shock syndrome is not effective in many cases and the mortality rate for this is 50%. Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections were first described in 1998 and it is a very rare complication of GABHS infection. It is unknown how the disease occurs. Symptoms including presence of a tick or an OCD disorder, beginning between the age of 3 years and the beginning of puberty and possibly a positive throat swab for GABHS are part of the criteria for diagnosis. There are very limited treatment options for this complication.

More common complications include; a peri tonsillar abscess (quinsy), which forms when a collection of pus gathers between one tonsil and the wall of the throat. Patients 21-40 years of age who are smokers have a much higher risk of developing this complication in primary care settings after initial presentation. Treatment with antibiotics is required upon presentation of this complication.

2.1.2 Diagnosis of GABHS – Clinical Prediction Rules
GABHS infection can be seen at any time of the year, however, it appears to be seasonal and varies from climate to climate. Acute tonsillitis is most likely to be seen in late autumn, winter and spring in temperate climates. Despite this knowledge, surveillance data is not gathered and therefore, GPs do not have the ability to monitor the magnitude of outbreaks locally on an annual basis.
Surveillance would allow monitoring of the infection, including prevalence in the community and antibiotic resistant pathogens and allow more accurate diagnosis of bacterial pharyngitis\textsuperscript{41,63}.

There is no one defining feature of GABHS pharyngitis. A culture of a throat swab is the gold standard for diagnosis\textsuperscript{81}. Signs and symptoms associated with GABHS infection include; a sore throat, a fever of $\geq 38^\circ C$ and exposure to GABHS in the past two weeks, cervical node adenopathy, inflammation of the tonsils or pharynx or presence of exudates\textsuperscript{81}. Specific symptoms to GABHS infection include palatal petechiae (small red spots on the soft palate) and a scarlet fever rash (sandpaper rash), however, these are rarely present in patients and therefore, cannot be relied upon for diagnosis\textsuperscript{81}.

Clinical prediction rules (CPR) have been developed to aid the diagnosis of GABHS infection due to the limitations which present with throat cultures including, a 1-2 day delay in obtaining results and the relative expense\textsuperscript{63}. CPRs are evidence based tools which allow patients to be stratified by their doctor, according to their probability of having the infection\textsuperscript{63}.

There are various CPRs which have been developed for the diagnosis of GABHS pharyngitis such as the Centor Score and the McIsaac score\textsuperscript{97}. The most commonly used CPR for GABHS is the Centor score, which consists of four signs and symptoms (tonsillar exudate; tender anterior cervical adenopathy; absence of cough; and history of fever ($>38^\circ C$)), with one point scored for each symptom present\textsuperscript{63}. The Centor score was developed over thirty years ago and has been validated across a range of clinical settings, including primary care, and is recommended in clinical guidelines including the American College of Physicians, Infectious Disease Society of America, the National Institute for Health and Care Excellence (NICE) and the Irish College of General Practitioners\textsuperscript{62,63,98-100}. It differentiates those patients suffering from viral pharyngitis from those with bacterial pharyngitis\textsuperscript{97}.

An estimated 25-86% patients with a Centor score of 4 are likely to have a GABHS infection. In contrast between 2-23% of cases scoring 1 are likely to have a GABHS infection\textsuperscript{78}. However, this is dependent on age, local prevalence and the season\textsuperscript{78}. NICE recommend that clinicians consider immediate
treatment with antibiotics for patients who have three or four Centor Criteria\textsuperscript{100}. However, the accuracy of the Centor score when used in children, is not as good as when it is used in adults, as during the first few years of life GABHS pharyngitis presentation is different\textsuperscript{101}. Children have been found to be asymptomatic carriers of GABHS in 20\% of cases. GABHS pharyngitis in children may present with fever, tender lymph nodes and tonsillar exudate, frequently there may not be an absence of cough. The Centor Criteria may not effectively differentiate the infective organisms\textsuperscript{101}.

While the Centor Criteria and the McIssac CPR have been validated in adult populations, they were developed based on the assumption that they would be used in populations 3 years and over. The McIsaac score is adjusted according to patients’ age\textsuperscript{97}. Patients under the age of 15 years receive an additional point with the score for those over the age of 45 being reduced by one point\textsuperscript{102}. The Centor Criteria does not take account of age and relies on the 4 clinical criteria\textsuperscript{63}.

Furthermore, the predictability of CPRs improves with peaks of incidence in the local area, as has been shown with the Centor Criteria\textsuperscript{97}. One study showed that by accounting for the proportion of people with GABHS in the localised area in recent time improved the predictability of the proportion of patients testing positive for GABHS. This improvement was seen across all scores of the Centor Criteria\textsuperscript{88}. The positive predictive value was 17\% higher than previous studies carried out which did not include bio surveillance information\textsuperscript{88}.

\textit{2.1.3 Diagnosis of GABHS - Point of Care Testing}

Diagnosis of GABHS can be improved when CPRs such as the Centor Criteria are used in combination with point of care testing\textsuperscript{103}. Point of care testing (POCT) refers to diagnostic testing at or around the medical care site\textsuperscript{104}. POCT kits have been developed to allow for quick and easy diagnostic testing with high specificity and sensitivity\textsuperscript{65}.

POCT is beneficial in primary care allowing for increased diagnostic capacity\textsuperscript{65}. There are various kits which have been developed to determine
international normalised ratios for warfarin levels, C-reactive protein (CRP) levels, blood glucose levels, lipid levels and rapid antigen detection testing for GABHS. These are used in primary and secondary care settings as well as pharmacy settings. GPs in various countries such as Sweden and Denmark regularly carry out POCT. In Denmark, point of care testing was used in 44% of cases presenting to their GPs to determine the presence or absence of GABHS pharyngitis which then informed the GP’s prescribing practice. POCT testing prior to the prescription of antibiotics has increased in Denmark by 45% since 2004, resulting in prescribing rates which were 21% lower than GPs who did not use POCT to aid diagnosis.

Rapid Antigen Diagnostic Tests can be used to aid accurate diagnosis of GABHS pharyngitis and improve antibiotic prescribing. RADTs were first developed in the 1980s, and since then, they have been developed and streamlined, moving from latex agglutination methods and optical immunoassays to what is found today such as DNA probes and fluorescence in situ hybridization methods.

Numerous studies have looked at the validity and appropriateness of RADT in clinical practice. One study, the PRISM study, investigated various aspects of RADT for the diagnosis of GABHS. This study found that RADTs are relatively inexpensive and are specific to group A streptococci. The sensitivity of the tests increases with increasing concentration of GABHS. Samples which have low concentrations of GABHS results in varying abilities across different RADT kits to produce a positive result. Different brands of the RADT kits have different sensitivities at high concentrations and in one study ranged from 62% to 95% sensitivity. Different strains of GABHS do not affect the sensitivity of the tests significantly. However, the type of swab used to collect specimens does affect the sensitivity of the RADT. Specificity has been shown to be high with one study, the PRISM study, carrying out test on five RADT kits which produced no false positives. A recent systematic review and meta-analysis carried out by Stewart et al., indicated that RADT, relative to throat cultures as the reference standard, has a sensitivity of between 70-95% and a specificity of up to 96%. 

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Studies have also shown the impact of RADT on inappropriate antibiotic prescribing. In one randomised control trial, there was a 33% reduction in inappropriate prescribing with the use of RADT in combination with the Centor Criteria in comparison to the Centor Criteria alone. Combining Centor Criteria and RADT was also associated with an overall reduction in antibiotic prescribing of 20%. Another study, of a primary care randomised controlled trial, relative to the Centor Criteria alone demonstrated that RADT with 95% specificity and 90% sensitivity, in combination with the Centor Criteria, was associated with a reduction in antibiotic prescribing by 23%. This study replicated findings of a previous study carried out in Switzerland which reduced antibiotic prescribing by 23% using RADT in combination with the Centor Criteria.

Furthermore, the use of RADT in combination with the Centor Criteria for the diagnosis of GABHS has been shown to improve patient adherence to their treatment regimen. A Spanish prospective observational study examined two different dosing regimens; twice daily and three times daily in those on which RADT was carried out and on those in which no RADT was carried out. The study determined an association between antibiotic compliance and RADT on patients, no effect was determined during this study. The results showed that for both dosing regimens adherence was 11.8% higher in those who had RADT carried out prior to prescription. The group on a thrice daily dosing antibiotic regimen had better compliance overall with a superior adherence reported of 70.8% without RADT versus 80.1% with RADT prior to prescription. In the group on a twice daily regimen compliance was reported as 76.5% without RADT and 88.1% in those with RADT prior to prescription.

In the US, the use of RADT, has also been shown to be cost-effective at diagnosing GABHS pharyngitis. Savings are made through the avoidance of unnecessary culture tests and allow optimal antibiotic prescribing. A study carried out in the US, found that when managed by pharmacists, management of GABHS pharyngitis was the most cost effective and least costly, compared to pharyngitis management by GPs. The cost of a physician carrying out RADT versus pharmacist management, including RADT was $88.97 versus $53.56 respectively. A feasibility study carried out in the UK on a community pharmacist pharyngitis management service stated approximate savings to the
National Health Service of £2747 via avoidance of 41 patient GP consultations\textsuperscript{115}. However, evidence on the cost effectiveness of POCT, in the UK, is limited and cannot be compared to the US due to the different healthcare structures between countries. Therefore, further study in the UK on cost-effectiveness of RADT is required\textsuperscript{119}.

The World Health Organisation last issued guidelines on the diagnosis and treatment of Strep A in 1999, which mainly focused on children\textsuperscript{120}. Since then they have carried out a report on the burden of disease but there has been no update to the recommended guidelines for diagnosis and treatment. Culture of throat swabs are recommended as gold standard by the WHO for the diagnosis of GABHS\textsuperscript{120}. However, the importance of correct sampling of the pharynx is stressed to avoid false negatives of these cultures. The World Health Organisation also recommended RADT however, the cost of these tests was a deterrent and RADT was not widely available. Sensitivity at the time was also seen as an issue. Both of these have been improved upon over the last 18 years\textsuperscript{120}.

The Infectious Diseases Society of America recommend the use of RADT in combination with the Centor Score\textsuperscript{98}. Guidelines recommend treating those with a positive rapid test and withholding antibiotics in rapid test negative patients. The RADT is a detection method for Group A Streptococcal antigen from throat swabs\textsuperscript{121}. The American College of Physicians, published in 2001, recommends treating patients with antibiotics in those presenting with three or four Centor Criteria or those with two or more Centor Criteria and a positive RADT result\textsuperscript{98}. If the result of a RADT is negative, for adults it is not recommended that this is confirmed via culture\textsuperscript{118}. However, for children and adolescents the opposite is recommended and a culture should be taken to confirm a negative RADT result\textsuperscript{122}.

In contrast to the American guidelines, the European Society for Clinical Microbiology and Infectious Diseases recommend the use of RADT in patients with a Centor Score of 3 or 4. It is not recommended for those with a score of 0-2\textsuperscript{123}. RADT should only be carried out following an evaluation of a patient’s clinical symptoms. Those with a cough or rhinorrhoea for example should not be tested as these symptoms suggest that it is viral pharyngitis\textsuperscript{124}. If the patient
tests positive for GABHS then it will be most likely due to the patient being a carrier of GABHS rather than it being an acute infection of GABHS\textsuperscript{124}. Various studies and guidelines, recommend that where the RADT result is negative, depending on patients’ clinical symptoms, throat cultures should be taken as there could be a number of false negatives\textsuperscript{96,125}. American guidelines recommend that this is done in children and adolescents as the prevalence of GABHS is much higher in this population\textsuperscript{112}. However, European guidelines do not recommend this\textsuperscript{123}.

RADTs are widely used in the US, France and Finland\textsuperscript{81}. The UK, Scottish and Irish guidelines do not currently recommend the use of RADT\textsuperscript{78,81,85,100,126}. However, RADT has been shown in a number of studies to reduce antibiotic prescribing for sore throats\textsuperscript{52,78}. The UK Review on Antimicrobial Resistance published in May 2016 recommends the use of RADT for all patients, prior to their doctor prescribing them antibiotics, however this has not been adopted into treatment guidelines\textsuperscript{127}.

Despite the level of evidence that RADT in combination with CPRs can reduce inappropriate antibiotic prescribing, national treatment guidelines in the UK and Ireland have not adopted RADT\textsuperscript{84,96}.

\subsection*{2.1.4 Recommended treatment of GABHS}

The World Health Organisation, Europe, the UK and Ireland have issued guidelines stating that first line treatment of GABHS is pheynoxymethylpenicillin three to four times daily, for ten days\textsuperscript{63,100,120,126}. The WHO, at the time, indicated that it was the only antibiotic shown clinically to prevent rheumatic fever\textsuperscript{120}. Ten days of treatment with antibiotics has been shown to have higher eradication rates of GABHS. Adherence to antibiotic treatment over the ten day period influences the success of the treatment and the WHO states that healthcare professionals should be promoting patient compliance to the treatment regimen\textsuperscript{120}. Antibiotics should be started in those with a Centor score of 3 or 4\textsuperscript{100,120}.  

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A recent Cochrane Review, concluded that the first line recommendation for the treatment of GABHS pharyngitis is a ten day course of phenoxy methylpenicillin, with second line treatment for those allergic to first line treatment, a macrolide such as erythromycin\textsuperscript{128}. This review stated that prescribers should take into consideration cost effectiveness, antibiotic resistance patterns and allergies\textsuperscript{128}.

First line treatment in the US is penicillin either amoxicillin, ampicillin or phenoxy methylpenicillin, for a duration of ten days\textsuperscript{122}. Macrolides such as erythromycin and clarithromycin are recommended for those allergic to penicillin and a suitable prescribed duration is 5 days \textsuperscript{122}.

Second line treatment for GABHS pharyngitis or those allergic to penicillin, includes macrolides, of which, in 1999, erythromycin was recommended due to its low cost\textsuperscript{120,126}. Cephalosporins can also be used to treat GABHS pharyngitis. Both classes of drugs can be prescribed for less than ten days. Resistance patterns in the local community should be used to influence prescribing patterns of antibiotics especially macrolides. The WHO states that sulphonamide antibiotics or tetracyclines should never be used to treat GABHS \textsuperscript{120}.

Follow up swabs are indicated after a full course of antibiotics for those patients who have a history of rheumatic disease, or who suffered an acute outbreak of GABHS pharyngitis during rheumatic fever, poststreptococcal acute glomerulonephritis or in close communities, such as family homes\textsuperscript{122}. Follow up swab cultures would not be recommended for those who are no longer symptomatic following a course of antibiotics\textsuperscript{122}.

The WHO recommends taking a second culture after a full course of antibiotics only in those who are at high risk of developing complications such as rheumatic fever\textsuperscript{120}. If patients have been compliant with their antibiotic treatment and they are still symptomatic then a second course of antibiotics may be prescribed, however, this should be rare\textsuperscript{120}.

The Irish College of General Practitioners guidelines do not recommend routine microbiological testing for those with a Centor Score of 3 or 4, rather the Centor Criteria is recommended to determine if an antibiotic is appropriate\textsuperscript{85}.
Both NICE and Irish guidelines state that immediate antibiotic treatment should be issued to patients who are systemically unwell or who present with signs or symptoms suggesting complications such as peri tonsillar abscess and pre-existing comorbidities which place patient at high risk of serious complications. Those who do not present with these symptoms should be offered a delayed antibiotic prescription. This method involves the patients taking a wait and see approach to first determine if symptoms will self resolve.

These guidelines also state that patients should be provided with the following information as part of all antibiotic prescribing strategies: advice about the history of the illness, the total length of the illness and how to manage symptoms. For those patients who are provided with a delayed antibiotic strategy they should be reassured as to the unlikely impact the antibiotics will have on their condition, when to use the antibiotic if symptoms are not improving or worsening and when to consult with the prescriber again.

Over the counter medications should be recommended to patients as treatment. This includes the use of analgesics such as paracetamol and ibuprofen, anti-inflammatory sprays and lozenges. Ibuprofen has been shown to provide greater symptom relief in the pharyngitis compared to paracetamol.

2.2 Current Treatment Practices for Pharyngitis
Accurate and effective treatment of GABHS is essential to minimise the development of GABHS becoming resistant to antibiotics. However, studies have shown inconsistencies with prescribing of recommended first line and second line therapies for the treatment of GABHS. For example, a Canadian study found that in 47% of cases, antibiotics prescribed were for amoxicillin rather than phenoxymethylpenicillin, which is recommended as first line treatment. Prescribing of broad spectrum antibiotics and those which are not first line for the treatment of pharyngitis could lead to drug resistance. Currently GABHS is susceptible to penicillin, however, antibiotic resistance has begun to emerge with other broad-spectrum antibiotics used to treat GABHS pharyngitis. One study has found an emerging trend of GABHS...
becoming drug resistant, including ampicillin and third and fourth generation cephalosporins. The American College of Physicians published pharyngitis diagnosis and treatment guidelines in 2001. However, it has been shown that the majority of physicians prescribing antibiotics for GABHS indication are not following any guidelines for either diagnosis or treatment. The top antibiotics prescribed by doctors were amoxicillin, macrolides, cephalosporins and amoxicillin/clavulanic acid. The American College of Physician at the time of publication estimated that these guidelines would result in antibiotic prescribing rates of 10.6% to 33%. However, the actual prescribing rate found was 59.1%. It has been found that guidelines are only adhered to in 57% of pharyngitis cases as well as upper respiratory tract and acute sinusitis infections. Further study is required to determine why these guidelines are not being adhered to and what can be done to reverse this behaviour. One study has postulated that explaining to the patient why antibiotics are not necessary requires greater time than issuing a prescription, as well as that, guidelines with various steps can require significant time periods deterring prescribers who are under time pressure.

A recent study in the US estimating the prevalence of inappropriate antibiotic prescribing during ambulatory care visits between 2010-2011, estimated that approximately 34 million antibiotics were prescribed unnecessarily for all indications. In that year 62.2% of visits for pharyngitis resulted in antibiotics being prescribed, highest in the 20-64 year age group with 72.4% of patients, presenting with pharyngitis, prescribed antibiotics. The mean annual rate of visits with antibiotics prescribed for pharyngitis for all ages was 43%. It was highest in the 0-19 age group at 91%. For all conditions included in the study there was an annual rate of 506 per 1000 population, however, only 353 per 1,000 antibiotic prescriptions were likely to have been appropriate. In the US low levels of education and income were associated with higher rates of antibiotic prescribing for respiratory prescriptions. To reduce the level of inappropriate antibiotic prescribing the Infectious Diseases Society of America recommend the use of a Rapid Antigen Detection Test (RADT) in combination with the Centor Criteria. Doctors have stated that RADTs are easy to use,
reduce antibiotic use, provide reassurance especially to inexperienced staff and
certify diagnosis, to allow education and reassurance of patients.

Similar to the US, overprescribing of antibiotics for pharyngitis is common
across Europe. However, there are between country differences in the
prevalence of inappropriate antibiotic prescribing. Healthcare structures vary
across Europe, with variations in accessing prescribers, accessing certain
medications and restrictions on the practice of pharmaceutical companies. In
general, there is more prescribing of antibiotics in southern Europe with lower
rate of antibiotics prescribed in northern Europe. In the Netherlands, 75% of
antibiotics prescribed were as per guidelines, which is good compared to other
countries. A rate of 52% in Netherlands has been reported for antibiotic
prescribing for pharyngitis, which is quite high compared to other indications for
which antibiotics would be prescribed in this country. It was reported in one
study that up to 75% of adult pharyngitis cases have been inappropriately
prescribed antibiotics. In France, it has been reported that inappropriate
prescribing of medication was prescribed in 88% of cases, which included
overdose, drug interactions and inaccurate targeting of the disease. In
countries where patients can attend any doctor, such as Poland, France and
Ireland, competition has been reported, influencing prescribing patterns.

In Denmark a survey found that GPs had issued prescriptions for
antibiotics for patients who did not require treatment with one in order to “follow
the wish of the patient and avoid conflict.” A Spanish, prospective, non-
randomised trial was carried out in 2014 which determined that 55% of GPs felt
pressurised into prescribing antibiotics for patients despite knowing they were
most likely not indicated for the patient’s condition. Patients who specifically
request an antibiotic are more likely to be prescribed one by their Spanish GP,
when they are suffering from an acute respiratory tract infection. This non-
randomised trial showed that GPs who carried out POCT, including RADT and
CRP testing significantly reduced antibiotic prescribing, compared to those who
did not undertake POCT in their surgeries and provided extensive education
and explanation of their diagnosis. Antibiotic prescribing was reduced in
those who asked for an antibiotic by 18.9%.
A Spanish study examined the adherence to pharyngitis prescribing guidelines and the use of rapid antigen detection testing to increase the rational use of antibiotics\(^{103}\). Previous studies including a systematic review and a meta-analysis regarding the diagnostic accuracy of the Centor Score had indicated that, although the Centor Score can enhance appropriate antibiotic prescribing, it should be used with caution as treating all patients with a score of \(\geq 3\) may lead to many patients being treated with antibiotics inappropriately\(^{63,78}\). This Spanish study found that co-amoxiclav, a broad-spectrum antibiotic, was the second largest prescribed antibiotic. This is inappropriate for the treatment of pharyngitis\(^{137}\). GPs prescribed antibiotics to 26.9% and 32.4% of patients presenting with Centor scores of 0 and 1 respectively. If prescribing guidelines had been adhered to and RADT used in patients with a Centor score of 2 or more only 77 patients in total would have been prescribed antibiotics, reducing the number of antibiotics prescribed by 84.5%\(^{137}\).

Reports have estimated that over prescribing of antibiotics for sore throats is prevalent across the UK. A UK survey on antibiotic prescribing found that half of all patients presenting to General Practitioners suffering with coughs, cold and viral sore throats were prescribed antibiotics\(^{53}\). In the UK between 1999 and 2011 antibiotic prescribing for coughs and colds (which are viral in origin) increased 40%, despite repeated requests to reduce antibiotic prescribing\(^{138}\).

A prospective observational study in the UK determined that GPs, in up to 44% of cases, do not follow recommended prescribing practices, i.e. the Centor Criteria, to diagnose and treat pharyngitis\(^{139}\). This has been shown to result in 58% of patients receiving antibiotics inappropriately, who did not respond to treatment. This study reported that in many cases patients are prescribed antibiotics, such as penicillin, at a dose which is below the therapeutic range for treating pharyngitis. This contradicts the purpose for which they are prescribed, which is to prevent complications\(^{139}\).

Adherence to prescribing guidelines is essential to ensure that antibiotics are not unnecessarily prescribed and when they are prescribed they are prescribed at the correct dose to prevent complications. One study reported that educational interventions including oral and written presentations resulted in an
increase in adherence to guidelines by 14% and a reduction in antibiotics of 22%\textsuperscript{140}.

Like America, Europe and the UK, prescribing practices in Ireland have been found to be questionable with high rates of inappropriate antibiotic prescribing reported\textsuperscript{76,141,142}. While 10% of patients could be prescribed antibiotics for pharyngitis as many as 53% have been prescribed antibiotics for pharyngitis by Irish GPs\textsuperscript{76}. Rates of antibiotic prescribing have been found to be higher in Ireland compared to other parts of the world. For example, in Canada, 5% of patients presenting to GPs with a complaint of upper respiratory tract infection were prescribed antibiotics. Ireland in comparison had 33.1% of patients presenting with the same complaint prescribed antibiotics\textsuperscript{69}.

A prospective observational study published in 2012 on antibiotic prescribing in the Republic of Ireland found that most prescriptions issued for antibiotics are not in accordance with guidelines\textsuperscript{69}. Several GPs were found to be prescribing second and third line antibiotics for respiratory infections in over 50% of cases presenting, rather than first line choice\textsuperscript{76}. Of those presenting with a sore throat, 53% of patients were prescribed an antibiotic\textsuperscript{69}. In 9.25% of the prescriptions issued, prescribers deemed them unnecessary. Compounding this, prescribers stated that they were unsure as to the necessity of 17.67% of prescriptions issued to patients with a sore throat. Amoxicillin was prescribed most commonly accounting for approximately one third of these prescriptions\textsuperscript{69}. In the 15-64-year age group, 60% of patients attending their GP received antibiotics, higher than any other age group. Those who prescribe have stated that they have a positive attitude towards the placebo effect which the antibiotic provides. In Ireland it has been shown that GPs tend to prescribe amoxicillin as a potential placebo\textsuperscript{69}.

These figures were not dissimilar to the those found for tonsillitis indicating that inappropriate prescribing is occurring for several conditions and not just pharyngitis\textsuperscript{76}. Co-amoxiclav was issued for a quarter of tonsillitis prescriptions. Antibiotic prescriptions were issued for immediate use and not issued on a delayed wait and see order, as would be expected for patients with a Centor score of 2\textsuperscript{69}. Only 13.8% of antibiotic prescriptions were prescribed with the intention of the patient using the wait and see approach\textsuperscript{69}.
Irish studies have found that a number of factors influence the inappropriate prescribing of antibiotics in Ireland including:

- the structure of the healthcare system\textsuperscript{142},
- whether patients are entitled to free GP care from the state or whether the patient is paying for the consultation which in Ireland is relatively high at an average cost of €51 for the patient\textsuperscript{142},
- diagnostic uncertainty\textsuperscript{69} and,
- a fear of being negligent\textsuperscript{69,142}.

Those who do not have access to free medical care in Ireland were found to be 1.29 times more likely to be prescribed antibiotics for a respiratory infection compared to those with free access\textsuperscript{142}. However, those private patients were more likely to be prescribed a delayed antibiotic due to the cost of attending their GP a second time\textsuperscript{142}. Barriers to reducing inappropriate use of antibiotics include patient expectations, lack of patient awareness of antibiotic resistance and the perceptions of both patients and practitioners that there is a theoretical risk of antibiotic resistance\textsuperscript{51}.

2.3 Point of care testing in the community pharmacy setting

The community pharmacy setting in the US and the UK has been identified as a useful setting for point of care testing for infectious diseases, including GABHS pharyngitis\textsuperscript{143}. Point of care testing has been used in community pharmacy to carry out numerous interventions for patients. Creatinine clearance, lipid profiling, C-reactive protein, international normalisation ratio, IgA as an indicator for coeliac disease, blood pressure, blood glucose and body mass index measurements have all been carried out in community pharmacy to name a few\textsuperscript{106,108,110,144,145}.

For example, community pharmacy anticoagulation clinics in New Zealand using INR measurements found that the percentage of patients remaining in a therapeutic range for a significant time frame, when monitored in the pharmacy, with their warfarin treatment was 78.6%. This is significantly
higher than those monitored by their GP, where less than 60% of patients had an appropriate time for therapeutic range when being monitored by the traditional GP system. This type of POCT in community pharmacy was much more efficient for patients and reduced the workload burden on GPs, resulting in reduced GP-patient consultations\textsuperscript{106}. Other studies have also shown an improvement in patient adherence with anticoagulant therapy, reduced cost burden, reduction in hospital admissions as well as improvement in the time in the therapeutic range and improvements in patient safety\textsuperscript{144}.

Similarly, a community pharmacy POCT for Immunoglobulin A service, as an indicator for coeliac disease, allowed for opportunistic screening of patients presenting with symptoms of IBS, diarrhoea and coeliac disease. Whilst the cost of the service in the UK was reported by patients to be a prohibitor, those patients who were diagnosed with coeliac disease due to this POCT in the community pharmacy had been self-treating their symptoms without diagnosis\textsuperscript{108}. Patients reported that pharmacists provided trustworthy advice and that it is an ideal setting for the professional intervention\textsuperscript{108}.

Community pharmacists have also demonstrated their potential in preventing disease and managing infections. Vaccination programmes throughout the US, UK and Ireland have increased uptake among populations for vaccines such as influenza, herpes zoster and pneumonia\textsuperscript{143,146}. In Ireland, of those who are vaccinated against influenza, over 10% are vaccinated by community pharmacists, facilitating the Irish health service to a target of 75% uptake target across those identified as ‘at risk’\textsuperscript{146}.

A survey carried out in America on the pharmacist perceived barriers to implementing vaccination services in the pharmacy included: vaccinations are offered in the GP surgery, lack of time for pharmacists, pharmacy staff disinterested, a lack of space, lack of demand among patients and patients not requiring the vaccines\textsuperscript{147}. To enable these pharmacists to implement vaccination services in their pharmacy it would require freeing up of the pharmacists’ time, increasing patient demand, change in attitudes of owner or staff and greater profit\textsuperscript{147}.
However, in Ireland some of these barriers have been addressed following legislation implemented in 2007. This legislation required all pharmacies to have a consultation room to allow for consultations to be had with patients in private\textsuperscript{146}. The Institute of Irish Pharmacists (IIOP) was created in 2013 to provide a platform for pharmacists to document their continuing professional development. As part of the IIOP agenda training programmes are also provided, facilitating the upskilling of pharmacists and the maintenance of quality services\textsuperscript{146}.

POCT of CRP for lower respiratory tract infections and RADT for GABHS pharyngitis in community pharmacy has been suggested as most patients with these conditions present first at their local pharmacy\textsuperscript{143,148}. Barriers to implementing this type of testing include the fear of duplicating work, as patients may still see their GP following a visit to their pharmacist\textsuperscript{148}. Cost-effectiveness of RADT in GP primary care settings, is dependent upon the specific countries health system\textsuperscript{118,119}. However, programmes such as the RADT testing in community pharmacy has shown to result in cost-effective treatment\textsuperscript{143}. A recent study in the US found RADT testing in community pharmacy to be cost effective, estimated at almost half the financial cost of a doctor’s patient work up in some cases\textsuperscript{118}. A prospective multi-centre feasibility study on a community pharmacist GP collaboration GABHS pharyngitis management programme showed a 55% reduction in antibiotic use\textsuperscript{62}. The advantages of community pharmacies for point of care testing include: accessibility, lower costs and no or minimum wait time\textsuperscript{62}. This study had a small sample size and no comparative group, therefore, further study would be required to determine the validity of these results\textsuperscript{62}.

For POCT results to be accurate, those using the tools must be trained appropriately and carrying out the tests as to the manufacturer specifications\textsuperscript{143}. As undergraduates, pharmacists receive no training in the implementation of POCT, including, the need for precision and accuracy when using these tests. Countries such as the US have changed requirements in the primary degrees of pharmacists so that when students graduate they understand the importance of quality control of diagnostic testing\textsuperscript{143}. 
Furthermore, implementation of POCT across community pharmacy is not consistent. Community pharmacy interventions are not adopted by all pharmacies especially in the US and Ireland\textsuperscript{143,149}. In both of these countries, POCT may be found in only a relatively small number of pharmacies, leading to the potential impact these POCT interventions have on the population being diluted and ignored by stakeholders\textsuperscript{143}. In order to overcome this it is recommended that there is greater engagement between pharmacy regulators and stakeholders during the set up and provision of these POCT interventions\textsuperscript{143}. This stakeholder engagement has been shown to be effective in the UK where the National Health Service has adopted a GABHS community pharmacy screening programme which they will look to roll out nationally to all community pharmacies with the aim of reducing antibiotic use\textsuperscript{149}.

While POCT is recognised as a method which could reduce inappropriate antibiotic use, awareness and educational campaigns carried out by community pharmacists are equally important\textsuperscript{143}. The World Health Organisation has identified pharmacists as a group of healthcare workers who can educate patients on the correct use of antibiotics, including adherence and when antibiotics are not appropriate\textsuperscript{150}. Pharmacists have been included as part of the World Health Organisation for World Antibiotic Awareness Week for 2017\textsuperscript{150}. Several interventions promoting antibiotic awareness have been carried out in the UK by pharmacy students\textsuperscript{29}. Educational interventions, such as questionnaires, antibiotic awareness workshops were carried out to assess the public’s knowledge of antibiotics with 21% of the population stating antibiotics could treat influenza. Following education seminars and one to one conversations, 40% of participants became antibiotic guardians, to improve antibiotic use in the future\textsuperscript{29}. Similarly other interventions in the US aimed at educating the public on correct use of antibiotics through health literacy skills and talks increased participants knowledge by 2 points on a 14 point knowledge index\textsuperscript{151}. The aim of these interventions was to evaluate awareness of antibiotic resistance and educate the public on antibiotic resistance. All types of interventions in the UK and US studies were interactive for the learner and could be easily carried out by all pharmacists\textsuperscript{29,151}. A combination of POCT such
as RADT with educational programmes has been postulated in order to reduce inappropriate antibiotic use, however, no studies to date have been found.

2.4 Current role of the community pharmacist in Ireland

Pharmacists in Ireland are the medicines experts in the Irish health system. Traditionally their role in Ireland has been the accurate and safe dispensing of medicines. Their role is now moving towards patient centred care, which involves healthcare professionals taking into account the patients views, thoughts and needs to provide the care that is best suited to the patient. In the last ten years changes in legislation have changed the regulation of pharmacists including the introduction of a code of conduct and continuing professional development.

Since 2010, pharmacists have begun vaccinating patients against certain viruses and bacteria and they have become involved with nationwide health promotion campaigns. However, community pharmacists still believe that they are an underutilised profession and would be open to extending their role and becoming more involved in the Irish primary healthcare model.

The Pharmaceutical Society of Ireland (PSI), the Irish pharmacy regulator published a report entitled “Future Pharmacy Practice in Ireland – Meeting Patients’ Needs”, in 2016. This report stated that by 2020, 40% of the population is expected to be suffering from at least one chronic illness. As of June 2016 there were 1,885 community pharmacies registered in Ireland.

There is currently opportunity for community pharmacist to positively impact patients' health and wellbeing. Among the list of areas in which pharmacists can influence this include; health and wellbeing, prevention and management of patients with chronic diseases and medicines management.

The role of the pharmacist varies from country to country. Pharmacists in Florida can prescribe medication from a formulary for patients. The only country in the EU which allows pharmacist prescribing is the UK. Pharmacists in the UK are legally allowed to supply specified medications to patient through Patient Group Directives (PGDs). Patients who are supplied these specified medications must be part of predefined groups of patients. In the UK
community pharmacists can also provide appropriate antibiotics to patients suffering from GABHS pharyngitis through a patient group directive\textsuperscript{115}. A patient group directive agreement with the authorising body, which includes medics, is developed to ensure that all governance criteria are met. A clear decision-making process must be outlined in the PGD to cover all possible risks and health benefits have been revealed. Following this those healthcare professionals carrying out the PGD must be appropriately trained and provide the patient service competently\textsuperscript{153}.

The PSI states that prescribing roles which are found in other countries such as the UK and the US could be implemented in Ireland, however, it would require a change in legislation. Introducing such changes would allow for improvements in medicines management and greater patient safety\textsuperscript{146}.

2.5 GP burden

As with the practice of community pharmacists in Ireland the Irish healthcare system is quite different to those found elsewhere in Europe. Patients of the Irish healthcare system can be categorised into two groups, those eligible for free medical care and those not. In Ireland, 39% of the population are eligible for free medical care\textsuperscript{154}. Patients are means tested and upon specific criteria being met, are granted free medical care including free doctors’ visits, access to public hospitals and a maximum monthly charge per family of €25 for medication\textsuperscript{154}. These patients are provided with a General Medical Services (GMS) number. A percentage of these patients, which includes children under 6 years and adults over 70 years, may not be eligible to receive free medication, and will only receive free general practitioner (GP) visits and access to public hospitals. The rest of the population pay for the first €144 of medication costs each month, all GP visits (the cost of which varies from €50 to €65), and €75 per night bed charge in public hospitals\textsuperscript{154}.

Currently there are an estimated 14 million visits to GPs in Ireland annually\textsuperscript{146}. Those who have access to free GP care reported between 27-39% higher usage of services than those without free access\textsuperscript{155}. However, figures from the EU Survey on Income and Living Conditions found that 19% of patients
in Ireland suffering medical issue did not discuss it with their doctor because of the cost, of which 26.3% had no access to free GP visits\textsuperscript{155}.

The four goals of the Irish Health Service Executive’s, “Healthy Ireland, A Framework for Improved Health and Wellbeing 2013-2025” is to; “increase the proportion of people who are healthy at all stages of life, reduce health inequalities, protect the public from threats to health and wellbeing and to create an environment where every individual and sector of society can play his or her part in achieving a healthy Ireland”\textsuperscript{146}. The PSI is determined to be a part of this framework and achieving these four goals. The PSI in its report on the future of pharmacy in Ireland states that the implementation of new technology in expanding the role of pharmacists is essential. It also looks to the role of community pharmacists in the UK and the impact they are having on patient health through minor ailment prescribing for conditions such as sore throat as well as thrush, backache and period pain to list a few\textsuperscript{146}.

\subsection*{2.6 Studies on community pharmacy pharyngitis programmes}

Few studies have been carried out on community pharmacy pharyngitis screening programmes and none in Ireland to date. A US study by Klepser et al. published in 2015, a prospective multicentre feasibility study, investigated a community pharmacist screening service for GABHS pharyngitis using the Centor Score in combination with RADT over a period of 10 months\textsuperscript{62}. This was carried out across 55 community pharmacies, who volunteered to take part in the study. Two care models were included; the first was similar to the Patient Group Directive model found in the UK whereby, there was a pre-arranged agreement with a local surgery. This model allowed pharmacists to dispense antibiotics to those who had a positive RADT result, which was carried out if the patient had a score of Centor Score of one or more\textsuperscript{62}. The second model involved the pharmacist consulting with the primary care physician of the patient\textsuperscript{62}. All pharmacists completed training prior to providing RADT in the pharmacy. The consultation with the primary care physician took place post examination of the patient. Discussion included treatment plan, referral
necessity, antibiotic dispensing and booking appointments. For both care models, pharmacists phoned patients within 48 hours after presenting at the pharmacy\textsuperscript{62}. There were 273 patients who underwent RADT and of those 48 were positive for GABHS\textsuperscript{62}. Of those who were positive, 47 patients were dispensed antibiotics and one patient was referred due to an inability to contact the primary care physician. The authors stated that the number of participants was small, however pharmacists conducted follow up with patients 24 to 48 hours following presentation in the pharmacy to provide after care, which included referral to doctors. Baseline characteristics including demographics and symptoms were gathered along with treatment outcome and healthcare utilization\textsuperscript{62}. This study concluded that the collaborative approach between pharmacists and physicians is feasible and could reduce inappropriate antibiotic prescribing by approximately 55\%\textsuperscript{62}. It also noted that 43.2\% of patients had no primary physician and 43.9\% of patients attended the pharmacy service outside of GP hours, resulting in the service increasing access to appropriate treatment in a timely and cost-effective manner\textsuperscript{62}. Limitations of this study included the potential for false positives or false negative results with no follow up culture to confirm correct use of RADT, a small sample size and that the pharmacies which took part in the study were voluntary and therefore the results in other pharmacies which may not have the time may not be similar\textsuperscript{62}. Additionally, there was also no control arm in the study and the sample size of the study was small resulting in an underpowered study. As well as this most pharmacies in the study were also well known to the researcher which could have influenced the recruitment of patients to the study\textsuperscript{62}.

A pilot community pharmacy pharyngitis management service was also introduced to a number of pharmacies in the UK in October 2014\textsuperscript{115}. This service was provided via a Patient Group Directive (PGD). This PGD included examination of patients presenting with sore throat by the pharmacist according to the Centor Criteria. Those with a score of 3 or 4 were recommended to undergo RADT by the pharmacist\textsuperscript{115}. Patients with a positive result for GABHS from the RADT were offered antibiotics, which the pharmacist could provide. Those with a negative result for GABHS were informed that antibiotics would not be appropriate. A feasibility study aimed to evaluate the use of the GABHS
screening service in the community pharmacy in patients over 12 years of age. This study gathered baseline characteristics for patients and estimated the social deprivation profiles for the participants. Savings to the UK health service were also estimated. The results from this feasibility study showed that of the 367 patients recruited into the study, 36 patients were positive for GABHS and were offered antibiotics. This study estimated that the community pharmacy service would have reduced the number of GP visits by approximately 48.8%. This was one of the first studies to be carried out in a UK community pharmacy setting. The study was relevant to the UK setting in which residents of the UK do not have to pay for their healthcare. This study does state that there were limitations to the study including a lack of control group. It also did not carry out follow up with patients to determine what they did once they left the pharmacy, therefore more patients could have visited their GP once they left the pharmacy. As well as these, the study consisted of a small sample size and patients were asked what they would have done had they not received the intervention. However, since the publication of this study the UK’s NHS Innovation Accelerator programme has stated that the service will be adapted and rolled out to all community pharmacies in the UK as part of their antimicrobial resistance strategy in the future. While the potential impact of this intervention was postulated in this study, it is unclear as to whether the impact of this intervention is generalizable.

2.7 Boots Sore Throat Test and Treat Service

The role of the pharmacist in Ireland is expanding and the pharmacy regulator, The Pharmaceutical Society of Ireland, has stated that community pharmacists play a role in tackling antibiotic resistance. Patients have also stated that they would like pharmacists to play more of a role in their healthcare needs and have the role expanded.

Studies have shown that the Centor Score in combination with Rapid Antigen Detection Testing (RADT) can be carried out by pharmacists in the community setting, resulting in reductions in General Practitioners (GPs) visits and antibiotic prescriptions. With antibiotic resistance, a growing burden
and, a post antibiotic era moving ever closer, pharmacists must be heavily involved in tackling antibiotic resistance. Pharmacists are ideally placed to do this with over 1,885 community pharmacies in Ireland and working as an interface between patients and GPs.

Boots Ireland developed a Sore Throat Test and Treat Service, which was piloted in 10 pharmacies from November 2015. The study intervention is based on a service model designed by Boots UK which was adapted for the Irish population by Boots Ireland. It is directed at patients presenting with an uncomplicated sore throat (duration of at least three days and less than 10 days). Patients are screened using the Centor Criteria and those with a score of three or four undergo RADT in the pharmacy. Patients with a positive RADT result are advised that they are likely to be experiencing a Strep A bacterial infection and that they should visit their GP. Patients with a negative RADT result, are informed that their sore throat is most likely due to a virus and antibiotics will not work. Pain relief is recommended, and patients are advised to see their doctor if their symptoms do not improve or get worse over the coming days.

To determine the impact of a GABHS intervention in Ireland, a comparative study along with follow up of patients is required. This will determine the feasibility and impact a community pharmacy sore throat screening service has on GP visits and antibiotic prescribing and also determine if it is an intervention which is applicable to the Irish healthcare setting.

2.8 Research Aims and Objectives

The aim of this study is to determine the feasibility and impact of a pharmacy-led intervention, involving the Centor score and rapid antigen detection testing (RADT) to identify Group A Beta Haemolytic Streptococcus in acute pharyngitis, on healthcare utilisation (GP visits), and utilisation of antibiotics.
3 Methodology

3.1 Introduction

This chapter sets out the method of this study. The research aims and objectives are described along with a detailed description of how the study was conducted.

This study was approved by the ethics board of the Royal College of Surgeons in Ireland on the 4th February 2016. The ethics reference number is REC 1211.

3.2 Study design

To determine the effectiveness of this intervention, a cluster randomised controlled trial would have been the preferred method of evaluation. However, prior to the development of this study Boots launched the Sore Throat Test and Treat Service, November 2015, on a pilot basis in 10 of the pharmacies across Ireland. Following the development of this study, the service was extended to all pharmacies in the chain nationwide, February 2016, except for those in the control group. Therefore, the preferred study design method of randomisation was not possible and is instead a prospective, non-randomised controlled, parallel trial with patients joining the study at the point of presentation to the pharmacy and followed up at day 7.

The validity of non-randomised control trials (non-RCTs) is often called into question. However, there are circumstances in which non-randomised control trials have shown the effectiveness of interventions. Unfortunately, non-RCTs are still subject to bias.

Selection bias in a non-RCT can occur when patients are allocated to an intervention, which can have an effect on the external validity of the study. Selection bias can be more prominent when the choice of the intervention is determined by the healthcare professional, especially if the study involves those who are severely ill, or those with different social class, varying educational levels and diet being present. Approaches to reducing the influence of
selection bias include; restricting the eligibility criteria to those that would be seen in clinical trials and implementing a zero-time point from which patients are followed up\textsuperscript{156}. These methods were included at study design to maintain the external validity of the study. However, potential confounders may still be present despite a clear protocol set out at study design and these were identified through adjusted analysis of data\textsuperscript{156}.

The study was designed initially to assess superiority of the Sore Throat Test and Treat Service based on a sufficient sample size of participants being recruited compared to usual care. Where the required sample size was not recruited non-inferiority was assessed.

The Transparent Reporting of Evaluations with Non-randomised Designs (TREND) standardised reporting guidelines for non-randomised control trials was followed to conduct and report on this study\textsuperscript{157} (Appendix 1). These guidelines were developed in response to the need for the use of non-randomised studies to be used to inform decisions and policies in the healthcare settings\textsuperscript{157}. The Consolidated Standards of Reporting Trials (CONSORT) statement was adapted, by the TREND group, to develop a checklist for transparent reporting of non-randomised studies.

3.3 Study population

The study population included both community pharmacies and patients. Community pharmacies were eligible to participate if they were already delivering the sore throat test and treat service. Control pharmacies were eligible if they were not, or never had been, delivering the service and if they matched intervention pharmacies on the following criteria:

- state funded prescription: private prescription dispensing ratio,
- healthcare sales and
- urban versus rural setting.

The matching process was undertaken to reduce selection bias and ensure baseline characteristics for the population presenting at each pharmacy were as similar as possible. Each pharmacy was assigned a unique study code.
3.3.1 Inclusion and exclusion criteria

All patients aged 18 years and over, presenting to the participating pharmacies with a sore throat lasting at least 3 days and less than 10 days, with no reported symptom improvement were eligible for inclusion in this study.

Patients were excluded if they had already taken antibiotics for their sore throat, or if they reported an improvement in symptoms, as previous antibiotic use can result in false negatives from RADT\textsuperscript{158}. Patients reporting the following specific ‘red flag’ symptoms were also excluded: presence of skin rash, dysphagia (difficulty swallowing), drooling, noisy breathing, breathing difficulties, stridor (a loud, harsh, high-pitched respiratory sound) muffled voice, severe pain and/or other severe symptoms and symptoms that worsen very quickly.

The study was conducted in 20 community pharmacies across Ireland between February 2016 and June 2017.

3.4 Recruitment Procedure

3.4.1 Pharmacy recruitment

The ten pharmacies delivering the Sore Throat Test and Treat Service were invited to participate in this study. They represented the intervention group. Having secured the intervention group, an additional 10 pharmacies within the pharmacy chain were matched to the intervention pharmacies based on the characteristics reported above. There was one round of pharmacy recruitment carried out, with all 20 pharmacies agreeing to take part in the study initially.

3.4.2 Participant recruitment

Consecutive patients presenting to one of the ten intervention pharmacies were invited to participate in the intervention group, if they fit the inclusion criteria reported in section 3.3.1 and reported having a history of fever and/or absence of cough (i.e. centor score of 1 or 2).
Consecutive patients presenting to one of the 10 control pharmacies, were invited to take part in the study, if they fit the inclusion criteria reported in section 3.3.1. These patients were given usual care in the pharmacy. Patients with a self-reported Centor score of 0 were excluded from the study.

Patients in the intervention group were invited to take part in this study at the time of the consultation with the trained healthcare advisor or pharmacist in the private consultation room. Those in the control group were invited to take part by a trained healthcare advisor at the time of presenting to the pharmacy counter with a sore throat. The trained pharmacy team member or pharmacist went through the patient information leaflet (Appendix 2: Patient Information Leaflet) with the patient, and each item on the consent form was read aloud to the participant to overcome issues around literacy (Appendix 3: Consent form). No compensation or incentive was offered to the participants. Upon consent patients were assigned a unique patient study code, based on order of presentation to the pharmacy. Patient refusal for the intervention and / or the study was recorded in the pharmacy.

Every effort was made by the researcher to ensure that sufficient numbers of patients were recruited consecutively. All pharmacists and managers in the 20 pharmacies were initially provided with study packs containing study participating flow charts and step by step guidance of the recruitment procedure for gathering all data accurately. Face to face meetings were held with pharmacists from both groups to explain the study process.

Phone calls were made to all pharmacies every two months to follow up with pharmacists and pharmacy staff to ensure that they were actively recruiting consecutive patients to the study. The detail of these phone calls was not documented and were not set out as questionnaires. Emails were sent to all pharmacists containing the study guidance packs (Appendix 4a: Sore Throat Study Guidance Pack Intervention and Appendix 4b: Sore Throat Study Guidance Pack Control) and all study materials at the beginning of the recruitment periods and when there was a change in pharmacist. Reminder emails to continue to recruit patients were sent on 12 occasions to pharmacists.
3.5 Description of Intervention

3.5.1 Pharmacist Training

All intervention group pharmacists completed a blended learning programme, which included both distance learning and face to face training. Each pharmacist was required to successfully pass the associated multiple-choice assessment. They also had to review the Standard Operating Procedure (SOP); ensuring that they conduct the service in the manner outlined in the SOP once they were authorised to deliver it. Pharmacists also completed training as reviewed by a general practitioner, designed to ensure competence in the skills necessary for examination of cervical lymphadenopathy and tonsillar exudate and collection of throat specimen. A clinical assessor, conducted an Objective Structured Clinical Examination (OSCE), approved by a general practitioner, to determine competence in these physical examination techniques and only pharmacists who passed this assessment were eligible to deliver the intervention. Finally, pharmacists were required to successfully pass a consultations skills OSCE with a supervising pharmacist, designed by the services development pharmacy chain team to assess their competence in delivering the service to prospective patients. Only when the pharmacist successfully completed all these steps were they eligible to deliver the service.

There were 30 pharmacists trained in the intervention. All pharmacists passed both the multiple-choice question examine and OSCE. There were three changes in pharmacists across the intervention pharmacists during the study period. Every effort was made to ensure that new pharmacists recruitment by the pharmacies were trained on the intervention and study criteria as quickly as possible to ensure minimum disruption.

Healthcare advisors in the intervention pharmacies were fully trained to screen patients. Healthcare advisors involved in the intervention, had to complete a training programme, delivered by a pharmacist, tailored for the delivery of the service. Healthcare advisors completed an online training programme. Competence of the healthcare advisor was assessed via an online multiple-choice question examine and an OSCE, of which all passed.
3.5.2 Intervention Process

Eligible patients’ initial Centor Score along with medication history, was determined, by healthcare advisors, according to two of the Centor Criteria: (1) history or presence of fever; and (2) absence of cough. Patients who responded positively to one or both of these Centor Criteria were then referred to the pharmacist for further assessment (i.e. score ≥1), in the private consultation room. The pharmacist examined the patient to determine whether the patient was experiencing the remaining Centor criteria (tonsillar exudate, and/or tender anterior cervical adenopathy). Patients with a centor score of ≥3, were invited to be tested using the RADT, as per the European Society for Clinical Microbiology and Infectious Diseases guidelines. Those with a positive RADT result were informed that they were likely to be experiencing a Strep A bacterial throat infection and that antibiotic therapy could be considered by their GP, to shorten the duration of infection, however, the symptoms could resolve over the coming days of their own accord. If the RADT result was negative or the patient had a Centor Score of 1 or 2 the patient was informed that it is unlikely that they have a GABHS throat infection and it is most likely due to a virus. Over the counter pain relief and self-care advice was recommended, as appropriate. The patient was reminded, as is the norm when responding to symptoms in the pharmacy, that if their symptoms do not improve or get worse that they should see their doctor. All information was gathered on the Consultation Record Form (Appendix 5: Consultation Record Form). Upon completion of the intervention, patients were provided with a form, a letter for their doctor which contains an explanation of the service along with the results of the pharmacist examination (Appendix 6: Doctor Letter). Patients if attending their GP could provide the pharmacist examination results at the time of consultation with the GP. No letter was sent directly from the pharmacist to the GP.

At the point of referral to the pharmacist for physical examination a fee of €7.50 was charged to the patient. While the cost is relatively low, it will be considered in the analysis for those who are entitled to state funded medical care may be less likely to avail of the intervention. Therefore, participation rates for the intervention were recorded to determine the impact of the fee and the perceived value of the pharmacy led intervention.
3.5.3 Rapid Antigen Detection Test

The OSOM Strep A Test\textsuperscript{159}, the chosen RADT for the intervention, uses immunochromatographic dipstick technology with rabbit antibodies coated on a nitrocellulose membrane\textsuperscript{121}. All pharmacists were trained in the technique required for accurate use of the test through the blended training programme provided by the pharmacy chain. Using a sterile swab, a throat specimen was collected from the tonsils and the back of the throat, avoiding the teeth, gums, tongue or cheek surfaces. This throat swab sample was then extracted using a carbohydrate antigen unique to \textit{Group A Streptococcus} (GAS), which then migrates along the membrane of the dipstick. The result was visible within 5 minutes. If the test was positive for GAS a blue line appeared (Figure 3.1). The test has a specificity of 97.8\% (95\% confidence interval: 96.6-99\%) and a sensitivity of 96\% (95\% confidence interval: 94.4-97.6\%)\textsuperscript{121}. The OSOM test has been shown to be 15\% more sensitive compared to other brands of RADT and it was shown to detect more strains of GABHS at lower concentrations\textsuperscript{84}.

The accuracy of the test was dependent on the quality of the throat swab specimen obtained and previous antibiotic use\textsuperscript{158}. Throat swabs should have been taken as described above to ensure sufficient collection of streptococci, any other areas are not appropriate.

\textbf{Figure 3.1} Process for extracting bacteria from throat and potential result. Reprinted with permission of Sekisui Diagnostics, LLC.
3.6 Usual Care – Control Group

Those in the control group eligible to take part in the study, presenting to the pharmacy counter with a sore throat lasting between 3 -9 days with no symptom improvement and exhibiting no red flag symptoms underwent usual care. Usual care involved the on-duty pharmacist or a trained healthcare advisor (working under the supervision of the on-duty pharmacist) providing appropriate over the counter pain relief, self-care advice and if necessary referral to the doctor. Following this consultation the healthcare advisor completed the patient survey (Appendix 7b: Patient Survey – Control) with the patients in the control group, which involved asking patients about their symptoms including all four Centor Criteria and their body temperature was taken; no physical examination by a pharmacist was completed. An overview of intervention and usual care processes are outlined in Figure 3.2 below.
Figure 3.2 Comparison of intervention versus usual care provided in pharmacies.
3.7 Outcome Measures

Patients were followed up via telephone seven days after presenting to the pharmacy. The outcome assessor (Claire O’Neill) was blinded to the participants group status.

The primary outcomes were:

1. GP visits (attended or did not attend) and
2. antibiotic prescriptions (prescribed antibiotics or no antibiotics prescribed) at 7 days.

Secondary outcomes included:

1. Appropriateness of antibiotic prescribed in the intervention group (based on Centor score, RADT results and type of antibiotic prescribed). This is a binary outcome taking into consideration the pharmacist reported Centor score. Those with a Centor of 3 or 4 and/or a swab result which was positive, who were prescribed first line or second line treatment for the recommended duration were deemed appropriate. The recommended first line antibiotic treatment is phenoxymethylpenicillin 500mg four times daily for ten days in non-penicillin allergic patients and clarithromycin 500mg twice daily for five days is recommended first line in penicillin allergic patients. Those with a Centor score of one or two or a negative RADT, prescribed antibiotics were deemed inappropriate, as well as those with antibiotics prescribed for a shorter duration recommended as per Irish guidelines, or not a first or second line antibiotic at the appropriate dose.

2. Self reported antibiotic adherence was defined by patients stating whether they took antibiotics as prescribed by their GP or pharmacist and if they finished the antibiotic course. Patients who answered yes to both of these were considered adherent and those who stated no to one or both of these questions were classified as non-adherent.

3. Time to recovery.

4. Patient satisfaction was measured via survey following the intervention using the Likert scale. The survey also involved qualitative methods allowing patients to freely comment on their pharmacy experience.
All primary and secondary outcomes, except time to recovery and patient satisfaction are binary.

Patient demographics including; recruitment season, free healthcare status, regular attendance at GP and Centor score were recorded as potential confounders. Figure 3.3 sets out the design of the study to determine the primary outcomes.

**Figure 3.3** Summary of the study design to determine effect of intervention on proportion of patients attending GP following pharmacist advice and the number of antibiotics prescribed.

### 3.7.1 Sample Size Calculation

A previous study had indicated that approximately 40% of adults with sore throat present to their GP\(^7_4\). Using this estimate, and assuming intracluster correlation coefficient of 0.01 to allow for potential clustering we estimated that we would need 270 (135 per group) to have 90% power to detect a reduction
from 40% to 20% in the intervention group, at alpha 0.05. A total of 298 (149 per group) would allow for a 10% loss to follow-up. To detect a reduction from 40% to 20% at alpha 0.05, with 80% power, would require 91 participants per group which is a total of 182. To allow for 10% loss to follow up would require 100 participants to be recruited in each group. Therefore, to have sufficient power, each pharmacy was asked to recruit 20 consecutive participants. The observation period, during which recruitment and follow up of participants was from February 2016 to June 2017.

3.7.2 Monitoring Patient’s Health

The participants’ health was monitored in the pharmacy by or under the supervision of the pharmacist during the consultation as per usual care. If any warning symptoms appeared which were of concern to the pharmacist on duty, the patient was referred to their doctor. Follow up was carried out by a pharmacist and if the patient’s health had not improved or had worsened the patient was advised to go to their doctor. All sore throats generally resolve after 8 days. At the point of follow up it was at least 10 days after sore throat symptoms first appeared and therefore symptoms should have resolved. If patient’s symptoms at follow up had not resolved they were referred to their doctor.

3.8 Data Management

The surveys used in this study at the point of recruitment were face to face and the follow up survey was conducted via telephone.

Face to face interviews were carried out in a standardised and structured manner (Appendix 7a & 7b – Patient Survey Control & Intervention). The researcher, the pharmacy team member in the case of this study, read the questions to the patient in the order they appeared on the survey. The researcher would only go ‘off script’ to clarify the meaning of a question. For telephone interviews the researcher read from the standardised script which is provided, only going ‘off script’ to clarify a misunderstanding.
Prior to completion of the physical examination by the pharmacist, participants were asked to fill out a self report of the Centor Criteria (Appendix 7a: Patient Survey - Intervention). Participants were followed up by telephone, approximately seven days after the consultation. The outcome assessor conducted telephone interviews and was blinded to patient group.

3.8.1 Patient survey
The purpose of the patient survey was to validate a self-reported Centor Score. In the intervention group, this was obtained prior to the pharmacist examining the patient. The Centor Score results of the pharmacist examination were then compared to the self-reported Centor score. This comparison was then used to internally validate the self-reported Centor score in the control group. For the latter group, the survey captured information which includes demographics and treatment outcome in the pharmacy.

3.8.2 Patient Feedback Survey
The patient feedback survey (Appendix 7c- Patient Feedback Survey) was provided to participants in the intervention group. Participants reported their satisfaction with the service on a 5-point Likert scale, ranging from very dissatisfied to very satisfied. Participants also reported how likely it is that they would use or would recommend the service to others.

This survey was completed by the patient in the private consultation room, once the pharmacist had left the room. The patient completed the survey and placed it in an envelope which was then sealed by the participant and given to the pharmacist to send to the lead researcher. This patient satisfaction survey was not read by the pharmacist, to ensure the confidentiality of the patient.

3.8.3 Data collection, management and protection
All data was collected for the study following written consent from the participant. Data included patient demographics, self-reported sore throat
symptoms, Centor score, RADT test results, patient satisfaction, and follow up information.

Upon presentation at the pharmacy, patients were assigned a unique identifier code. The ID code was created using a pharmacy location ID, which each pharmacy was assigned, followed by the number decided by the order in which the patients presented to the pharmacy. All information gathered was kept confidential. Using the patient ID codes and the patient information, the pharmacy created a ‘key’, on an encrypted excel file spreadsheet on the password protected pharmacy computer. The ‘key’ and coded file, were sent under the supervision of the pharmacist through a password protected and encrypted programme directly to the lead researcher, in the Royal College of Surgeons. All paperwork used to create the key was kept in a locked drawer, which only the pharmacist has access to. Once information was received and confirmed, the pharmacist then destroyed the information gathered in the pharmacy for the purpose of the study, via their confidential waste process, which every pharmacy must legally follow\textsuperscript{162}. 

All pharmacy ‘keys’ were amalgamated to create a complete ‘key’ for the data, which was a password protected, encrypted file, kept in the Royal College of Surgeons Dublin.

All paperwork, including patient surveys and consultation record forms were coded in the pharmacy using the unique patient identifier code. The paperwork was then sent via a registered postal service to the Superintendent Pharmacist Office, upon which it was scanned, encrypted and sent to the lead researcher in the Royal College of Surgeons Dublin. Consent forms were also sent via this system, however, separately from the patient surveys and consultation record forms. Information was sent via a password protected electronic programme to the lead researcher. HEAnet, a secure network site which is RCSI supported, allowed information to be uploaded to which the lead researcher had access to. All hardcopies of study data were destroyed once they had been scanned electronically.

All patient data was then coded and kept in one file. This file was also password protected and encrypted. Information in the coded file was not
identifiable to anyone without the ‘key’. The ‘key’ was then deleted once analysis of information had been clarified and the investigator was happy all information was correct.

The data was encrypted and securely stored and password protected as per Data Protection Law, in electronic encrypted files, on a secure server in The Royal College of Surgeons in Ireland for 5 years. Only those involved in the study had access to the data.

3.8.4 Statistical Analysis

The baseline data are described and presented using descriptive statistics; means (standard deviations), and proportions to assess differences in the baseline characteristics of participating pharmacies and patients in the two arms. Stata Statistical Software: Release 14 (StataCorp, College Station, TX: 2015) was used for all statistical analysis.

The primary analysis was intention to treat and random effects logistic regression modelling (adjusting for clustering and baseline differences among study groups) was used to test the impact of the pharmacy led intervention on GP visits and antibiotic prescribing. Pearson’s chi squared test was used to determine statistical differences between the intervention and control groups at baseline for categorical outcomes. Missing data was dealt with via complete case analysis.

3.8.4.1 Sensitivity Analysis

The prevalence of GABHS is seasonal. In UK and Irish climates it is seen mostly in autumn and winter months. Recruitment took place across more than one season, resulting in the potential for different strains circulating in the community. Sensitivity analysis was carried out to determine any impact the two seasons may have had on data, using random effects logistic regression models (adjusting for clustering and baseline differences among study groups).
3.8.5 Process Evaluation

A process evaluation was carried out to determine the feasibility of the intervention. Intervention participation rates, response rates and reasons why patients decided to take part in the intervention were analysed. The delivery of the intervention was also considered along with patient’s history of treatment for sore throats.
4 Results

4.1 Pharmacy Profile

4.1.1 Profile of Participating Pharmacies

Twenty pharmacies were recruited to the study, however only 14 pharmacies recruited patients (5 intervention, 9 control). All 14 pharmacies were in urban settings. Of the 5 participating intervention pharmacies, four were in urban suburb shopping centres and one in a city shopping centre setting. In the control group, there were 5 pharmacies in an urban suburb shopping centre setting, one pharmacy in a non-suburb setting and 3 pharmacies located in an urban high street setting.

Three of the intervention pharmacies had two full-time and one part-time pharmacists working, with the remaining two pharmacies employing two full time pharmacists due to shorter opening hours. All pharmacies which participated had suitably trained pharmacy support staff working in the dispensary and on the healthcare counter. The profile of participating pharmacies is described in table 4.1.
Table 4.1 Profile of participating pharmacies by group.

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pharmacies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruited to study</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Recruited participants</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>GMS: Private dispensing</td>
<td>0.58–1.7</td>
<td>0.67–1.56</td>
</tr>
<tr>
<td>Average number of hours open per week</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td>Average number pharmacists per pharmacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full time</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Part time</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Average number of hours per week where two pharmacists were working simultaneously in one pharmacy</td>
<td>6 hours</td>
<td>4 hours</td>
</tr>
</tbody>
</table>

4.1.2 Profile of Non-Participating Pharmacies

Of the intervention pharmacies that failed to recruit participants, in contrast to all participating pharmacies, one was in a rural high street setting. The remaining were in similar locations to the participating intervention pharmacies; three in a suburban shopping centre and one in a city centre location. The one control pharmacy was in an urban high street setting, similar to those found in the participating control pharmacies.

Opening hours were slightly longer for those in the intervention groups with an average of 74 hours of trading hours per week and 68 hours per week in the control pharmacy, however, for both pharmacy groups the hours were shorter than the participating pharmacies. The pharmacies which did not participate following matching and the recruitment period did not affect the baseline characteristics of the pharmacies which did recruit patients.
### Table 4.2 Profile of non-participating pharmacies.

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMS: Private dispensing</td>
<td>0.7-2.1</td>
<td>0.77</td>
</tr>
<tr>
<td>Average number of hours open per week</td>
<td>74</td>
<td>68</td>
</tr>
<tr>
<td>Average number pharmacists per pharmacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full time</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Part time</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Average number of hours per week where two pharmacists were working simultaneously in one pharmacy</td>
<td>6 hours</td>
<td>2 hours</td>
</tr>
</tbody>
</table>

### 4.2 Profile of patients at initial presentation

#### 4.2.1 Demographic characteristics at initial presentation

Baseline characteristics for all patients by group are described in table 4.3. The intervention and control groups were balanced at baseline across all characteristics except time. The number of patients recruited in the intervention group was balance across both seasons. In contrast, control patients were significantly more likely to be recruited at the start of the study between February 2016 and August 2016 (70%) relative to intervention pharmacies (49%). The remaining control patients were recruited from September 2016 to June 2017 ($\chi^2 (1, N = 114) = 4.62, p = 0.03$).
Table 4.3 Characteristics of patients at initial presentation.

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group Patients %</th>
<th>Control group Patients %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35</td>
<td>100%</td>
<td>79</td>
</tr>
<tr>
<td>Season recruited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both seasons</td>
<td>17</td>
<td>49%</td>
<td>55</td>
</tr>
<tr>
<td>Season 1: Feb 2016 - Aug 2016</td>
<td>18</td>
<td>51%</td>
<td>24</td>
</tr>
<tr>
<td>Season 2: Sept 2016 – Jun 2017</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-19 years</td>
<td>2</td>
<td>6%</td>
<td>2</td>
</tr>
<tr>
<td>20-29 years</td>
<td>13</td>
<td>37%</td>
<td>30</td>
</tr>
<tr>
<td>30-39 years</td>
<td>8</td>
<td>23%</td>
<td>21</td>
</tr>
<tr>
<td>40-49 years</td>
<td>5</td>
<td>14%</td>
<td>13</td>
</tr>
<tr>
<td>50-78 years</td>
<td>7</td>
<td>20%</td>
<td>13</td>
</tr>
<tr>
<td>Average age years</td>
<td>37.03</td>
<td>14.78</td>
<td>35.34</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
<td>86%</td>
<td>54</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>14%</td>
<td>25</td>
</tr>
<tr>
<td>Have access to free GP care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>11%</td>
<td>17</td>
</tr>
<tr>
<td>No</td>
<td>28</td>
<td>80%</td>
<td>53</td>
</tr>
</tbody>
</table>

* Percentages may not add to 100% due to missing data. Significance values were determined using Chi-squared test of independence for proportions and independent sample t-test for mean age.

The mean age in the intervention group was 37 years (SD = 14.78) the first and third quartiles, 26 years and 44 years respectively with an interquartile range of 18 years (figure 4.1). The mean age of the control group was 35.3 years (SD = 13.75) with the first and third quartile 25 years and 42 years respectively and an interquartile range of 17 years.
Figure 4.1 Box plot of age by group.

A higher proportion of women presented to both intervention and control pharmacies with a sore throat. The proportion of women presenting to the intervention group was higher than the control group, however, this was not statistically significant ($\chi^2 (1, N = 114) = 3.77, p = 0.05$).

The control group had the highest percentage of patients with a medical card, with 17 patients (22%) in total (table 4.3). Patients with access to free GP care, including those with access to free medication, were not reported to be more prevalent in either group. No women reported being pregnant or breastfeeding (table 4.3).

4.2.2 Clinical profile of patients at initial presentation

The proportion of patients reporting Centor Criteria across the treatment groups are displayed in figure 4.2. Significant differences were observed across groups for the criteria of absence of cough, presence of tender lymph nodes and tonsillar exudate. Patients in the intervention group (83%) were significantly
more likely to report an absence of cough relative to the control group (OR = 3.67, 95%CI 1.28, 10.55, p = 0.02). Similarly, patients in the intervention group (65.71%) were significantly more likely to have tender lymph nodes compared to the control group (35%) (OR = 3.74, 95% CI 1.43, 9.77, p = 0.007). Again, tonsillar exudate was significantly different across treatment groups, with the intervention group (77%) more likely to report the presence of exudate (OR = 2.84, 95% CI = 1.33, 6.04, p = 0.01).

Figure 4.2 Prevalence (%) of all four Centor Criteria across treatment groups.

Approximately half (46%) of the intervention group had a Centor score of ≥3, following the pharmacist’s assessment (figure 4.3). In contrast, less than one in five (19%) of the control group had a Centor score ≥3. The intervention group had almost four times the odds of having a Centor score ≥3 relative to the control group (OR 3.91, 95% CI 1.05, 14.60, p = 0.04).
However, differences in patients Centor scores across treatment groups, may be an artefact of measurement. The Centor score for the intervention group was based on pharmacist assessment at baseline, whereas the control group was based on self-report. To determine the validity of using a self-report measure of each of the Centor Criteria, the intervention group were asked to complete a self-reported measure, prior to pharmacist assessment.

4.2.2.1 Validity of self-reported Centor Score: Comparing self-report to pharmacist assessment in intervention group

Temperature and absence of cough were recorded in the same way when using self-report or pharmacist assessment, therefore no differences were observed.

In contrast, the pharmacist assessment of swollen lymph nodes and tonsillar exudate was different to the patient assessment of same (table 4.4). Assuming the pharmacist assessment of the lymph nodes and tonsillar exudate represents the reference standard, a comparison of the self-reported tender lymph nodes and tonsillar exudate versus the pharmacist reported examination was carried out.

Figure 4.3 Proportion of patients with a Centor score ≥3 across treatment groups.
**Table 4.4** Prevalence of all four Centor Criteria, across models of assessment (self-report versus pharmacist assessment for intervention group.

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group Self-reported Patients %</th>
<th>Intervention Group Pharmacist reported Patients %</th>
<th><strong>P-value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (1 point)</td>
<td>7 20%</td>
<td>7 20%</td>
<td>N/A</td>
</tr>
<tr>
<td>No</td>
<td>28 80%</td>
<td>28 80%</td>
<td></td>
</tr>
<tr>
<td>Cough absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (1 point)</td>
<td>6 17%</td>
<td>6 17%</td>
<td>N/A</td>
</tr>
<tr>
<td>Yes</td>
<td>29 83%</td>
<td>29 83%</td>
<td></td>
</tr>
<tr>
<td>Tender lymph nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (1 point)</td>
<td>23 66%</td>
<td>23 66%</td>
<td>0.07</td>
</tr>
<tr>
<td>No</td>
<td>1 3%</td>
<td>9 16%</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>11 31%</td>
<td>3 9%</td>
<td></td>
</tr>
<tr>
<td>Tonsillar exudate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (1 point)</td>
<td>27 77%</td>
<td>18 51%</td>
<td>0.51</td>
</tr>
<tr>
<td>No</td>
<td>6 17%</td>
<td>14 40%</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3 9%</td>
<td>3 9%</td>
<td></td>
</tr>
</tbody>
</table>

*Significance values were determined using Chi-squared test of independence for proportions.*

There were 4 false positives reported by patients for self-reported tender lymph nodes. Only 17 patients’ responses, of a reported 21 matched the pharmacist examination of the lymph nodes (table 4.5). Therefore, if 81% of observations are accurate in the self-reported surveys in the intervention group, then in the control group 64 responses for tender lymph nodes are likely to be accurate.
<table>
<thead>
<tr>
<th>Table 4.5 Pharmacist assessment of tender lymph nodes compared to self-reported tender lymph nodes.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacist tender lymph nodes positive</strong></td>
</tr>
<tr>
<td>Self-report: Tender lymph nodes positive</td>
</tr>
<tr>
<td>Self-report: Tender lymph nodes negative</td>
</tr>
</tbody>
</table>

Fifteen false positives were reported for the self-reported tonsillar exudate. In total there were 29 patients self-reported tonsillar exudate which could be compared with the pharmacists for tonsillar exudate (table 4.6). Of these only 13 (45%) self-reported tonsillar exudate was reported accurately, 11 true positives and 2 true negatives. Therefore, in the control group only 35 responses are likely to be accurate.

<table>
<thead>
<tr>
<th>Table 4.6 Pharmacist assessment of tonsillar exudate compared to self-reported tonsillar exudate.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacist tonsillar exudate positive</strong></td>
</tr>
<tr>
<td>Self-report: Tonsillar exudate positive</td>
</tr>
<tr>
<td>Self-report: Tonsillar exudate negative</td>
</tr>
</tbody>
</table>

Furthermore, of 32 possible self-reported and pharmacist assessment Centor score comparisons, only 20 (57%) self-reported Centor scores matched the pharmacist assessment scoring (table 4.7). Following this if 57% of patients can accurately determine their Centor score then approximately 45 self-reported Centor scores in the control group, out of 79 observations are accurate. A p value of 0.05 was found ($\chi^2 (12, N = 33) = 20.95$), indicating a significant difference between the self-reported Centor score and the pharmacist reported Centor score.
Table 4.7 Pharmacist record of Centor ≥3 compared to self-reported Centor ≥3.

<table>
<thead>
<tr>
<th></th>
<th>Pharmacist Centor ≥3</th>
<th>Pharmacist Centor &lt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-report: Centor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Self-report: Centor</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>&lt;3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.3 Rapid Antigen Detection Test Results

There were 25 patients in the intervention group who underwent Rapid Antigen Detection Testing (RADT) (figure 4.4). Of these, 22 throat swabs were negative and 4 were positive, with 3 results missing.

![Flowchart of RADT](image)

**Figure 4.4 Flowchart of RADT.**

The proportion of patients in the intervention group for whom antibiotic treatment is indicated dropped from 46% (16 patients) based on the Centor score of ≥3, to 11% (4 patients), when RADT results were considered.
4.4 Additional patient symptoms at baseline and medication taken prior to assessment at initial presentation.

Patients reported if they were suffering additional symptoms. Those patients who reported viral symptoms such as a runny nose, headache, aching muscles and tiredness were noted. There was no significant difference between groups for viral symptoms (OR = 0.35, 95% CI 0.05, 2.66, p = 0.31).

Those in the intervention group were found to be significantly more likely to have taken medication for their sore throat (OR = 3.75, 95% CI 1.37, 10.25, p = 0.01) (table 4.8). Considering the greater severity of presentation at baseline as per the Centor score this would be expected. The proportions of type of medication taken was found to be significantly different between the groups (χ² (4, N = 63) = 9.83, p = 0.04).

Appropriate dose (OR = 11.87, 95% CI 1.44, 98.69, p = 0.02) taken was also significant which indicates that those in the intervention group were almost 12 times more likely to have taken a correct dose of medication which may have masked a fever, which at baseline, 80% of patients did not report a fever (figure 4.2).
Table 4.8 Additional symptoms reported at baseline and medication taken by patients across treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group Patients %</th>
<th>Control Group Patients %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you take any medication in the last 8 hours?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 74%</td>
<td>37 47%</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>6 17%</td>
<td>32 41%</td>
<td></td>
</tr>
<tr>
<td>If yes, what did you take?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>paracetamol</td>
<td>14 40%</td>
<td>16 20%</td>
<td>0.04</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>9 26%</td>
<td>5 6%</td>
<td></td>
</tr>
<tr>
<td>aspirin</td>
<td>3 9%</td>
<td>4 5%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 3%</td>
<td>12 15%</td>
<td></td>
</tr>
<tr>
<td>Appropriate dose of medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 60%</td>
<td>23 29%</td>
<td>0.02</td>
</tr>
<tr>
<td>No</td>
<td>1 3%</td>
<td>13 16%</td>
<td></td>
</tr>
<tr>
<td>How long have you been taking this dose?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>only one dose</td>
<td>5 14%</td>
<td>2 3%</td>
<td>0.24</td>
</tr>
<tr>
<td>one day</td>
<td>4 11%</td>
<td>11 14%</td>
<td></td>
</tr>
<tr>
<td>two days</td>
<td>5 14%</td>
<td>5 6%</td>
<td></td>
</tr>
<tr>
<td>since beginning of sore throat</td>
<td>11 31%</td>
<td>14 18%</td>
<td></td>
</tr>
</tbody>
</table>

* Percentages may not add to 100% due to missing data. Significance values were determined using Chi-squared test of independence for proportions and logistic regression analysis (adjusting for clustering) for appropriate dose of medication.

4.5 Indication for treatment and pharmacist recommendation

The intervention protocol indicated that 11% of patients in the intervention group required referral to the GP for an antibiotic prescription. In the control group 19% of patients required referral for an antibiotic prescription (figure 4.5). There was no significant difference across treatment groups, however patients in the intervention group were half as likely to have a clinical profile based on Centor
score and / or RADT which would require referral to the GP (OR = 0.58, 95% CI 0.15, 2.33, p = 0.43).

**Figure 4.5** Indication for GP referral and pharmacist recommendation.

### 4.5.1 Pharmacist recommendation

Seven patients (20%) in the intervention group were referred to the GP. Three patients had a positive swab, the pharmacist recommendation is missing for one positive swab. One patient with a positive RADT result had a Centor score of 1. Of the seven patients, 3 patients had a positive RADT result, 2 patients had a negative RADT result and 2 patients with a Centor score of 2 and 3 did not undergo RADT (table 4.9). There is no data indicating reasons as to why pharmacists deviated from the intervention protocol. Patients may have specifically requested the swab and there may have been other symptoms unrelated to the sore throat which required deferral from the protocol.

There were 11 patients (14%) in the control group referred to the GP, of which 4 patients (5%) had a self-reported Centor score ≥ 3 (table 4.9). There was no significant difference in the rate of referral between treatment groups (OR = 1.96, 95% CI 0.41, 9.35, p = 0.71). As per usual care, pharmacists and healthcare advisors in these pharmacies had no training on the Centor score this would indicate that inaccurate referral to GPs using self-reported Centor
Criteria is currently common practice. As per RADT, 3 patients were correctly referred to their GP and two were inappropriately referred to the GP, according to the clinical profile of patients recorded, which included Centor score and/or RADT result.

**Table 4.9** Pharmacist recommendation, comparing recommendation as per Centor Criteria and RADT with pharmacist action following intervention.

<table>
<thead>
<tr>
<th>Intervention Group</th>
<th>Centor treatment indication (Patients, %)</th>
<th>Pharmacist action (Patients, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centor 1 7 20% No referral</td>
<td>3 9% No referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 6% RADT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 6% Missing</td>
<td></td>
</tr>
<tr>
<td>Centor 2 12 34% No referral</td>
<td>3 9% No referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 3% Referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 23% RADT</td>
<td></td>
</tr>
<tr>
<td>Centor 3 10 29% RADT</td>
<td>9 26% RADT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 3% Referral</td>
<td></td>
</tr>
<tr>
<td>Centor 4 6 17% RADT</td>
<td>6 17% RADT</td>
<td></td>
</tr>
<tr>
<td>RADT +ve 4 11% Referral</td>
<td>3 9% Referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 3% Missing</td>
<td></td>
</tr>
<tr>
<td>RADT -ve 18 51% No referral</td>
<td>14 43% No referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 6% Referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 6% Missing</td>
<td></td>
</tr>
<tr>
<td><strong>Control Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR - Centor 1 27 34% No referral</td>
<td>3 4% Referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 27% No referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 4% Missing</td>
<td></td>
</tr>
<tr>
<td>SR - Centor 2 29 37% No referral</td>
<td>4 5% Referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 27% No referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 5% Missing</td>
<td></td>
</tr>
<tr>
<td>SR - Centor 3 12 15% Referral</td>
<td>3 4% Referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 9% No referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 3% Missing</td>
<td></td>
</tr>
<tr>
<td>SR - Centor 4 3 4% Referral</td>
<td>1 1% Referral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 3% Missing</td>
<td></td>
</tr>
</tbody>
</table>
4.6 Summary of results at initial presentation

The profile of participating pharmacies and participants was similar at baseline except for season recruited ($\chi^2 (1, N = 114) = 4.62, p = 0.03$). The clinical profile of patients across treatment groups was found to be significantly more severe (OR 3.91, 95% CI 1.05, 14.60, $p = 0.04$) in the intervention group, which may have been due to an artefact of measurement, with 57% of patients accurately self-reporting a Centor score $\geq 3$ in the intervention group.

Sixteen patients (46%) in the intervention group had a Centor $\geq 3$. Following RADT, four patients (11%) in the intervention who had a positive RADT result should have been referred to the GP, however, 7 patients (20%) from this group were referred. In the control group 15 patients (19%) had a clinical profile (Centor $\geq 3$), however, 11 patients (14%) of patients were referred to the GP across all self-reported Centor scores 1-4.

4.7 Post intervention results

One hundred and fourteen patients were recruited to the study between February 2016 to June 2017. There were 35 patients recruited to the intervention; five were lost to follow up and one refused to participate in the follow up interview, resulting in a sample of 29 patients. Seventy-nine patients were recruited to the control group with eleven lost to follow up and two refused to participate in the follow up, resulting in a sample of 66 patients. This is markedly below the proposed number of 149 patients per arm which was required for 90% power, or 100 patients per arm for 80% power to detect a treatment effect on attendance at GP and antibiotic prescribing.

A total drop-out rate of 17% resulted. For the intervention group 35 patients were recruited and 29 were followed up. The lost to follow up rate was 14% and the refusal rate was 3%. The control group had a lost to follow up rate of 14% and a refusal rate of 3%, with 79 patients recruited and 66 followed up. This is depicted in figure 4.6.
Figure 4.6 Flow diagram of study, including number of patients recruited in each arm and those lost to follow up.
4.7.1 Patient demographics post intervention

Patient demographics at follow-up following drop out were not found to be significantly different across treatment groups (table 4.10). Patient group profiles were similar at baseline, with most patients aged under 40 years and female.

**Table 4.10** Baseline characteristics of participants followed up and lost to follow-up for primary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Followed up</th>
<th>Lost to follow up</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention Group Patients %</td>
<td>Control group Patients %</td>
<td>Intervention Group Patients %</td>
</tr>
<tr>
<td>Season recruited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both seasons</td>
<td>29 83%</td>
<td>66 84%</td>
<td>6 17%</td>
</tr>
<tr>
<td>Season 1: Feb 2016 - Aug 2016</td>
<td>13 37%</td>
<td>46 58%</td>
<td>4 11%</td>
</tr>
<tr>
<td>Season 2: Sept 2016 – Jun 2017</td>
<td>16 46%</td>
<td>20 25%</td>
<td>2 6%</td>
</tr>
<tr>
<td>Age category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 years</td>
<td>2 6%</td>
<td>2 3%</td>
<td></td>
</tr>
<tr>
<td>20-29 years</td>
<td>10 29%</td>
<td>23 29%</td>
<td>3 9%</td>
</tr>
<tr>
<td>30-39 years</td>
<td>7 20%</td>
<td>19 24%</td>
<td>1 3%</td>
</tr>
<tr>
<td>40-49 years</td>
<td>4 11%</td>
<td>12 15%</td>
<td>1 3%</td>
</tr>
<tr>
<td>50-78 years</td>
<td>6 17%</td>
<td>10 13%</td>
<td>1 3%</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>25 71%</td>
<td>46 58%</td>
<td>5 14%</td>
</tr>
<tr>
<td>Male</td>
<td>4 11%</td>
<td>20 25%</td>
<td>1 3%</td>
</tr>
<tr>
<td>Have a medical card?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 9%</td>
<td>11 14%</td>
<td>1 3%</td>
</tr>
<tr>
<td>No</td>
<td>27 77%</td>
<td>55 70%</td>
<td>1 3%</td>
</tr>
</tbody>
</table>

*Percentages may not add to 100% due to missing data. Significance values were determined using Chi-squared test of independence for proportions.*
4.8 Outcomes

4.8.1 GP visits post intervention

Analysis of the data to determine if the intervention reduced GP visits and antibiotic prescribing was carried out using random effects logistic regression analysis, adjusting for clustering, season and Centor ≥3. The null hypothesis states that the intervention has no effect on GP visits and antibiotic prescribing with α=0.05. There was no difference in attendance at GPs across groups (OR = 1.27, 95% CI 0.35, 4.57, p = 0.71) (table 4.11).

Table 4.11 Primary outcome: attending GP, random effects logistic regression, adjusted for clustering firstly, followed by season and Centor score ≥3.

<table>
<thead>
<tr>
<th>Outcome = Visit doctor</th>
<th>Odds Ratio</th>
<th>Standard error</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>1.24</td>
<td>0.68</td>
<td>0.42</td>
<td>3.63</td>
</tr>
<tr>
<td>Intervention</td>
<td>1.27</td>
<td>0.83</td>
<td>0.35</td>
<td>4.57</td>
</tr>
<tr>
<td>Season</td>
<td>1.08</td>
<td>1.16</td>
<td>0.13</td>
<td>8.90</td>
</tr>
<tr>
<td>Centor ≥3</td>
<td>3.10</td>
<td>2.05</td>
<td>0.84</td>
<td>11.36</td>
</tr>
</tbody>
</table>

At the time of follow up 7 patients (24.14%) in the intervention group and 14 patients in the control group (21.12%) had visited their GP (table 4.12). Treatment choice by patient was then compared to the recommendation by the pharmacist following the interaction in the pharmacy. Among those in the intervention group, three patients attended the GP as recommended. Similarly, in the control group three attend the GP as recommended by the pharmacist (table 4.11).
Table 4.12 GP visits by patients following pharmacist advice.

<table>
<thead>
<tr>
<th>Patient visited GP</th>
<th>Intervention pharmacist recommended visit GP</th>
<th>Control pharmacist recommended visit GP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes Patients (%)</td>
<td>No Patients (%)</td>
</tr>
<tr>
<td>Yes</td>
<td>3 10%</td>
<td>12 41%</td>
</tr>
<tr>
<td>No</td>
<td>4 14%</td>
<td>4 14%</td>
</tr>
</tbody>
</table>

*Percentages may not add to 100% due to missing data.

Consultation outcome indicates that the pharmacist referred 7 patients to their GP, however, 15 went. These patients included two of the four patients who tested positive for GABHS and three patients who tested negative for GABHS and were not referred to their GP by the pharmacist.

4.8.2 Antibiotic prescription post intervention

While attending the GP, no patient had their throat swabbed. No throat culture or rapid antigen detection testing was carried out for patients. Six patients (21%) in the intervention group and 13 patients (20%) in the control group were prescribed antibiotics for their sore throat.

Random effects logistic regression analysis, adjusting for clustering was used, to determine an association between the intervention and antibiotic prescribing. The results are reported in table 4.13.
Table 4.13 Primary outcome: antibiotic prescription, random effects logistic regression, adjusting for clustering, to determine an association between the intervention and antibiotic prescribing.

<table>
<thead>
<tr>
<th>Antibiotic prescription</th>
<th>Control Group</th>
<th>Intervention Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td>21%</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2%</td>
<td></td>
<td>3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Odds Ratio</th>
<th>Standard error</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.46</td>
<td>0.58</td>
<td>0.04</td>
<td>5.37</td>
<td>0.54</td>
</tr>
</tbody>
</table>

The results show that there is no significant association between the intervention and antibiotic prescribing with a p value of 0.54.

Adjusting for season antibiotic prescribing was not significant different across treatment groups (p = 0.54) (table 4.14).

Table 4.14 Primary outcome: antibiotic prescription, random effects logistic regression analysis adjusting for clustering and season.

<table>
<thead>
<tr>
<th>Outcome: Antibiotic prescribed</th>
<th>Odds Ratio</th>
<th>Standard error</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>0.51</td>
<td>0.56</td>
<td>0.06</td>
<td>4.35</td>
</tr>
<tr>
<td>Season</td>
<td>1.24</td>
<td>1.02</td>
<td>0.24</td>
<td>6.27</td>
</tr>
</tbody>
</table>

All patients took the antibiotics. One patient (3%) in the intervention group and three patients (5%) in the control group were told to wait a few days to see if the sore throat improved or got worse before starting the antibiotic.

4.8.3 Appropriateness of GP visits post intervention without RADT result

Figure 4.7 shows the proportion of patients by group according to the Centor score, for the intervention group, and self-reported Centor score for the control group who received pharmacist advice following presentation in the pharmacy and whether they visited their GP.
Figure 4.7 Flow chart by group of patients with Centor score, for the intervention group and self-reported Centor score for control group, of <3 or ≥3 following pharmacist advice.
There was no significant difference within groups as to whether patients visited their GP based on the Centor score for the intervention group and self-reported Centor score for the control group (table 4.15).

**Table 4.15** Patient attendance at the GP as per Centor score for intervention group and self-reported Centor score for control group.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th></th>
<th>Control</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 3</td>
<td>≥ 3</td>
<td>&lt; 3</td>
<td>≥ 3</td>
</tr>
<tr>
<td>Attend GP</td>
<td>4 (14%)</td>
<td>3 (10%)</td>
<td>8 (14%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>No GP</td>
<td>12 (41%)</td>
<td>7 (24%)</td>
<td>38 (68%)</td>
<td>7 (13%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>Standard error</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>1.13</td>
<td>0.84</td>
<td>0.26</td>
<td>4.83</td>
</tr>
</tbody>
</table>

Table 4.16 shows the number of patients as per Centor score for the intervention and self-reported Centor for the control group, referred to the GP by the pharmacist. The pharmacist advice based on the Centor Criteria and irrespective of the RADT result was not found to make a significant difference on the proportion of appropriate appointments ($\chi^2 (1, N = 16) = 2.29, p = 0.131$). However, 62.02% of patients in the intervention group and 82.14% of patients in the control group were referred or not referred to their GP appropriately by the pharmacist.

**Table 4.16** Patients referred or not referred to the GP, as appropriate for an antibiotic as per the Centor Criteria, irrespective of RADT result in the intervention.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th></th>
<th>Control</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 3</td>
<td>≥ 3</td>
<td>&lt; 3</td>
<td>≥ 3</td>
</tr>
<tr>
<td>Referred to GP as per Centor</td>
<td>Yes</td>
<td>13 (45%)</td>
<td>5 (17%)</td>
<td>40 (71%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>2 (7%)</td>
<td>5 (17%)</td>
<td>8 (14%)</td>
</tr>
</tbody>
</table>
4.8.4 Secondary Outcomes

4.8.4.1 Appropriateness of antibiotic prescribed

Appropriateness of antibiotic prescribed was defined according to table 4.17.

Table 4.17 Requirements for deeming antibiotic prescription appropriate.

<table>
<thead>
<tr>
<th>First line antibiotic</th>
<th>Phenoxy methylpenicillin</th>
<th>Clarithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended dose</td>
<td>500mg</td>
<td>250-500mg</td>
</tr>
<tr>
<td>Recommended intervals</td>
<td>Four times daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Recommended duration</td>
<td>10 days</td>
<td>5 days</td>
</tr>
<tr>
<td>Clinical profile at baseline</td>
<td>Positive RADT (intervention)</td>
<td>Positive RADT (intervention)</td>
</tr>
<tr>
<td></td>
<td>Centor ≥3 (control)</td>
<td>Centor ≥3 (control)</td>
</tr>
</tbody>
</table>

At follow-up, there were 12 patients (92%) in the control group and 5 patients (83%) in the intervention group who started the antibiotic on the day they saw the GP, only 1 patient in each group carried out the wait and see approach (table 4.18).

The proportions of type of antibiotic prescribed did not differ across groups ($\chi^2 (4, N = 19) = 1.41, p = 0.84$). First line treatment for pharyngitis, phenoxy methylpenicillin, was prescribed to approximately one third of patients in the intervention (33%) and in the control group (31%) (table 4.18). Cephalosporins were the second largest group of antibiotics prescribed to patients (26%). Amoxicillin was also prescribed to two patients (15%) in the control group and one patient (17%) in the intervention group.
Most antibiotics prescribed to patients were at appropriate intervals (table 4.19). In 22% of cases the antibiotics prescribed were at inappropriate intervals. Inappropriate intervals are defined as those which are not prescribed as per treatment guidelines, to achieve therapeutic levels. Figure 4.7 describes the appropriateness of each element of the antibiotic prescribed and does not include the clinical profile of the patient.

Patients were prescribed antibiotics for durations from 5 days to 10 days (table 4.19). One patient in the intervention group and two patients in the control group were prescribed phenoxymethylpenicillin for 10 days, as per guidelines. In the intervention group, according to the type of antibiotic prescribed 50% of patients were prescribed appropriate durations and in the control group 25% of patients received appropriate durations of prescribed antibiotics (figure 4.8).
Table 4.19 Details of prescription of antibiotic, including interval dosing of antibiotics, duration they were prescribed and the appropriateness of duration.

<table>
<thead>
<tr>
<th>Follow up Survey Responses</th>
<th>Intervention Group Patients %</th>
<th>Control Group Patients %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Took the antibiotics at:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate intervals</td>
<td>1 17%</td>
<td>3 25%</td>
<td></td>
</tr>
<tr>
<td>Inappropriate intervals</td>
<td>5 83%</td>
<td>8 67%</td>
<td>0.677</td>
</tr>
<tr>
<td>Unsure</td>
<td></td>
<td>1 8%</td>
<td></td>
</tr>
<tr>
<td>Number of days they were taken</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 days</td>
<td>2 33%</td>
<td>2 17%</td>
<td>0.129</td>
</tr>
<tr>
<td>&gt; 5 days</td>
<td>1 17%</td>
<td>7 58%</td>
<td></td>
</tr>
<tr>
<td>7 days</td>
<td>1 17%</td>
<td>3 25%</td>
<td></td>
</tr>
<tr>
<td>10 days</td>
<td>2 33%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate duration of antibiotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 50%</td>
<td>3 25%</td>
<td>0.289</td>
</tr>
<tr>
<td>No</td>
<td>3 50%</td>
<td>9 75%</td>
<td></td>
</tr>
</tbody>
</table>

*Significance values were determined using Chi-squared test of independence for proportions for appropriate intervals and number of days taken and logistic regression analysis (adjusting for clustering) for appropriate antibiotic duration.

Figure 4.8 Appropriate antibiotic prescription including first or second line treatment, intervals and duration of antibiotic and all three combined. Significance values were determined using random effects logistic regression analysis adjusting for clustering.
Figure 4.9 shows the percentage of antibiotics which were prescribed inappropriately to patients considering the patients self-reported Centor score in the control group, pharmacist reported Centor score and RADT results in the intervention group, the name of the antibiotic prescribed, the dose and the duration of antibiotic. One patient in the intervention group out of a total of 6 patients who were prescribed antibiotics were prescribed antibiotics appropriately. This number was lower in the control group at 8%.

**Figure 4.9** Appropriate prescription of antibiotic based on guidelines for treatment of pharyngitis considering patients’ clinical profile – following the intervention (Centor and RADT) and as per SR-Centor score.

Those in the intervention group were twice as likely to be prescribed antibiotics appropriately than those in the control group (OR = 2.2, 95% CI 0.12, 39.49, p = 0.59), however, this was not found to be significant.
4.8.4.2 Patient reported antibiotic adherence

Patients were then asked did they finish the course of antibiotics prescribed. Figure 4.10 shows that most patients finished the course. In the control group, 1 patient (8%) did not complete the course and in the intervention again 1 patient (17%) did not complete the antibiotic course. Of the 19 that were asked ‘Was this how the GP or pharmacist told you how to take the antibiotics’ one patient in the control group responded ‘no’. There was no significant difference found between groups with an odds ratio of 1 determined.

![Bar chart of patient reported antibiotic adherence.](image)

**Figure 4.10** Bar chart of patient reported antibiotic adherence.

4.8.4.3 Time to recovery

The majority of patients’ sore throats lasted less than ten days. Patients’ sore throats ranged from less than four days to longer than ten days (table 4.20). In the intervention group 8 patients 30% reported a similar duration. In the control group 26 patients (41%) reported it lasting less than seven days. There were no significant differences (>0.05) between groups for duration of sore throats ($\chi^2 (3, N=90) = 1.18, p = 0.76$).

Two patients in the intervention group and four patients in the control group stated that they were still suffering from a sore throat at follow up. The cost of the GP was cited by one patient in the control group as to why they had
not attended and lack of time to attend the doctor were cited by both one patient in the intervention and one in the control. The remaining patients had stated no reason as to why they did not attend their GP.

Table 4.20 Time to recovery of patients.

<table>
<thead>
<tr>
<th>Follow up Survey Responses</th>
<th>Intervention Group Patients %</th>
<th>Control Group Patients %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still have a sore throat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 6%</td>
<td>4 5%</td>
<td>0.88</td>
</tr>
<tr>
<td>No</td>
<td>27 77%</td>
<td>62 78%</td>
<td></td>
</tr>
<tr>
<td>Since the beginning of your sore throat, how many days did the sore throat last?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4 days</td>
<td>4 11%</td>
<td>7 9%</td>
<td>0.76</td>
</tr>
<tr>
<td>≤7 days:</td>
<td>8 23%</td>
<td>26 33%</td>
<td></td>
</tr>
<tr>
<td>≤10 days</td>
<td>7 20%</td>
<td>13 16%</td>
<td></td>
</tr>
<tr>
<td>&gt;10 days</td>
<td>8 23%</td>
<td>17 22%</td>
<td></td>
</tr>
</tbody>
</table>

*Percentages may not add to 100% due to missing data. Significance values were determined using random effects logistic regression analysis adjusting for clustering for still have a sore throat and Chi-squared test of independence for proportions for duration of sore throat.

4.8.4.4 Treatment Choice Following Pharmacy Visit

Treatment choice by group is listed in table 4.21. Treatment choice for both groups was predominantly over the counter medication, with approximately three-quarters of patients in both treatment groups choosing this method either solely or in combination with other methods. These OTC treatment methods included sprays for sore throats and analgesia such as paracetamol and ibuprofen (table 4.21).

Self-management methods were used by 22 patients (24%). These methods included gargling with salt and water or taking a warm honey and lemon drink. Some patients who visited the GP also used over the counter treatments and, or, self-management methods.
Table 4.21 Details treatment choice from follow up survey carried out with all patients, with researcher blinded.

<table>
<thead>
<tr>
<th>Follow up Survey Responses</th>
<th>Intervention Group Patients %</th>
<th>Control Group Patients %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OTC treatment: more than one treatment possible</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OTC spray</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>OTC lozenge</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Paracetamol</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>other type of OTC medicine</td>
<td>3</td>
</tr>
<tr>
<td>Treatment with self-management methods:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>salt and water gargle</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>honey drink</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Other self-management</td>
<td>0</td>
</tr>
</tbody>
</table>

* Percentages may not add to 100% due to missing data.

4.9 Process Evaluation

4.9.1 Patient recruitment

Pharmacists in pharmacies which did not recruit patients were contacted at intervals throughout the recruitment process to determine if they were actively attempting to recruit study participants. Response rate data was collected from 6 pharmacies (43%). The response rate for the intervention and control groups are shown in table 4.22 and 4.24.

Those in the intervention who refused to take part in the intervention service cited the following reasons; they had a medical card and they would go to the GP instead, they could not wait to see the pharmacist and they already had an appointment with the doctor (table 4.22). This could indicate that the €7.50 fee which was charged at this point may have been a deterrent for patients. The participation rate in the intervention was 60.53% in one pharmacy location (1) and 100% in another pharmacy location (2), with an average of 80.27%, which were the only intervention pharmacies to record data for this.
Table 4.22 Intervention participation and study response rate for two pharmacies which recorded this data.

<table>
<thead>
<tr>
<th>Pharmacy</th>
<th>Asked to take part in service intervention</th>
<th>Asked to take part in study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. asked</td>
<td>No. agreed</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

In part one of the intervention patients stated why they chose the service. A number of patients (51.43%) stated that they referred themselves to the service following signage in the pharmacy. Out of the five reasons listed on the form as to why patients chose the service only three were chosen; self-referral (51.43%), pharmacy team recommendation (28.57%) and in 5 cases (14.29%), patients were recommended it by a family member or friend (table 4.23).

Table 4.23 Details recorded on the consultation record form in the intervention pharmacies.

<table>
<thead>
<tr>
<th>Patient's reason for choosing service</th>
<th>Total Intervention Patients %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-referral</td>
<td>18</td>
</tr>
<tr>
<td>Referred by friend or family member</td>
<td>5</td>
</tr>
<tr>
<td>Pharmacy team recommendation</td>
<td>10</td>
</tr>
</tbody>
</table>

* Percentages may not add to 100% due to missing data.

There was an average response rate for the study of 57.61% from those who were eligible for the study who were taking part in the intervention. Reasons cited for not consenting to the study included time pressure and simply that they did not want to participate.

Response rates varied in season 2 for which data is more complete, from 3.85% to 50%. Reasons cited for patient refusal to participate in the study in the
control group included: time, use of antibiotics, and they did not want to be contacted following the consultation in the pharmacy.

**Table 4.24** Response rate data for patient recruitment in 4 control pharmacies.

<table>
<thead>
<tr>
<th>Pharmacy</th>
<th>Season 1: February 2016-August 2016</th>
<th>Season 2: September 2016-June 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. asked</td>
<td>No. agreed</td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Missing</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Missing</td>
<td>14</td>
</tr>
</tbody>
</table>

4.9.2 Delivery of intervention to patients

No patients exhibited red flag symptoms at part 2 of the consultation in the intervention, and, therefore were not referred to the GP at this point. Some pharmacists deviated from the study protocol and swabbed patients who had Centor scores of 1 and 2, they also referred patients with a negative RADT result or a Centor score of 1 or 2. There are no details as to why this occurred. No adverse events were recorded during the intervention or at follow up in both groups.

4.9.3 Patient Sore Throat History at Follow Up

History of past sore throat experience was gathered for all patients at follow up. Patients were asked if they suffer frequently from sore throats (table 4.25). Those who stated yes, were then asked how often. Answers varied considerably from once a year to more than four times per year.

The differences between the intervention and the control group was not found to be significant for treatment history of sore throat previously suffered by patients, with most patients in both groups attending the pharmacy for treatment (p = 0.08) (table 4.25). Patients who stated that in the past they had usually gone to the GP for their sore throat were asked if they were prescribed antibiotics each time they went. In the intervention 12 patients (71%) and in the
control group 5 patients (26.32%) stated yes. This was a significant difference indicating that those in the intervention group were 6.7 time more likely to have attended their GP and received antibiotics from their doctor in the past for a sore throat (95% CI 2.00, 22.56, p = 0.002).

**Table 4.25 Responses to follow up survey by all patients.**

<table>
<thead>
<tr>
<th>Follow up Survey Responses</th>
<th>Intervention group Patients %</th>
<th>Control Group Patients %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequently suffer from sore throats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 37%</td>
<td>28 35%</td>
<td>0.87</td>
</tr>
<tr>
<td>No</td>
<td>16 46%</td>
<td>35 44%</td>
<td></td>
</tr>
<tr>
<td>Number of times in the past year suffered from a sore throat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once</td>
<td>13 37%</td>
<td>21 27%</td>
<td>0.93</td>
</tr>
<tr>
<td>twice</td>
<td>4 11%</td>
<td>14 18%</td>
<td></td>
</tr>
<tr>
<td>three times</td>
<td>4 11%</td>
<td>13 16%</td>
<td></td>
</tr>
<tr>
<td>four times</td>
<td>2 6%</td>
<td>5 6%</td>
<td></td>
</tr>
<tr>
<td>&gt;4 times</td>
<td>2 6%</td>
<td>6 8%</td>
<td></td>
</tr>
<tr>
<td>How have you treated sore throats in the past?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gone to GP</td>
<td>12 41%</td>
<td>10 15%</td>
<td>0.08</td>
</tr>
<tr>
<td>Maybe gone to GP depending on severity</td>
<td>1 3%</td>
<td>1 2%</td>
<td></td>
</tr>
<tr>
<td>Gone to pharmacy</td>
<td>22 76%</td>
<td>55 83%</td>
<td></td>
</tr>
<tr>
<td>Used self-management methods</td>
<td>4 14%</td>
<td>13 20%</td>
<td></td>
</tr>
<tr>
<td>Suffer from sore throats frequently, how would always treat sore throat – yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26 87%</td>
<td>51 77%</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5 29%</td>
<td>14 74%</td>
<td></td>
</tr>
<tr>
<td>Usually prescribed antibiotics from GP when present with sore throat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 71%</td>
<td>5 26%</td>
<td>0.002</td>
</tr>
<tr>
<td>No</td>
<td>5 29%</td>
<td>14 74%</td>
<td></td>
</tr>
</tbody>
</table>

* Percentages may not add to 100% due to missing data. Significance values were determined using random effects logistic regression analysis adjusting for clustering for binary outcomes and Chi-squared test of independence for proportions for number of sore throats in the past year and treatment of sore throats.
Random effects logistic regression analysis, adjusting for clustering and significant baseline characteristics (suffering sore throats frequently and history of past sore throat treatment from the doctor), showed that those in the intervention group were three times more likely to visit the doctor (OR = 3.03, 95% CI 0.82, 11.24, p = 0.10) if they had previously visited their GP for sore throats. Those in the intervention had an odds ratio of 1.63 (95% CI 0.54, 4.87, p = 0.38) of visiting the doctor if they suffered frequently from sore throats (table 4.26). This was not significant with a p-value of 0.07. Therefore, those who suffer frequently from sore throats and who attended their GP in the past for sore throat treatment are not likely to be patient drivers for visiting the GP.

**Table 4.26** Primary outcome: GP visits, random effects logistic regression analysis, adjusting for clustering, frequently suffer from sore throat and past attendance at GP for sore throat.

<table>
<thead>
<tr>
<th>Outcome = Visit doctor</th>
<th>Odds Ratio</th>
<th>Standard error</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>0.31</td>
<td>0.20</td>
<td>0.09</td>
<td>1.09</td>
</tr>
<tr>
<td>Suffer frequently</td>
<td>1.63</td>
<td>0.91</td>
<td>0.54</td>
<td>4.87</td>
</tr>
<tr>
<td>Past treatment doctor</td>
<td>3.03</td>
<td>2.03</td>
<td>0.82</td>
<td>11.24</td>
</tr>
</tbody>
</table>

**4.10 Patient Satisfaction**

Patient satisfaction was reported at different time points during the study. Immediately after completing the intervention, patients were left to complete a Patient Satisfaction Survey in the consultation room in private.

At follow up several patients commented on the service they received from the pharmacy they attended. This occurred at the end of the survey when patients were asked if they had any comments or questions they would like to make or ask. Both types of feedback are now described.
4.10.1 Patient Feedback Survey

Following completion of the intervention with the pharmacist patients were asked to complete a satisfaction survey. There were 34 patients who completed the survey out of the 35 patients who agreed to take part in the study.

For the question ‘How satisfied were you with the service?’ patients used only two responses out of five on the Likert scale, very satisfied and satisfied with 29 patients (85%) and 5 patients (15%) choosing them respectively (figure 4.11). The same responses were received for the statement ‘The pharmacist answered any questions you had’.

All 34 patients (100%) stated that the pharmacist explained things in an easy to understand way.

Patient satisfaction was high also for the pharmacist addressing all the patients’ symptoms, with 82% stating very satisfied and 18% stating satisfied on the Likert scale (figure 4.12).
Figure 4.12 Proportion of patients who were satisfied that all their symptoms were addressed.

Most patients (62%) stated that they were very confident managing their symptoms based on the advice they had received in the consultation and 26% stating that they were confident. There were 3 patients (9%) who were neutral and one patient (3%) was very uncertain (figure 4.13).

Figure 4.13 Patients’ confidence on how to manage their symptoms based on the advice given in the pharmacy.
No appointments were made by any of the patients prior to attending the pharmacy. Most patients, 94%, waited less than 10 minutes to see the pharmacist. There were 11 patients (32%) who did not wait at all to see the pharmacist and 13 patients (38%) who waited less than 5 minutes. There were only 2 patients (6%) who waited longer than 10 minutes to see the pharmacist.

All patients were happy with the privacy they received with 31 patients (91%) stating they were very satisfied and 3 patients (9%) stating they were satisfied.

Patients found out about the service from different sources, the main one being in the pharmacy (58%). Patients also heard about it through advertising (15%), a friend or relative (15%), referred from another pharmacy (6%) or online (3%).

Patients stated that they chose to take part in the service due to convenience (41%), because they wanted to know if they needed to go to the GP (35%), they did not want to pay to see the GP (24%) and, because they trusted the pharmacist (24%) (figure 4.14).

![Figure 4.14 Reasons why patients chose the service.](image_url)
When asked if they would use the service again in the future, 32 patients (94%) responded yes and 2 patients (6%) stated that they didn’t know. All patients (100%) did state that they would recommend the service.

Following the satisfaction survey patients were asked to write any other comments they had on the service. The following comments were received:

“The service is excellent already”

“Think this is a very useful service and would use it in the future if it becomes permanent”

“It would be handy if this service and others were available. Thank you”

“Quick, extremely helpful, all round great service”

“A very practical service, thank you”

“Pharmacist and healthcare assistant were amazing”

These comments are all positive and mirror those which were received during the follow up survey.

4.10.2 Follow up survey comments

The following were comments made by patients during follow up when asked if they had any further comments they would like to make, which are divided into the control group and the intervention group.

**Control group comments:**

“Good service when he was in the pharmacy”

“Great to be told you’re doing the right thing and to keep doing what you’re doing. Very reassuring.”

“Great staff in Boots”

“Great not to have to go to the GP”

“Really great service, the pharmacy team are fantastic”

“Really nice colleague who helped. They gave great advice”
“Very happy with the girl in Boots, I really appreciated her help”

“The girl was really nice and was very helpful”

**Intervention group comments:**

“Glad I went to the pharmacy”

“Very grateful to Boots. Great service”

“Really helpful and good service. Would never have gargled Disprin, which pharmacist recommended and was very useful.”

“Very pleased with the service in the pharmacy. Woman treating was very helpful. Great to have the service in the pharmacy.”

“Service is really great. It really helps you focus on how you need to treat your symptoms”

All comments from both groups are extremely positive. There were no negative comments made by any of the patients who were followed up.
5 Discussion

5.1 Summary of main findings

The aim of this pilot non-randomised parallel controlled trial was to determine the feasibility of the intervention and the impact of a community pharmacy led intervention on GP visits and antibiotics prescribing. The results of this study showed that the intervention, the Sore Throat Test and Treat Service, did not have a significant impact on either GP visits or antibiotic prescribing.

5.1.1 Results of initial presentation characteristic

Pharmacies in both intervention and control groups had similar characteristics. While the groups were unbalanced (5 intervention pharmacies, 9 control pharmacies) the pharmacies in both groups had similar dispensing ratios of GMS to private prescriptions and were based in similar settings, all of which were urban and in areas with high footfall, such as shopping centres and high street locations.

The failure of pharmacies to recruit patients may have been due to a number of reasons. Pharmacies in both the intervention and control pharmacy groups who did not recruit patients had slightly shorter opening hours than those who recruited patients. In addition, there were fewer hours during the week in which pharmacists overlapped compared to the intervention and control pharmacies which recruited patients. Other factors such as the financial environment and administrative workload may have had an impact on patient recruitment also due to time which pharmacists could dedicate to recruiting patients. These factors would have been similar across all pharmacies.

Demographic characteristics at baseline and at follow up were similar across treatment groups. The majority of patients were reported to be younger, with the majority of patients under 40 years of age. This is similar to validation and prevalence studies which have reported mean ages of 40 years \(^{95,97,68,163}\). The majority of participants were female. While this was not found to be significant across treatment groups \((\chi^2 (1, N = 114) = 3.77, p = 0.05)\), it allows for the possibility of bias to be introduced in the findings.
There were no reports of a virulent strain circulating in either season by the Health Protection Surveillance Centre. However, a significant difference in recruitment of patients, ($\chi^2 (1, N = 114) = 4.62, p=0.03$), was found between treatment groups across the two seasons, February 2016 to August 2016 and September 2016 to June 2017. In the control group one third of the patients (30%) were recruited in season 2. In the intervention group, similar numbers were recruited across seasons. There is no documentation to state why this may have been the case.

5.1.2 Clinical profile of patients at initial presentation

Overall patients presented with more severe symptoms in the intervention group (OR 3.91, 95% CI 1.05, 14.60, p = 0.04), compared to the control group. Specifically (OR = 3.67, 95%CI 1.28, 10.55, p = 0.02), tender lymph nodes (OR = 3.74, 95% CI 1.43, 9.77, p = 0.007) and tonsillar exudate (OR = 2.84, 95% CI = 1.33, 6.04, p = 0.01) were more prevalent in the intervention group. Patients who underwent the intervention were almost four times more likely to have a clinical profile which warranted an antibiotic prescription, i.e. a Centor score ≥3. The significance of this is most likely due to the initial pre-screening of the patient, by the healthcare assistant in the pharmacy which occurs prior to the pharmacist consultation. This screening process does not occur during usual care in pharmacies and therefore, the intervention identifies those who are more at risk of suffering from a GABHS infection, which may require referral.

However, patients’ self-reported Centor score was not reliable for the control group with 57% of the intervention group accurately determining their Centor score, using the pharmacist assessment as the reference standard. Patients in the intervention group struggled to recognise swollen lymph nodes, with less than half of patients (38%) describing the presence or absence of tonsillar exudate to match the pharmacist examination report. This is in contrast to findings published by Lindgren et al., which found that doctors and patients in a study of 320 patients were able to agree to a moderate extent on patient reported symptoms75.
The Rapid Antigen Detection Testing (RADT) did reduce the number of patients requiring referral to the GP from 46% with the Centor score to 11%, a 34% reduction. Point of Care Testing (POCT) kits such as the RADT are developed to aid rapid diagnosis of conditions in a healthcare setting, avoiding the need for blood cultures, which could take 48 hours. Rapid Antigen Diagnostic Testing for the detection of GABHS pharyngitis in combination with the Centor score has been shown to reduce antibiotic prescriptions by up to 40%. If patients were to follow pharmacist recommendations as per the intervention protocol, GP visits could be reduced by one-third (34%) which is similar to previously published research. It also highlights the need for efficiencies to be made in the communication and referral pathways between healthcare professionals. Patients may not provide GPs with the necessary information in order to make an informed decision.

Following the intervention patients were half as likely to have a Centor score or RADT result which required referral to their GP for further evaluation and an antibiotic prescription (OR = 0.58, 95% CI 0.15, 2.33, p = 0.43). While this was not found to be significant, the difference in the clinical profile of both groups showed that despite a greater proportion of patients in the intervention group having a Centor ≥ 3, they were less likely to require referral to their GP due to clinical assessment in the pharmacy. In contrast, those in the control group who went through usual care show that patients across all self-reported Centor scores were referred to their GP indicating that there is unnecessary GP referral of patients under usual pharmacy protocols.

Patients underwent RADT with Centor scores 1 through 4. Patients with a Centor score of 1 or 2 may have had RADT for different reasons. The patient may have asked for RADT despite being informed that the sensitivity and specificity of the test was lower or also they could be a latent carrier of GABHS. However, reasons are not specified by pharmacists as to why patients underwent RADT with a Centor of 1 or 2.

Pharmacists in the intervention group referred seven patients to their GP including; 3 patients with a positive RADT result, 2 patients with a negative RADT result and 2 patients with a Centor score of 2 and 3 who did not undergo RADT. Again, there is no documentation as to why pharmacists deviated from
the intervention protocol and referred patients to the GP. However, patients may have presented to the pharmacy with other symptoms, unrelated to their sore throat which required referral.

5.1.3 Primary outcome post intervention

5.1.3.1 GP visits
No significant difference between treatment groups of GP visits and antibiotic prescribing was determined. In the intervention group 3 of the 7 patients (43%) referred by the pharmacist went to the GP. This included two patients who had a positive RADT result. The remaining two patients who tested positive did not attend their GP. At the time of the result pharmacists informed patients that when the result is positive antibiotics may help reduce symptoms by approximately 16 hours, however, it should resolve within 10 days. Patients considering this advice, may have decided not to attend the GP following referral by the pharmacist. Therefore, pharmacists can have an impact on the rational use of medicines.

However, patients in the intervention group were not more likely to visit their doctor (OR = 1.27, 95% CI 0.35, 4.57, p = 0.71). Despite the significant difference between seasons and clinical profile at baseline, these did not have a significant impact on the number of GP visits at follow up.

5.1.3.2 Antibiotic prescription post intervention
The analysis showed that the intervention did not result in a reduction or increase in antibiotic prescribing, with 21% of patients in the intervention group and 20% of patients in the control group prescribed antibiotics. Patients who were prescribed antibiotics were more likely to have been prescribed antibiotics as Centor score increased. The Centor score, is a clinical prediction rule and was developed to improve diagnosis of Group A β-Haemolytic Streptococci (GABHS) pharyngitis. The Irish and UK guidelines incorporate this Centor score, however, to date RADT has not been incorporated into guidelines, which is reflected in the practice of GPs in Ireland as no patient who attended their GP
had their throat swabbed. Had GPs made use of RADT, the prescribing rates would have been much lower in the intervention group at 29% rather than the 86%, which was found in this study.

5.1.3.3 Appropriateness of GP visits following pharmacist advice
The pharmacist advice following the intervention did not have a significant impact on the number of GP visits which were appropriate (OR = 1.13, CI 95% 0.26, 4.83, p = 0.87). A significant limitation to this analysis was the comparison of the Centor score in the intervention group and the self-reported Centor score in the control group as these measurements were found to be significantly different ($\chi^2 (12, N = 33) = 20.95$, $p = 0.05$) and therefore not a reliable comparison. There were a higher number of patients in the control group (82%) who were referred or not referred as per the Centor score which was higher than the intervention group (62%). However, this would be expected as patients who received a negative RADT result would not have been referred to their GP. Furthermore, patients who were referred to their GP in the intervention group despite a Centor score of less than 3 may have presented with other symptoms which warranted referral to the GP for further investigation. However, numbers analysed were small and therefore greater numbers in the study would be required to determine what if any impact the pharmacist advice based on the intervention has on the appropriateness of GP visits.

5.1.4 Secondary outcomes post intervention
5.1.4.1 Appropriateness of antibiotic prescribed
The intervention did not have a significant impact on the appropriateness of antibiotics prescribed (odds ratio 2.2, 95% confidence interval 0.12, 39.49). Prescription of antibiotics was found to be inappropriate in 83% of patients ($n = 7$) in the intervention group and 92% of prescriptions in the control group ($n = 14$). Patient self-reported Centor score, pharmacist Centor score, RADT result, type of antibiotic prescribed, dose and duration were accounted for when determining appropriateness of antibiotic prescription. One-third of patients in the intervention group were prescribed antibiotics which are not first line
treatment for GABHS and in the control group this was higher at 46%. This figure is lower than other studies carried out in Ireland in GP practices, in which 66% of patients were found to be prescribed a broad spectrum antibiotic for symptoms which met the Centor Criteria\textsuperscript{141}.

Across both treatment groups 50% of patients with a self-reported Centor score of 1 or 2, at the time of presentation in the pharmacy, were inappropriately prescribed antibiotics for pharyngitis. This highlights the varying adherence to guidelines across prescribing practices nationally which has been previously reported\textsuperscript{164}. Most prescriptions for pharyngitis, or sore throat, have been shown to be inappropriate for patients. Of those presenting to GPs in Ireland with pharyngitis it is expected that only 10% require prescriptions, however, as many as 53% receive antibiotics\textsuperscript{69}. During the 7 days following presentation in the pharmacy, it must be considered that during this time patients’ symptoms may have worsened, which could have possibly warranted an antibiotic prescription. Additionally, patients with a negative RADT result who received antibiotics may not have informed their GP that they underwent RADT or brought the doctor letter provided by the pharmacist to their GP. If GPs assessed patients based on the Centor Criteria and patients had a score of 3 or 4, antibiotics would have been indicated.

Barriers to reducing inappropriate use of antibiotics include; patient expectations, lack of patient awareness of antibiotic resistance and the perceptions of both patients and practitioners that there is only a theoretical risk of antibiotic resistance\textsuperscript{51,115}. The results of this study show that antibiotics are inappropriately prescribed for pharyngitis and that guidelines are not being followed. This is similar to published literature which states that up to 62% of antibiotics are issued to patients suffering with pharyngitis when approximately 10% of prescriptions are appropriate. This intervention provides patients with advice and guidance on treatment for pharyngitis thereby reducing barriers of patient expectations and lack of patient awareness. In this study all patients should have followed the pharmacist recommendation resulting in fewer GP visits and fewer antibiotic prescriptions.
5.1.4.2 *Patient reported antibiotic adherence*

In general patients reported to be adherent to their medication across both treatment groups, completing the antibiotic course in full. This contradicts previous studies which have measured antibiotic adherence for pharyngitis, with patients’ reporting non-adherence to antibiotic courses\(^\text{117}\). There has been many educational campaigns in Ireland in recent years on the importance of antibiotic adherence and these may have helped improve patients’ antibiotic adherence\(^\text{165}\).

5.1.4.3 *Time to recovery*

Nearly all patients’ sore throats had resolved, as expected, at the time of follow up. The majority of sore throats had resolved within 10 days across both groups. Most patients were recommended over the counter medications and self-management treatment methods. In the control group, approximately 90% of patients used over the counter and self-management treatment methods. In the intervention group this number was similar at 86%. Pharmacist advice encouraged rational use of medicines, through appropriate treatment recommendations.

5.1.5 *Process evaluation*

5.1.5.1 *Delivery of intervention*

The delivery of the intervention in general followed the protocol set out. There were some deviations from the protocol with patients receiving RADT with Centor scores of 1 or 2. While sensitivity for a culture of a single throat swab on a blood agar plate, for GABHS is 90-95% and in general, the sensitivity of RADTs in comparison with blood agar plate culture is 70-90%, the sensitivity of RADT decreases, the lower the Centor score, increasing the likelihood of obtaining a false positive result\(^\text{158,166}\). The guidelines of the American College of Physicians, recommend carrying out RADT in those with a Centor score of 2 and if the result is positive they should be treated with antibiotics\(^\text{96}\). These guidelines state that if the result of RADT is negative, confirmation via culture is
not necessary as the likelihood of an asymptomatic carrier is much lower than children\textsuperscript{118}.

There are two reasons why pharmacists may have deviated from the protocol. Patients may have expected to have their throat swabbed regardless of the outcome of the Centor score. This may have been due either to the way in which they were provided information about the intervention by staff members in the pharmacy or they wanted the result regardless of the accuracy of the test. Pharmacists may also have felt pressurised to provide RADT testing as the patient had paid for the full service. As per the American College of Physicians guidelines, those with a Centor score of 2 and a positive RADT can be treated with antibiotics. Those with a Centor score of 1 and a positive RADT should have been informed at the time that the accuracy of the test was lowered, as they did not have a high probability of having a GABHS pharyngitis infection. However, the conversation with this one patient was not recorded. Overall, the design of this community pharmacy pharyngitis intervention allowed for timely diagnosis of GABHS and if necessary appropriate referral to the doctor to obtain a prescription for antibiotics.

\subsection{Sore throat history}
A crude odds ratio of 1.24 (95\% CI 0.42, 3.63, \textit{p} = 0.7) was found for the intervention on GP visits. Logistic regression analysis results showed that when adjusted for those who frequently suffer from sore throats and those who have usually gone to their GP in the past for their sore throat the odds ratio reduced to 0.31 (95\% CI 0.09, 1.09, \textit{p} = 0.07). While neither of these results were significant the difference in the odds ratios may hint at potential confounders.

\subsection{Patient satisfaction}
Patient satisfaction was high for the intervention. The data gathered highlights the accessibility of pharmacists. No appointments were made by patients prior to attending the pharmacy for the intervention. Patients stated that they chose the service due to the convenience (41\%), trust in the pharmacist (21\%), to avoid the cost of the GP (15\%) and to confirm if the infection was viral (24\%). Patients
stated that they would like this intervention to be available on a continuous basis. There were 33 patients out of the 35 which stated that they would use the service again in the future and 100% of patients stating they would recommend it to others. The feedback received through the satisfaction survey was positive indicating patients' willingness to choose services such as this in the future.

Community pharmacists are considered to be a valued member of the multidisciplinary team, with the potential to ease the burden on the health service\textsuperscript{146}. The advantages of community pharmacy providing interventions such as the pharyngitis programme described here include, convenient opening hours, location and access to a healthcare professional without delay\textsuperscript{167}.

5.1.6 Feasibility of intervention

This study determined feasibility and efficacy of a pharmacy intervention programme involving point of care testing. This is the first community pharmacy led non-randomised control trial to examine the effects of a GABHS pharmacy screening service for GABHS in Ireland. It follows on from a feasibility study of a similar intervention conducted in Boots UK in 2014/15 which found that RADT in combination with the Centor Criteria has the potential to reduce inappropriate antibiotic use\textsuperscript{115}. This study therefore builds on the evidence by examining the delivery of such a service in a different healthcare system\textsuperscript{115}. Few other studies have examined the effects of a community pharmacy pharyngitis management programme\textsuperscript{62}.

Antibiotic treatment for GABHS has been shown to shorten the duration of infections by approximately 16 hours\textsuperscript{73}. Complications of GABHS can result in both medical and surgical interventions\textsuperscript{129}. However, complications such as sepsis are rare\textsuperscript{160}. Those who have been confirmed as suffering from a GABHS infection should be prescribed antibiotics, most notably those who are at risk of complications. Taking this into account it can be argued that the majority of adult patients who suffer from pharyngitis do not need to see their GP, as in most cases it is viral, which can be monitored by a community pharmacist, and referral can be made if necessary. Results of this study show that the intervention reduced unnecessary referral of patients to their GP by 14%. Furthermore, the results
show that in the intervention group the use of RADT following examination of the Centor Criteria has the potential to reduce antibiotic prescription by approximately one-third (34%) if guidelines are adhered to. However, this was not found to be significant and further investigation is required to determine if this potential reduction is significant in a larger population. Furthermore, patients did not necessarily follow the pharmacists’ advice which could have been due to several reasons such as worsening of symptoms and therefore in this small sample sized study it is not possible to determine if the advice pharmacists provided to patients could have appropriately reduced GP visits.

The implementation of a point of care testing intervention such as the one described requires the provider to overcome many challenges. Lack of education and training in differential diagnosis during undergraduate degree, state regulation and lack of specific Irish guidance for pharmacists on GABHS testing, were addressed in the planning of the intervention. Specialised training for the pharmacists delivering the intervention was provided by a tailored intervention training programme. Technical training in the use of RADT was carried out to ensure that the test is accurately carried out, therefore, improving the diagnostic accuracy of the test.

Various studies and guidelines, recommend that where the RADT result is negative, depending on patients’ clinical symptoms, throat cultures should be taken as there could be false negatives. American guidelines recommend that this is done in children and adolescents. However, European guidelines do not recommend throat cultures following RADT negative results. In this study adults aged 18 years and over were recruited, therefore removing the potential requirement for follow up cultures.

Prevention and management of infections can be positively altered by community pharmacists. It has been shown that pharmacy led interventions can improve prescribing appropriateness in the elderly. Similarly, pharmacy interventions such as vaccination programmes in the US, have shown a reduction in the number of patients attending their GPs for vaccinations and an increase in vaccinations in their community pharmacies. This shows the potential impact pharmacists can have on healthcare utilisation. Patients are responsive to pharmacist roles expanding, with 94% of patients surveyed in Ireland salutary to
new roles in pharmacy\textsuperscript{170}. This provides support for the role of community pharmacy to be expanded. This study determines the feasibility of one of these interventions and the potential impact it can have on healthcare utilisation.

The intervention presented should augment, and not, negatively impact on the quality of traditional services provided for by pharmacists. Recruitment of patients for the intervention was low and 5 pharmacies failed to recruit patients to the study. It is not clear as to why this occurred however, lack of time may have played an important role, with pharmacists carrying out their traditional duties in the pharmacy first and foremost. However, those pharmacists who did recruit patients were in busier pharmacies, indicating that time may not have been an influencing factor in the delivery of this intervention.

This study analyses how patients managed their sore throat following consultation in the pharmacy. Despite the high level of satisfaction reported by patients in the intervention group, pharmacist participation in the recruitment of patients to the study was low and, failure of five intervention pharmacies and one control pharmacy to recruit patients does question whether the provision of this service is feasible in all community pharmacies across Ireland. Certainly, the reassurance that patients reported that they were treating their sore throat in the correct manner and other studies stating that patients reported reassurance from the results of the RADT with preference for not taking antibiotics informs that patients benefit from a pharmacy service such as this\textsuperscript{84}. However, the barriers to implementing these services and whether community pharmacy has the resource to provide such a service is still yet to be determined. In order to fully determine the feasibility of the intervention greater engagement with pharmacists is required. Pharmacist time for which they can dedicate to the intervention should be taken into account, which is reflected in the participation rates for the study. Patient satisfaction data does however, confirm that this is a service which provides them with timely access to appropriate treatment options, and indicates that they would like more services such as this to continue.
5.2 Strengths and limitations

This is one of the first trials in Ireland to be carried out to evaluate the impact of a pharmacy led intervention on healthcare, which is a strength of this study. One of the main limitations is the non-randomised design of the study, which could impact both the external and internal validity of the study. To reduce the potential for bias the following has been ensured:

- A robust recruitment protocol was defined for both groups, with strict inclusion and exclusion criteria,
- sample size was calculated to allow for drop out, and,
- the outcome assessor was blinded to follow up.

Baseline characteristics for both groups of pharmacies were very similar and the control group was matched according to the characteristics present in the pharmacies in the intervention group. Patients were recruited consecutively upon presentation to the pharmacy. However, the required sample was not obtained. This was due to the failure of five intervention pharmacies and one control pharmacy to recruit patients resulting in no engagement of pharmacists in these pharmacies combined with low recruitment numbers across participating pharmacies in both groups.

Quantitative methods were used to gather patient data to determine primary and secondary outcomes. In addition, quantitative and qualitative methods were used to determine patient satisfaction in the intervention group. This resulted in a comprehensive outcome whereby the qualitative methods used for patient satisfaction informed the quantitative data obtained to determine the feasibility of the intervention.

5.2.1 Sample size, recruitment and retention

It is inappropriate to determine non-inferiority or superiority of the community pharmacy based intervention as the study is underpowered. A sample size of 298 participants with 149 in each arm was required to detect a reduction of 20%, from 40% to 20%, in the intervention group. This would have allowed for 10% loss to follow up, with 90% power.
Failure of 5 intervention pharmacies and 1 control pharmacy to participate in the study influenced the sample size of the study. As well as this patient recruitment was low for both arms of the study and response rates were reported for two pharmacies in the intervention group and four pharmacies in the control group. Of the four control pharmacies, there was data missing from these forms. Response rates were lower than expected in both groups. In the intervention group the average participation rate in the intervention provided was 80% and of those taking part the response rate for study participation was 58%. Previous studies carrying out point of care testing in a community pharmacy setting reported response rates of 85%\textsuperscript{110}.

Drop out was also greater than expected (10%) as in the control group 14% were lost to follow up and 3% refused to participate. In the intervention group 11% were lost to follow up and 3% refused to participate. This again affected the power of the study. Further recruitment of patients is required to determine if the intervention affects GP visits and antibiotic prescribing.

5.2.1.1 External influences on the community pharmacy setting
To determine possible reasons as to why pharmacies did not participate and why pharmacy participation was low across both groups the current reality of community pharmacy must be reviewed. Over the past 24 months there have been numerous changes to the workload of the community pharmacist in Ireland. These include the additional documentation of continuing professional development via an online portfolio system, an increase in administrative workload for processing of payments from the Health Service Executive, changes in legislation for the provision of controlled drugs, introduction of pneumococcal and herpes zoster vaccination provision and administration of medication in emergency situations, an audit system imposed by the pharmaceutical regulator and an increase in pharmacy student placements in patient facing roles with the introduction of the 5 year integrated pharmacy degree programme\textsuperscript{146,171,172}. These changes have increased the workload for pharmacists and their teams, including technicians and healthcare advisors. On top of this the outbreak of influenza at the beginning of 2017 resulted in a spike
in influenza vaccinations being provided by pharmacists, which was unexpected.

The increased demands on pharmacist time for delivery of consultations and audits, results in pharmacists carrying out only essential tasks such as clinical checks and delegation of the more traditional aspects of community pharmacy to other members of the team. Therefore, in the design of this study, the research questions, the type of research used to test the hypothesis, time management for completion of informed consent and study surveys along with the use of other staff members in the pharmacy were crucial. Considering all changes in the last number of years in pharmacy and the time pressure pharmacists are under recruitment of patients for this study, was most likely not a top priority for pharmacists or pharmacy teams involved in recruitment of patients.

Furthermore, patients do not expect community pharmacies to be conducting research. Their expectations when they conduct business in a pharmacy is to receive advice or medication on their health needs. If they are sick, they can be quite surprised to be recruited into a study. Little research involving patient recruitment has been carried out in Ireland to date and is not necessarily something that patients and pharmacy staff associate within the Irish community pharmacy setting. This could have impacted patient recruitment as patients may be wary of providing a commercial chain with contact details, despite this information only being sent to the researcher.

The landscape of community pharmacy in Ireland has changed and is continuing to change. An increasing administrative workload as well as patient expectations across the community pharmacy sector in Ireland will continue to change in the future due to budgetary constraints and an ageing population. Pharmacists are learning to adapt to these changes. As pharmacists were not interviewed as part of this research it is difficult to determine why pharmacist participation was low. The external influences on the community pharmacy sector which were discussed may shed some light on the environment in which community pharmacists work and account for low participation rates of pharmacists. However, while pharmacists may not have had the resources to deliver the intervention it is not an indicator of their willingness to deliver the
intervention to patients and therefore, further research is required to explore this which would indicate the feasibility of the intervention.

5.2.2 Internal validity

Deeks et al. (2003) stated that the quality of a study can be defined as “the confidence that the trial design, conduct and analysis has minimised or avoided biases in its treatment comparisons”\textsuperscript{156}. However, if the study is not internally valid then the external validity of the study and its generalisability is largely irrelevant\textsuperscript{156}. If the study has been internally validated then the probability of the study achieving what it was designed to do and therefore the findings are more likely to be accurate\textsuperscript{161}. There are many types of bias which possibly affected the results of this study. Although randomisation as not possible in this study it must be remembered that non-randomised controlled trials are not always biased, however, they should only be used where randomisation is not possible\textsuperscript{156}. Types of bias which have the potential to impact the internal validity of this study will now be discussed.

5.2.2.1 Selection bias

To minimise the presence of selection bias in the study, selection of participants into each group was controlled through the matching of pharmacies and the recruitment of patients in a consecutive manner. Matching was not possible on an individual basis\textsuperscript{174}. However, it was possible to match clusters in each arm of the trial. Pharmacies in the intervention were matched to the control group. Failure of pharmacies to recruit could have resulted in selection bias, however, characteristics of pharmacies and patients were similar indicating that this was not the case.

Baseline outcome measurements were similar for both treatment groups. It was expected that the cost of the intervention of €7.50 would result in lower participation rates in the intervention group for those who are entitled to state funded medication. However, this was not the case as the proportion of patients with free access to GPs was low in the intervention group (11%). Other approaches were used to reduce the influence of selection bias in the study and
these included; restricting the eligibility criteria to those that were eligible for the intervention and implementing a zero-time point from which patients are followed up\textsuperscript{156}.

Selection bias may have been introduced through the screening process involved in the intervention group at the point of patient presentation at the pharmacy, potentially resulting in a more severe symptom profile presenting in the intervention group.

Contamination of the groups was also possible if one of the participants in the control group were to subsequently go to a pharmacy providing the intervention. This was identified during follow up with one patient.

5.2.2.2 Attrition bias

There is potential for attrition bias in the study, due to a higher than expected drop-out rate of participants\textsuperscript{156, 161}. To minimise the effect of attrition bias, those drop outs from the study in one group should be comparable to drop outs in the other group\textsuperscript{175}. Comparison of baseline characteristics at follow up show that this did not create differences between treatment groups and drop-out rates were similar across treatment groups. Patients were also contacted ten times prior to them deemed lost to follow up.

5.2.2.3 Detection bias

Detection bias occurs when there is no standardisation of assessment or the analysis of the data is not blinded\textsuperscript{156}. To ensure pharmacists and healthcare assistants did not vary in the delivery of the intervention and the method of data collection the following was carried out to reduce the likelihood of detection bias influencing the study:

- detailed study protocols were provided to pharmacies (Appendix 4a & 4b),
- individual calls were made to pharmacists to talk them through recruitment process,
- scripts were provided for pharmacy staff to read with the patient to complete patient surveys,
standardised training was provided for all pharmacists delivering the intervention, only one pharmacy researcher (CON) carried out follow up,
the pharmacy researcher was blinded to patient allocation, and,
a script was provided to the researcher to read to each patient at follow up\textsuperscript{175}.

The validity and reliability of surveys was addressed at the design phase. Quantitative methods were used to create surveys\textsuperscript{161}. Validated instruments were used to create the patient satisfaction survey. The surveys created were used to determine baseline characteristics, clinical profile of patient, consultation outcome, patient satisfaction and treatment outcome. No validated tools were used in this study as there was no tool applicable for the collection of data which was relevant to the study. Therefore, there is the potential that the tools used such as the patient survey were not reliable for data collection in the uniform, intended way.

The Likert scale was used to determine the level of satisfaction. It has been reported that participants will frequently only use the middle response rate on a Likert scale or participants will only use the extreme ends of the scale\textsuperscript{161}. Different personalities result in different responses\textsuperscript{161}. Interestingly patients in this study mostly used the responses ‘very satisfied’ and ‘satisfied’, showing a range of middle responses and extreme responses. However, the telephone interviews used for follow up and to collect satisfaction were disadvantaged in that the researcher could not read the body language of the participant\textsuperscript{161}.

\textit{5.2.3 External validity}

If the research is externally valid it implies that the research can be generalised and extended to other groups\textsuperscript{161}. Non-randomised trials are viewed as having greater external validity than randomised control trials\textsuperscript{156}. 

5.2.3.1 Setting of the trial
This trial was carried out in the Irish community pharmacy setting, in a large chain pharmacy group. This is one of the first such studies to be carried out on RADT in Ireland. To date most research in community pharmacy interventions, has been carried out in the UK\textsuperscript{167}. Unfortunately, the quality of the research published has not been strong and more research is required to determine if interventions carried out in pharmacies such as alcohol management, smoking cessation and GABHS screening services are beneficial to patients\textsuperscript{115,167}.

Community pharmacists do not take part in research regularly in Ireland\textsuperscript{173}. Therefore, pharmacists are not familiar with recruiting patients for research and often do not get to adequately follow through, as they are focusing on their day job and, the research is not a top priority\textsuperscript{173}. However, the use of the full pharmacy team in the pharmacy, as was carried out across both treatment pharmacy groups, for recruiting patients has been stated as an important aspect of successful recruitment of patients\textsuperscript{173}.

The setting of this study is in a large chain community pharmacy across Ireland, it is not a dominating body within the market, and therefore may not accurately reflect on the feasibility across the community pharmacy setting. Pharmacies which recruited patients were matched and set in urban shopping centres and suburban shopping centres. Similar baseline characteristics obtained verify that matching was carried out accurately during the development of this study, therefore, increasing the probability that the results of the study are reflective of the wider population.

5.2.3.2 Difference between trial protocol and routine practice
This intervention is not current practice across community pharmacy in Ireland. This study compares the intervention to usual practice. However, the study did create an awareness of pharyngitis among pharmacy staff in the control group despite them providing usual care to patients, which could have possibly influenced advice provided to patients in the control pharmacies.
5.3 Impact of findings

There is very little evidence published for interventions provided in the community pharmacy setting\textsuperscript{176}. Non-experimental studies and opinions compose much of the research that has been published to date in this setting. Where research has been published governments have been shown to adopt pharmacy interventions into the healthcare system\textsuperscript{176}.

In Ireland, research on community pharmacy interventions is scant. Pilot programmes have been launched in Ireland, such as the Minor Ailments Scheme. This is a pilot launched by the Health Service Executive and the Irish Pharmacy Union\textsuperscript{177}. However, research outcomes are not available to date for this pilot. Online searches carried out for interventions in community pharmacy in Ireland, resulted in very few results.

The Pharmaceutical Society of Ireland (PSI) has stated that the future of pharmacy involves pharmacists improving the health and wellbeing of the population and supporting the management of minor ailments and self-limiting conditions\textsuperscript{146}. The PSI base their recommendations on evidence based practices. The Health Service Executive (HSE) use evidence based research to inform policy and practices in healthcare\textsuperscript{178}. Therefore, to implement any intervention across community pharmacy, there must be strong evidence to support this.

Considering this, further robust research is required to determine the feasibility and impact, that point of care testing interventions have in the community pharmacy setting in Ireland. The failure of pharmacies to recruit patients resulting in an underpowered study may indicate that from pharmacists’ perspective an intervention such as this is not feasible. However, this research feeds a growing demand for pharmacist expertise to be utilised, taking advantage of unrivalled access to the public, convenient locations and opening hours. It also showcases the value of pharmacists’ expertise in the primary healthcare setting and the impact on patient care, potentially reducing the burden on the Health Service Executive.

This service could potentially relieve some of the burden on the healthcare system while strengthening the antimicrobial resistance agenda. The
results of this study show that the advice pharmacists provided did not make a
significant impact on GP visits following the intervention. However, a larger
sample size, may find that pharmacist advice following the intervention could
potentially reduce GP visits. While there is no significant evidence there is
potential for pharmacists’ advice, once followed by patients, to promote
rationale use of medicines, resulting in cost saving measures for patients. As
has been done in the United Kingdom, policy makers should look to incorporate
point of care testing services into pharmacy settings including RADT for GABHS
into antimicrobial strategies to reduce inappropriate antibiotic prescription and
preserve antibiotic function, however, were this to occur a larger feasibility study
should occur simultaneously\textsuperscript{149}.

5.3.1 Research reflection
Upon reflection of the study design a larger number of pharmacies ideally would
have been recruited into the study to allow for greater patient recruitment. This
would have resulted in less chance of the study being underpowered.

Random allocation of pharmacies to study arms would have also
occurred. This was not possible due the pharmacy chain piloting the service
prior to agreeing to the research being carried out on the intervention.

The design of this intervention included the use of the OSOM Strep A
test. Sensitivity and specificity can tend to vary considerably depending on the
RADT product\textsuperscript{112}. Sensitivity depends on the severity of the disease, the
amount of bacterial inoculum on the swab and the technique used by the
user\textsuperscript{179}. The high specificity and sensitivity in combination with the robust
training pharmacists underwent provides confidence in the results of the RADT
results carried out on patients and the advice provided to patients by the
pharmacist.

5.3.2 Recommendations for future study
This is one of the first trials in Ireland to be carried out to evaluate the impact of
a pharmacy led intervention on healthcare. In Ireland the pharmacy regulator,
the Pharmaceutical Society of Ireland, foresees the expansion of services
provided by pharmacists in the community setting. With approximately 20 million visits to community pharmacists in Ireland each year, it is a skilled profession readily accessible to the general population\textsuperscript{146}. It is an ideal time to determine if community pharmacists can have an impact on GP visits and antibiotic prescribing for pharyngitis.

This study presents results which require repetition with greater power to determine the full impact of the intervention. Pharmacist and pharmacy team views on the provision of such an intervention should also be determined in future studies.

An analysis of pharmacist tools required to provide point of care testing services in community pharmacy should be carried out to determine what impact staffing, costs and workload have on the delivery of these interventions to patients. If policy makers are to expect community pharmacists to provide patient care which results in meaningful outcomes for patients with significant savings, pharmacies should be fairly reimbursed to ensure interventions such as this are resulting in positive public health measures and state savings.

Another area which should be analysed is patient expectation and patient education. Pharmacist training which is required in order to deal with patient expectations should be reflected upon. Similarly, to the GPs it is likely that patient expectation influences the outcome of patient consultation\textsuperscript{69}.

A cost-effectiveness study should also be carried out to determine the savings which could possibly be generated for the health services.

5.4 Conclusion

Antibiotic resistance threatens global health. Despite only one cause of pharyngitis, GABHS, out of the numerous aetiologies, requiring treatment with antibiotics, there is still overprescribing of antibiotics occurring\textsuperscript{68}. GABHS pharyngitis effects an estimated 616 million patients, globally each year, placing a huge burden on GPs and the health service\textsuperscript{68}. RADT in combination with the Centor Score is effective in improving appropriate antibiotic use. This method
provides GPs and patients with confidence in the diagnosis and removes the need for swab cultures\textsuperscript{84}.

This study has demonstrated the expertise and potential which pharmacists offer to patients daily. From the results presented it is difficult to determine if this intervention can reduce GP visits and antibiotic prescribing. Further study is required to determine if a reduction in GP visits can occur through pharmacist advice on foot of the intervention. Inappropriate prescribing of antibiotics is occurring on a national level. Patients are open to community pharmacists providing such point of care testing services, with many stating they would like to have more of these services on offer through the pharmacy. Interventions such as this have been shown to potentially improve efficiencies in health services on a national level\textsuperscript{115,118,180}. Therefore, further research with a larger sample size is warranted along with an analysis of pharmacist viewpoint of the intervention to determine the impact this intervention can have on patient care, public health and financial savings to the health service.
6 References


34. Centre HPS. EARS-Net data on antimicrobial resistance in Ireland Quarter 4 2016. Available from http://www.hpsc.ie/a-


85. Health Service Executive, Irish College of General Practitioners, Royal College of Physicians of Ireland, Centre HPS. Guidelines for Antimicrobial Prescribing In Primary Care in Ireland. 2016.


110. Geerts AF, De Koning FH, De Vooght KM, Egberts AC, De Smet PA, van Solinge WW. Feasibility of point-of-care creatinine testing in community


## Appendices

### Appendix 1: TRENDS Statement Checklist

<table>
<thead>
<tr>
<th>Paper Section / Topic</th>
<th>Item No</th>
<th>Descriptor</th>
<th>Reported?</th>
<th>Pg #</th>
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<td>o Structured abstract recommended</td>
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<tr>
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<td></td>
<td>o Information on target population or study sample</td>
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<td><strong>Introduction</strong></td>
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<td>o Scientific background and explanation of rationale</td>
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<td></td>
<td>o Theories used in designing behavioural interventions</td>
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<td><strong>Methods</strong></td>
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<td>Participants</td>
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<td>o Eligibility criteria for participants, including criteria at different levels in</td>
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<td></td>
<td></td>
<td>recruitment/sampling plan (e.g., cities, clinics, subjects)</td>
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<td>o Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented</td>
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<td></td>
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<td>o Recruitment setting</td>
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<tr>
<td></td>
<td></td>
<td>o Settings and locations where the data were collected</td>
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<td>Interventions</td>
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<td>o Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:</td>
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<td></td>
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<td>▪ Content: what was given?</td>
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<td></td>
<td></td>
<td>▪ Delivery method: how was the content given?</td>
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<td></td>
<td></td>
<td>▪ Unit of delivery: how were the subjects grouped during delivery?</td>
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<tr>
<td></td>
<td></td>
<td>▪ Deliverer: who delivered the intervention?</td>
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<td></td>
<td>▪ Setting: where was the intervention delivered?</td>
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<td></td>
<td>▪ Time span: how long was it intended to take to deliver the intervention to each unit?</td>
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<td>▪ Activities to increase compliance or adherence (e.g., incentives)</td>
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<td><strong>Objectives</strong></td>
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<td>o Specific objectives and hypotheses</td>
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| Outcomes                  | 6 | - Clearly defined primary and secondary outcome measures  
|                          |   | - Methods used to collect data and any methods used to enhance the quality of measurements  
|                          |   | - Information on validated instruments such as psychometric and biometric properties | Y | 85 |
| Sample Size              | 7 | - How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules | Y | 86 |
| Assignment Method        | 8 | - Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)  
|                          |   | - Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)  
|                          |   | - Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching) | Y | 79 |
| Blinding (masking)       | 9 | - Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed | Y | 78 |
| Unit of Analysis         | 10| - Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)  
|                          |   | - If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error) | Y | 80 | N/A |
| Statistical Methods      | 11| - Statistical methods used to compare study groups for primary methods outcomes(s), including complex methods of correlated data  
|                          |   | - Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis  
|                          |   | - Methods for imputing missing data, if used  
|                          |   | - Statistical software or programs used | Y | 90 |
|                         |   | N/A |
| Results                 |   | N/A |
| Participant flow        | 12| - Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)  
<p>|                          |   | - Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study | Y | 107 |</p>
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<td>o Description of protocol deviations from study as planned, along with reasons</td>
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<td>o Dates defining the periods of recruitment and follow-up</td>
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<td>o Baseline comparisons of those lost to follow-up and those retained, overall</td>
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<td>if not, description of how non-compliers were treated in the analyses</td>
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<td>o Inclusion of null and negative findings</td>
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<tr>
<td></td>
<td>o Inclusion of results from testing pre-specified causal pathways through</td>
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<td>which the intervention was intended to operate, if any</td>
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<td>Description</td>
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<td>Adverse events</td>
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<td>Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)</td>
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<td>DISCUSSION</td>
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<td>Interpretation</td>
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<td>Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study</td>
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<td>Discussion of the success of and barriers to implementing the intervention, fidelity of implementation</td>
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<td>Discussion of research, programmatic, or policy implications</td>
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<td>Generalizability</td>
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<td>Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues</td>
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<td>Overall</td>
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<td>General interpretation of the results in the context of current evidence</td>
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Appendix 2a: Patient Information Leaflet – Intervention Group

Study title: Sore Throat Study

Principal investigator’s name: Dr. Gráinne Cousins
Principal investigator’s title: Lecturer in School of Pharmacy
Telephone number of principal investigator: 01-402 2551
Co-investigator’s name: Claire O’ Neill
Co-investigator’s title: Community Pharmacist

You are being invited to take part in a research study carried out at your pharmacy, which is being co-ordinated by the School of Pharmacy in the Royal College of Surgeons in Ireland.

Before you decide whether or not you wish to take part, you should read the information provided below carefully and, if you wish, discuss it with your family, friends or Pharmacist. Take time to ask questions – do not feel rushed or under pressure to make a quick decision. You do not have to take part in this study and a decision not to take part will not affect your medical care. You can change your mind about taking part in the study at any time. Even if the study has started, you can still opt out. You do not have to give us a reason. If you do opt out, it will not affect the quality of treatment you get in the future.

Why is this study being done?

This study is being carried out to determine if the Sore Throat Test and Treat Service, particularly screening for the presence of a bacterial infection is beneficial to patients attending the service. This involves comparing patients who attend the screening service and those who receive usual care (advice from pharmacist). This may identify
ways to improve care for patients with sore throats presenting to their pharmacy in the future.

Who is organising and funding this study?
This research is being carried out by the School of Pharmacy in the Royal College of Surgeons in Ireland. Dr. Gráinne Cousins, Lecturer in the School of Pharmacy, has responsibility for all aspects of this study. Her contact details are listed below. The research is also part of Pharmacist, Claire O’Neill’s Masters by Research programme. This Masters by Research programme involves gathering information from this study, interviewing patients, who agree to the interview, and then analysing this information. The Pharmacy Researcher (Claire O’Neill) is an employee of Boots Ireland. However, there is no external funding for the study.

Why am I being asked to take part?
There are 20 pharmacies across Ireland taking part in this study. You have agreed to take part in the Sore Throat Test and Treat Service in Boots Ireland. Your Pharmacist has volunteered to take part in this study. All patients aged 18 years and over, taking part in the Sore Throat Test and Treat Service are being invited to take part in this study.

How will the study be carried out?
Patients taking part in the Sore Throat Test and Treat Service will be invited to take part in this study by a member of the pharmacy team. The pharmacy team member will go through this patient information leaflet with each patient, and if the patient agrees to take part they will sign the consent form. In seven days time, a Pharmacist will contact you by phone, to complete a short questionnaire to see how you are getting on. Information recorded will include the patient record form, the consultation record form, which the pharmacist will fill out during this service today, a short feedback survey and the answers provided in the telephone questionnaire.

What will happen to me if I agree to take part?
If you agree to take part in this study it will involve:
- Taking part in the Sore Throat Test and Treat Service. This service involves a few short questions, taking a reading of your temperature and an examination of your throat. This examination of your throat by a pharmacist involves looking at your tonsils and checking to see if the lymph nodes on the outside of your neck are tender. Depending on your symptoms you may be offered to have your sore throat tested for a particular bacteria, Strep A. This involves taking a
swab of the back of your throat and testing this swab to determine if this bacteria is present. You will receive the results of this test in 5 minutes.

- Completing a brief anonymous Patient Feedback Survey on the service
- Completing a brief (5-10 minute) phone interview in approximately 7 days in relation to your sore throat.

**What are the benefits?**

We would be very grateful if you would agree to take part in this study. The aim of the study is to determine if unnecessary antibiotic prescribing and doctor visits for sore throats can be reduced. The best way to do this is by asking people like you. This study will allow Pharmacists and Doctors to determine if a pharmacy Sore Throat Test and Treat Service results in improved outcomes for patients.

**What are the risks?**

There are no risks to taking part in the study. If you find any of the questions difficult, you do not have to complete them and we would encourage you to talk to your Pharmacist. However, if your sore throat symptoms get worse, or do not improve over the coming days please speak to your Pharmacist or GP.

**Is the study confidential?**

All your information will remain strictly confidential. After the service and interview are completed, your details will be encrypted and stored on a single password protected computer in the Royal College of Surgeons in Ireland and only the lead researcher, Dr. Gráinne Cousins, and the Pharmacist Researcher (Claire O’Neill) will have access to the data. The data will be securely stored and password protected in the Royal College of Surgeons in Ireland for a maximum of 5 years. Your data will be analysed together with all other participants’ data and you will not be identifiable from any papers arising from this study. We will provide each of the Pharmacies with a summary of the results to share with you. You will not be identifiable in this summary as it will be a summary of all participants’ data together.

**Where can I get further information?**

If you have any further questions about the study or if you want to opt out of the study, you can rest assured it won’t affect the quality of treatment you get in the future. If you need any further information now or at any time in the future, please contact:

Name: Dr. Gráinne Cousins
Address: School of Pharmacy, Royal College of Surgeons in Ireland, Dublin 2.
Phone No: 01- 402 2551 (Mon-Fri 9am -5pm)
Alternatively, you can speak to your Pharmacist at any time.
You are being invited to take part in a research study carried out at your pharmacy, which is being co-ordinated by the School of Pharmacy in the Royal College of Surgeons in Ireland.

Before you decide whether or not you wish to take part, you should read the information provided below carefully and, if you wish, discuss it with your family, friends or Pharmacist. Take time to ask questions – do not feel rushed or under pressure to make a quick decision. You do not have to take part in this study and a decision not to take part will not affect your medical care. You can change your mind about taking part in the study any time. Even if the study has started, you can still opt out. You do not have to give us a reason. If you do opt out, it will not affect the quality of treatment you get in the future.

Why is this study being done?

This study is being carried out to determine if a Sore Throat Service in a pharmacy, particularly screening for the presence of a bacterial infection is beneficial to patients. This involves comparing patients who attend the screening service and those who
receive usual care (advice from pharmacist). This may identify ways to improve care for patients with sore throats presenting to their pharmacy in the future.

**Who is organising and funding this study?**

This research is being carried out by the School of Pharmacy in the Royal College of Surgeons in Ireland. Dr. Gráinne Cousins, Lecturer in the School of Pharmacy, has responsibility for all aspects of this study. Her contact details are listed below. The research is also part of Pharmacist, Claire O’Neill’s Masters by Research programme. This Masters by Research programme involves gathering information from this study, interviewing patients, who agree to the interview, and then analysing this information. The Pharmacy Researcher (Claire O’Neill) is an employee of Boots Ireland. However, there is no external funding for the study.

**Why am I being asked to take part?**

There are 20 pharmacies across Ireland taking part in this study. Your Pharmacist has volunteered to take part in this study. All patients aged 18 years and over, coming into the pharmacy with a sore throat lasting between 3 and 10 days are being invited to take part in the Sore Throat Study.

**How will the study be carried out?**

Patients with a sore throat lasting between 3 - 10 days, coming into the pharmacy will be invited to take part in this study by a member of the pharmacy team. The pharmacy team member will go through this patient information leaflet with each patient, and if the patient agrees to take part they will sign the consent form. In approximately seven days, a Pharmacist will contact you by phone, to complete a short questionnaire to see how you are getting on. Information recorded will include the patient record form, which the healthcare assistant will fill out today and the answers provided in the telephone questionnaire.

**What will happen to me if I agree to take part?**

If you agree to take part in this study it will involve:

- Answering a few questions today about your sore throat
- Completing a brief (5-10 minute) phone interview in approximately 7 days in relation to your sore throat.
What are the benefits?

We would be very grateful if you agree to take part in this study. The aim of the study is to determine if unnecessary antibiotic prescribing and doctor visits for sore throats can be reduced. The best way to do this is by asking people like you. This study will allow Pharmacists and Doctors to determine if a sore throat pharmacy service results in improved outcomes for patients.

What are the risks?

There are no risks to taking part in the study. If you find any of the questions difficult, you do not have to complete them and we would encourage you to talk to your Pharmacist. However, if your sore throat symptoms get worse, or do not improve over the coming days please speak to your pharmacist or GP.

Is the study confidential?

All your information will remain strictly confidential. After the service and interview are completed, your details will be encrypted and stored on a single password protected computer in the Royal College of Surgeons in Ireland and only the lead researcher, Dr. Gráinne Cousins, and the Pharmacist Researcher (Claire O’Neill) will have access to the data. The data will be securely stored and password protected in the Royal College of Surgeons in Ireland for a maximum of 5 years. Your data will be analysed together with all other participants’ data and you will not be identifiable from any papers arising from this study. We will provide each of the Pharmacies with a summary of the results to share with you. You will not be identifiable in this summary as it will be a summary of all participants’ data together.

Where can I get further information?

If you have any further questions about the study or if you want to opt out of the study, you can rest assured it won't affect the quality of treatment you get in the future.

If you need any further information now or at any time in the future, please contact:

Name: Dr. Gráinne Cousins
Address: School of Pharmacy, Royal College of Surgeons in Ireland, Dublin 2.
Phone No: 01- 402 2551 (Mon-Fri 9am -5pm)
Alternatively, you can speak to your Pharmacist at any time.
Appendix 3a: Consent Form – Intervention Group

**PATIENT CONSENT FORM**

**Title of Study:** Sore Throat Study

<table>
<thead>
<tr>
<th>Statement</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have read and understood the <em>Information Leaflet</em> about this research project. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>I understand that I don’t have to take part in this study and that I can opt out at any time. I understand that I don’t have to give a reason for opting out and I understand that opting out won’t affect my future medical care.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>I understand that I will be contacted in 7 days to complete a brief telephone interview.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>I agree to the pharmacy giving information collected on the consultation record form to the Lead Researcher, Dr Gráinne Cousins and the Pharmacy Researcher, Claire O’ Neill, in RCSI, for the purposes of research for this study.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>I have been assured that information about me will be kept private and confidential.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>I have been given a copy of the <em>Information Leaflet</em> and this completed consent form for my records.</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Storage and future use of information:**

*I give my permission for information collected about me to be stored for the purpose of scientific research and to be used in related studies or other studies in the future but only if the research is approved by a Research Ethics Committee.*

<table>
<thead>
<tr>
<th>Statement</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage and future use of information:</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Participant Name (Block Capitals):** __________________________

**Participant Signature:** __________________________  **Date:** __________

---

**To be completed by the Pharmacist**

I the undersigned have taken the time to fully explain to the above patient the nature and purpose of this study in a manner that they could understand. I have explained the risks involved...**
as well as the possible benefits. I have invited them to ask questions on any aspect of the study that concerned them.

**Name (Block Capitals):** ______________________________

**Signature:** ___________________  
**Date:** __________

________

2 copies to be made: 1 for patient and 1 for PI.

If you have any questions, please contact the Principal Investigator, Dr. Gráinne Cousins.  
Address: School of Pharmacy, Royal College of Surgeons in Ireland, Dublin 2.  
Phone No: 01- 402 2551 (Mon-Fri 9am -5pm)
Appendix 3b: Consent Form – Control Group

PATIENT CONSENT FORM

Title of Study: Sore Throat Study

I have read and understood the Information Leaflet about this research project. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.

Yes ☐ No ☐

I understand that I don’t have to take part in this study and that I can opt out at any time. I understand that I don’t have to give a reason for opting out and I understand that opting out won’t affect my future medical care.

Yes ☐ No ☐

I understand that I will be contacted in 7 days to complete a brief telephone interview.

Yes ☐ No ☐

I agree to the pharmacy giving information collected on me in the patient survey to the Lead Researcher, Dr Gráinne Cousins and the Pharmacy Researcher, Claire O’Neill, in RCSI, for the purposes of research for this study.

Yes ☐ No ☐

I have been assured that information about me will be kept private and confidential.

Yes ☐ No ☐

I have been given a copy of the Information Leaflet and this completed consent form for my records.

Yes ☐ No ☐

Storage and future use of information:

I give my permission for information collected about me to be stored for the purpose of scientific research and to be used in related studies or other studies in the future but only if the research is approved by a Research Ethics Committee.

Yes ☐ No ☐

Participant Name (Block Capitals): __________________________

Participant Signature: __________________________  Date: _____________

To be completed by the Healthcare Assistant

I the undersigned have taken the time to fully explain to the above patient the nature and purpose of this study in a manner that they could understand. I have explained the risks involved
as well as the possible benefits. I have invited them to ask questions on any aspect of the study that concerned them.

Name (Block Capitals): ____________________________________________
Signature: ___________________________ Date: ____________________

2 copies to be made: 1 for patient and 1 for PI.

If you have any questions, please contact the Principal Investigator, Dr. Gráinne Cousins. Address: School of Pharmacy, Royal College of Surgeons in Ireland, Dublin 2. Phone No: 01- 402 2551 (Mon-Fri 9am -5pm)
Sore Throat Study

Study Guidance Pack

Intervention Pharmacies
Sore Throat Study

*Impact of a Pharmacy-led screening service for Group A β-haemolytic streptococci, on general practitioner visits and antibiotic consumption: a non-randomized control study*

1. Introduction

Most people suffer between two to three sore throat episodes per year (1). Approximately 40% of people experiencing a severe sore throat visit their GP (2) and sore throats account for 3.5% of GP visits in Ireland (3). The majority of sore throats occur due to a viral infection (80%), with 85% of cases being fully resolved after 7 days (1, 4). It is estimated that between 5-17% of sore throats are caused by a bacterial infection, generally a strain of the many β-haemolytic streptococci (5). Antibiotic treatment is only recommended for one particular strain, Group A β-haemolytic Streptococci (GABHS) (5).

To reduce the level of prescribing of inappropriate antibiotics, the Infectious Diseases Society of America recommend the use of a Rapid Antigen Detection Test (RADT) in combination with the Centor Criteria (6). The RADT is a detection method for Group A Streptococcal antigen from throat swabs (7). They recommend treating those with a positive rapid test and withholding antibiotics in rapid test negative patients.

In November 2015 Boots Ireland introduced a Sore Throat Test and Treat Service. This service involves a clinical assessment based on the Centor Criteria, in conjunction with a diagnostic test (where indicated) designed to identify the presence of GABHS. The service aims to support the differential diagnosis of uncomplicated sore throats of between 3 and 9 days duration with the aim of reducing unnecessary antibiotic usage where this may not be clinically indicated.

In order to determine if the service does indeed support more rational use of antibiotic therapy Boots has partnered with the Royal College of Surgeons in Ireland to conduct a research study "Impact of a Pharmacy-led screening service for Group A β-haemolytic streptococci, on general practitioner visits and antibiotic consumption: a non-randomized control study".
2. The Sore Throat Study

From February 2016 twenty Boots pharmacies will begin recruiting patients to the Sore Throat Study. The study is designed as a non-randomised controlled, parallel trial of adults aged 18 years and over, presenting to one of 20 Boots community pharmacies in Ireland with an uncomplicated sore throat. Ten pharmacies will be assigned to the Intervention Group, where patients availing of the Boots Sore Throat Test and Treat Service will be eligible to join the study. The other ten pharmacies will be assigned to the Control Group and in this pharmacy recruited patients will receive usual care (i.e. they will NOT receive the Boots Sore Throat Test and Treat Service).

The remainder of the information in this guide relates to conduct of the study in the Intervention Group ONLY.

3. Patient Journey

3.1 Patient Recruitment

Patients will present as normal to the pharmacy. In patients presenting with a sore throat the usual patient questioning using WWHAM will take place at the healthcare counter. Patients presenting with a sore throat who are eligible to avail of the Sore Throat Test and Treat Service will be given the option to avail of the service.
Patients must be recruited consecutively. This means that every patient as they approach the healthcare counter that is eligible for the study must be invited to join the study. If patients are not recruited consecutively it results in selection bias in the study, which could result in the study population differing from the general population. Thereby giving false results.

Patients availing of the service will then complete Step 1 of the service, the healthcare advisor consultation.

Patients scoring 1 or 2 on the initial Centor assessment will then be invited to participate in the study provided they fulfil the following eligibility criteria:

- aged ≥ 18 years*
- presenting to pharmacy with a sore throat lasting at least 3 days and less than 10 days, with no reported symptom improvement.

*NB As the service is available to patients aged 16 years and older please be very careful when recruiting patients to ensure that they are over 18 years of age.

Patients will be excluded if:

- they have already taken antibiotics for their sore throat
- they report an improvement in symptoms.

Patients reporting the following specific ‘red flag’ symptoms will also be excluded: presence of skin rash, dysphagia (difficulty swallowing), drooling, noisy breathing, difficulty breathing, stridor (a loud, harsh, high-pitched respiratory sound) muffled voice, severe pain and/or other severe symptoms, symptoms that worsen very quickly.

Patients eligible to avail of the study should be informed that the Royal College of Surgeons is carrying out a research project on how patients treat their sore throat and they should be asked at this point if they wish to participate.
3.2 Patient Enrolment

If the patient is eligible to enrol in the study and is happy to enrol in the study it will be necessary to then make sure that they understand exactly what participation in the study will mean for them. The pharmacy team member enrolling the patient to the study should now provide the patient with a copy of the Patient Information Leaflet. The patient should be given time to fully read the Patient Information Leaflet, to ask questions and discuss the study. Once the pharmacy team member is happy that the patient understands what the study involves, the patient is asked to give informed consent to each of the items listed on the Consent Form. The pharmacy team member must sign the Consent Form to declare that they have fully explained everything to the patient and that they are satisfied that the patient has the capacity to provide informed consent to enrol in the study. The patient must also sign the consent form. If the patient refuses to take part in the study or they cannot participate in the study for any reason (e.g. one of the exclusion criteria as noted above applied to them) this must be noted in the patient refusal form (Appendix 1).

The patient refusal form is a screening log to track the number of patients who refuse to take part in the study when, asked or they are excluded due to the exclusion criteria listed above.

3.3 Conducting the Patient Survey

Once the patient has enrolled on the study they can then proceed to complete the patient survey, “Patient Survey”. The patient survey requires the patient to carry out a self-assessment of the 4 Centor Criteria for the study. Following this the pharmacist will then complete the physical examination of the patient. The purpose of this is to compare the patients’ self-reported symptoms in both the intervention group and the control group.
3.4 Pharmacist Consultation

Once the patient has completed this survey, the pharmacist can then proceed with the service as normal. In addition to all materials required for the service, a Patient Feedback Survey must also be brought into the consultation room. The pharmacist will then carry out part 2 of the service in accordance with the training completed for the Sore Throat Test and Treat Service. All records on the Consultation Record Form must be completed accurately, clearly and in full. The pharmacist should confirm the patients’ contact details with them and ensure that all other details are correct. The carbon copy of the Consultation Record Form will be collected as part of the study data. The form should be checked to ensure the original copy and the carbon copy of the Consultation Record Form are lined up correctly so that information is transferred clearly to the carbon copy. It is essential that every section of the Consultation Record Form is filled out fully. At the end of the service, the patient will complete the Patient Feedback Survey. Before leaving the patient to fill out the Patient Feedback Survey, the patient should be informed that in approximately 7 days’ time a pharmacy researcher will phone them to conduct a short questionnaire on their sore throat.

3.5 Feedback Survey

At the end of the consultation the patient will be given a Patient Feedback Survey. Before handing this survey to the patient ID should be filled out on the form. This form will be given to the patient along with an envelope. The patient will be left in the consultation room by themselves to fill out the feedback survey. The patient will then place the survey in the envelope provided and seal it. This sealed envelope must then be sent back to Dr Gráinne Cousins along with a copy of the Consultation Record Form and the Patient survey.
3.6 Post Consultation Follow Up

In approximately 7 days time a pharmacy researcher will contact the patient for a follow up telephone interview. This will take between 5-10 minutes and the patient is asked about their sore throat.

4. Data Collection and Record Keeping

4.1 Creating a Patient ID

Each pharmacy has been assigned a pharmacy code for the study. This has been emailed to you by the Pharmacy Office team. The pharmacy code will be used to create a patient ID for every patient enrolled in the study. The patient ID will be made up of the pharmacy code followed by the order in which they enrol in the study. For example store 1711 has a pharmacy code of B1 and the first patient to sign up to and be eligible for the study is B1_01. All patient forms for the study, except the consent form, must have the relevant patient ID clearly marked.

4.2 Data Collection

The following forms should be completed, in full, for the study:

1. The Consultation Record Form
2. The Patient Survey
3. The patient ID on the Patient Feedback Survey
4. The Patient Identifier List, in an Excel file, which will be sent back to RCSI via email through HEAnet
5. The participation form (for those excluded or refused to join the study)
The patient ID should be filled out on every page on each of these documents. In order to have accurate data collection the pharmacist should check that every question has been answered.

4.3 Forwarding information electronically to RCSI

Information for follow up should be inputted into an Excel Spreadsheet, the Patient Identifier List, excel file and sent to Dr Gráinne Cousins in RCSI, every Monday and Thursday by 5pm as per SOP STS 1 Electronic Data Transfer. This information includes:

- Patient ID
- Patient name
- Date of birth
- Gender
- Contact number
- Date joined study
- Convenient time for follow up.

The Patient Identifier List excel file, will be sent to the pharmacy via email. This Patient Identifier List excel file should be saved to the desktop on the pharmacy computer. As the patients are enrolled in the study, the patient details should be inputted into the Patient Identifier List excel file. Before sending the Patient Identifier List excel file to RCSI, the file must be encrypted. In order to do this, use the AxCrypt encryption software, which has been sent to your master PC in your dispensary. If the AxCrypt software is not visible on your master PC please contact the lead researcher Claire O’Neill for further assistance. In the event that Claire is not available please contact the Pharmacy Office. The Patient Identifier List Excel file will be encrypted using this software and then sent to RCSI via a secure email network called HEAnet (https://filesender.heanet.ie). The full process for this is found in “Step by Step Guide 1 Sore Throat Study: Electronic Transfer” Appendix 2. This will be sent to RCSI twice weekly, so that follow up with the patient can be carried out on time.
4.4 Forwarding paperwork to RCSI via BIRD

Paperwork including the Consultation Record Form, the Patient Survey and the Patient Feedback Survey will be stapled together and sent back as soon as possible to RCSI, via BIRD (SOP STS 2 Document Transfer).

*Please note that any paperwork relating to the study cannot be kept in the pharmacy. All information is to be forwarded on to The Superintendent Pharmacist as soon as the paperwork for each patient, for the study, is completed.

When sending the carbon copy of the Consultation Record Form, the patient details on the left of the Consultation Record Form should be removed and the patient ID should be placed on the top of the remaining form as per SOP STS 2 Document Transfer and as shown below.

Please note the consent form must be sent to RCSI, via BIRD separately to the patient’s paperwork, this is a requirement of ethics the committee (SOP STS 2 Document Transfer).
This information will be gathered and provided to Claire O’Neill and Dr Gráinne Cousins in the Royal College of Surgeons, Stephens Green, Dublin 2. All information will be kept strictly confidential and will not be shared with any other third parties.

Appendix 1 Participation form

Sore Throat Study Participation Form

Store number:

Please note the date, whether the patient agreed to the service, if they agreed or refused the study and the reason why if they refused to participate in the study.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Date</th>
<th>Patient agreed to service? (Y/N)</th>
<th>Patient refused study? (Y/N)</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>12</td>
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</tr>
</tbody>
</table>

Appendix 2 SOP STS 1 Electronic Data Transfer
Please note: If your pharmacy has an intern, please follow SOP STS 1 Electronic Data Transfer A. If your pharmacy has no intern please follow SOP STS 1 Electronic Data Transfer B.

A. SOP Electronic Data Transfer A – with Intern

1. This SOP is to be completed by the Pharmacy Intern
2. Open the Excel file sent to the pharmacy via email on the pharmacy computer.
3. For each study participant input the following under the correct headings:
   a. Patient ID
   b. Patient name
   c. Gender
   d. Date of birth
   e. Contact number
   f. Date joined study.
4. Save the excel file on the desktop with the pharmacy code and the date e.g. B1_02092016.
6. Create a zipped folder. Right click on the file, go to ‘Send to’ and then click on ‘Compressed (zipped) folder.'
7. Open Ax Crypt2Go. Select the Patient ID file. Right click on the file and select ‘Encrypt’.

8. Every Monday and Thursday send this saved file to Dr Gráinne Cousins via the HEAnet.

9. Logon to https://filesender.heanet.ie using your RCSI username/password
Step 1

Step 2

Step 3

10. Send the encrypted Excel file to gcousins@rcsi.ie
   
   a. Please put Pharmacy Name and Pharmacy Code (e.g. B1) in the subject heading.
b. Please enter your name and site number in the message and any additional information you wish to include

c. Expiry date (click in this box and tick the last day available – last day will be one month from the day you are sending the message – e.g. today is January 20\textsuperscript{th}, latest expiry date available is 19\textsuperscript{th} February)

d. Click on browse, and upload the encrypted Excel file you saved & send.

e. Once the lead applicant has received and verified the data transfer, instructions will be sent to delete the patient information.
B. SOP STS 1 Electronic Data Transfer B – no Intern

1. This SOP is to be completed by the Pharmacist.

2. Open the Excel file sent to you via email on the pharmacy computer.

3. For each study participant input the following under the correct headings:
   a. Patient ID
   b. Patient name
   c. Gender
   d. Date of birth
   e. Contact number
   f. Date joined study.

4. Save the excel file on the desktop with the pharmacy code and the date e.g. B1_02092016.


   Choose AxCrypt2Go.exe

6. Create a zipped folder. Right click on the file, go to ‘Send to’ and then click on ‘Compressed (zipped) folder.’
7. Open AxCrypt2Go. Select the Patient ID file. Right click on the file and select ‘Encrypt’.

8. Every Monday and Thursday send this saved file to Dr Gráinne Cousins via the HEAnet.

9. A separate email will be received from Dr Gráinne Cousins. This contains a link to the HEAnet, a secure website for sending electronic files. Note that this can only be used once. When you are ready to transfer the data, please click the link (see below). If you have not yet received an email with an invite please email gcousins@rcsi.ie to obtain one.
When you click on the link you will be brought to the following page:

10. Send the Excel file to gcousins@rcsi.ie

   a. Please put Pharmacy Name and Study ID (e.g. B1) in the subject heading
   b. Please enter your name in the message and any additional information in relation to the interviews you wish to include.
   c. Expiry date (click in this box and tick the last day available – last day will be one month from the day you are sending the message – e.g. today is January 13th, latest expiry date available is 12th February).
d. Click **Choose File**, and upload the encrypted zipped file you saved and click **Send**.

e. Once the lead applicant has received and verified the data transfer, instructions will be sent to delete the patient information.
Appendix 3 SOP STS 2 Document Transfer

1. This SOP is to be completed by a pharmacy team member and checked by the pharmacist.

2. The following information is to be sent via registered post to the address listed below:
   a. Patient Consent Form
   b. Patient Record Form
   c. Consultation Summary Form
   d. Patient Survey
   e. Patient Feedback Survey (in sealed envelope)
   f. Refusal Form

3. For each patient ensure each section is filled in on the following documents:
   i. Patient Consent Form
   ii. Patient Record Form
   iii. Consultation Summary Form
   iv. Patient Survey

4. Place all consent forms in a separate envelope and send via REGISTERED post Dr Gráinne Cousins.

5. Remove all patient details from the carbon copy of the Patient Record Form and the Consultation Summary Form, as outlined below.

*Add patient ID*

*Cut off sections*
6. Place the patient ID on the top of every page of each document.

7. Staple the the carbon copy (with the patient details removed) of the Consultation Record Form, the Patient Survey and the sealed envelope containing the Patient Feedback survey together.

8. This documentation will be sent via the Boots Internal Recorded Delivery (BIRD), to the Superintendent Pharmacist in Park West.

9. Complete a BIRD Duo label with the full delivery address to the Superintendent Pharmacist in Park West and place attach it to the envelope. (Item code 99 03 607)

10. Complete the BIRD despatch list with the following information: (Item code 99 03 631)

   a. The delivery details
   b. Your shop number in the 'FROM' box
   c. Your name in the 'CONSIDED BY' box
   d. The serial number from the Duo label in the 'BIRD No' box
   e. The type of UOD in the 'CARTON ETC' box
   f. The name or shop number of who it's being sent to in the 'CONSIDED TO' box

11. Ask the driver to sign the despatch list and give him the top copy.

12. Obtain the driver's signature on the bottom of the despatch list and give them the top (pink) copy.


14. Fill in the number of BIRD UODs being despatched on the GIT note.

15. If you wish to enquire about any BIRD items please:

   a. Contact the recipient to check if they have received the item, if not:

      • Contact mailing services, D6 Beeston (telephone (0044) 115 968 9234) and advise them of the BIRD serial number and the despatch date
      • If there is no trace of the item; D6 will inform loss prevention immediately.
Appendix 4 FAQs Intervention Group

Why participate in research?

The services agenda is becoming more profitable for pharmacy and expanding our role as pharmacists in a positive way. In order for the pharmacy profession to expand their role in Ireland scientific evidence is required which shows that pharmacists are delivering services which are having a positive impact on patient care and the healthcare system. It is hoped that this study will show that the Sore Throat Test and Treat Service reduces the number of people attending their GP for the treatment of their sore throat and therefore reducing antibiotic prescribing.

Do I have to record if the patient is not eligible for the study or they do not want to participate in the study?

Yes. A refusal form is included in the study pack. Patient details are not required for this form. The date, the order in which they present to the pharmacy and the reason why (if they give it) are recorded on the form.

How many patients do I have to recruit?

Every pharmacy taking part in the study has a target of 25 patients to recruit. Patients must be recruited consecutively. This means that every patient as they approach the healthcare counter that is eligible for the study must be invited to join the study. If patients are not recruited consecutively it results in selection bias in the study, which could result in the study population differing from the general population. Thereby giving false results.

When do I have to recruit patients by?

We would like to recruit patients and gather data as quickly as possible to ensure this study is not part of an ongoing workload for the pharmacy team and to ensure that those pharmacies which part of the control group can implement the service in those stores as soon as possible. This type of infection tends to be in low circulation during the Spring and Summer months. Therefore, we would aim to have all patients recruited by the end of February, however, the study will run until the required number of patients have been recruited.
Who can provide information to patients and obtain informed consent?

The pharmacist or the trained Sore Throat Test and Treat healthcare team member can go through the patient information leaflet with the patient and obtain informed consent. However the pharmacist must be confident that anyone who is carrying out the study in the pharmacy is fully competent in obtaining informed consent.

Do I have to read the full patient information leaflet each time with the patient, or can I just give the rough details to the patient about what the study involves?

In order to obtain informed consent and for informed consent to be valid, the patient must fully understand the study. Therefore you must read through the patient information leaflet in full with every patient.

What if I forget to write the Patient ID on the Patient Feedback Survey before giving it to the patient to fill out?

If this happens, do not open the envelope, instead place the patient ID on the envelope.

How will information be sent back to RCSI?

Information will be sent back in two ways. These are outlined in Appendix 7 & 8. The Patient Identifier List must be sent electronically via HEAnet. All other forms must be sent back anonymised via registered post.
Contact Details

Study Supervisor:

Dr. Gráinne Cousins
Address: School of Pharmacy, Royal College of Surgeons in Ireland, Dublin 2.
Phone No: 01- 402 2551 (Mon-Fri 9am -5pm)

Pharmacy Researcher

Claire O’ Neill
Phone No: 01-4969700
Email: claireoneill@rcsi.ie

References

Appendix 4b: Sore Throat Study Guidance Pack – Control Group

Sore Throat Study

Study Guidance Pack
Control Pharmacies
Sore Throat Study

Impact of a Pharmacy-led screening service for Group A β-haemolytic streptococci, on general practitioner visits and antibiotic consumption: a non-randomized control study

1. Introduction

Most people suffer between two to three sore throat episodes per year (1). Approximately 40% of people experiencing a severe sore throat visit their GP (2) and sore throats account for 3.5% of GP visits in Ireland (3). The majority of sore throats occur due to a viral infection (80%), with 85% of cases being fully resolved after 7 days (1, 4). It is estimated that between 5-17% of sore throats are caused by a bacterial infection, generally a strain of the many β-haemolytic streptococci (5). Antibiotic treatment is only recommended for one particular strain, Group A β-haemolytic Streptococci (GABHS) (5).

To reduce the level of prescribing of inappropriate antibiotics, the Infectious Diseases Society of America recommend the use of a Rapid Antigen Detection Test (RADT) in combination with the Centor Criteria (6). The RADT is a detection method for Group A Streptococcal antigen from throat swabs (7). They recommend treating those with a positive rapid test and withholding antibiotics in rapid test negative patients.

In November 2015 Boots Ireland introduced a Sore Throat Test and Treat Service. This service involves a clinical assessment based on the Centor Criteria, in conjunction with a diagnostic test (where indicated) designed to identify the presence of GABHS. The service aims to support the differential diagnosis of uncomplicated sore throats of between 3 and 9 days duration with the aim of reducing unnecessary antibiotic usage where this may not be clinically indicated.

In order to determine if the service does indeed support more rational use of antibiotic therapy Boots has partnered with the Royal College of Surgeons in Ireland to conduct a research study “Impact of a Pharmacy-led screening service for Group A β-haemolytic streptococci, on general practitioner visits and antibiotic consumption: a non-randomized control study”. The aim of this study is to determine the impact of the Boots
Sore Throat Test and Treat Service, on the number of people visiting their GP and the use of antibiotics for sore throat treatment.

2. The Sore Throat Study

From February 2016 twenty Boots pharmacies will begin recruiting patients to the Sore Throat Study. The study is designed as a non-randomised controlled, parallel trial of adults aged 18 years and over, presenting to one of 20 Boots community pharmacies in Ireland with an uncomplicated sore throat. Ten pharmacies will be assigned to the Intervention Group, where patients availing of the Boots Sore Throat Test and Treat Service will be eligible to join the study. The other ten pharmacies will be assigned to the Control Group and in this pharmacy recruited patients will receive usual care (i.e. they will NOT receive the Boots Sore Throat Test and Treat Service).

The remainder of the information in this guide relates to conduct of the study in the Control Group ONLY.
3. Patient Journey

3.1 Patient Recruitment

Patients will present as normal to the healthcare counter. In patients presenting with a sore throat a normal OTC consultation will take place following the SOMP, with referral to pharmacist if necessary.

As the OTC consultation is coming to a close, patients will be invited to participate in the study* provided they fulfil the following eligibility criteria:

- aged ≥ 18 years
- presenting to pharmacy with a sore throat lasting at least 3 days and less than 10 days, with no reported symptom improvement.

Patients will be excluded if:

- they have already taken antibiotics for their sore throat
- they report an improvement in symptoms.

Patients reporting the following specific ‘red flag’ symptoms will also be excluded: presence of skin rash, dysphagia (difficulty swallowing), drooling, noisy breathing, difficulty breathing, stridor (a loud, harsh, high-pitched respiratory sound) muffled voice, severe pain and/or other severe symptoms, symptoms that worsen very quickly.

Patients eligible to avail of the study should be informed that the Royal College of Surgeons is carrying out a research project on how patients treat their sore throat and they should be asked at this point if they wish to participate.

*Please note: Patients must be recruited consecutively. This means that every patient, as they approach the healthcare counter, that is eligible for the study must be invited to join the study. If patients are not recruited consecutively it results in selection bias in the study, which could result in the study population differing from the general population. This could result in an inaccurate study.

3.2 Patient Enrolment

If the patient is eligible to enroll in the study and is happy to enroll in the study it will be necessary to then make sure that they understand exactly what participation in the
study will mean for them. The pharmacy team member enrolling the patient to the study should now provide the patient with a copy of the Patient Information Leaflet. The patient should be given time to fully read the Patient Information Leaflet, to ask questions and discuss the study. Once the pharmacy team member is happy that the patient understands what the study involves, the patient is asked to give informed consent to each of the items listed on the Patient Consent Form. The pharmacy team member* must sign the Patient Consent Form to declare that they have fully explained everything to the patient and that they are satisfied that the patient has the capacity to provide informed consent to enroll in the study. The patient must also sign the Patient Consent Form. Two copies of the Patient Consent Form are required to be completed, one copy is given to the patient and the second copy is placed in an envelope and sent to The Superintendent Pharmacist in Park West as per details in Appendix 3.

*Please note: the pharmacist must be confident that those pharmacy team members who are obtaining informed consent from the patient, are fully competent and understand the process in full before carrying this out.

If the patient refuses to take part in the study or they cannot participate in the study for any reason (e.g. one of the exclusion criteria as noted above applied to them) this must be noted in the Sore Throat Study Refusal Form (Appendix 1).

The Refusal Form is a screening log to track the number of patients who refuse to take part in the study when asked, or who are excluded due to the exclusion criteria listed above.

3.3 Conducting the Patient Survey

Once the patient has enrolled on the study they can then proceed to complete the patient survey, “Patient Survey”. The Patient Survey requires the patient to carry out a self-assessment of the 4 Centor Criteria for the study. The purpose of this is to compare the patients’ self-reported symptoms in both the intervention group and the control group. The Patient Survey should be carried out by a pharmacy team member who has been trained in the study; it should not be carried out by the pharmacist. The reason for this being that, pharmacists will have received training in the Sore Throat Test and Treat Service and may influence the patient.
The pharmacy team member should go through the Patient Survey with the patient, asking them each question and noting the patient’s response. The Patient Survey requires the patient’s temperature to be taken by the pharmacy team member. The thermometer that will be used to assess a patient’s temperature is Boots Pharmaceuticals Non-Contact Thermometer (item code 60-95-208). Instructions for use of this thermometer are provided in the product packaging and a brief outline is provided as follows:

i. Check that forehead is free from perspiration and hair is moved aside

ii. Avoid drafts

iii. Ensure that the thermometer display is in ‘Forehead Temperature’ mode and that the acoustic signal is switched on

iv. Direct the thermometer at the forehead (not the eyebrows), holding it about 2-3cm from the forehead

v. Press the SCAN button and move the thermometer from side to side over the forehead area

vi. The temperature is displayed within 2-30 seconds. Note that during the measurement you will hear short beeps which signal that a new highest temperature is reached.

vii. The end of the measurement is signalled by a long beep. Once you hear the long beep you can read the measured value

3.4 Closing the Study Consultation

Prior to closing the consultation the pharmacy team member should check that all information and questions have been filled in on the Patient Survey and that the patient’s contact details are correct.
Once the patient has completed this survey, the pharmacy team member should inform the patient that a RCSI pharmacy researcher will contact the patient in approximately 7 days time, to conduct a short questionnaire on their sore throat.

3.5 Post Consultation Follow Up

In approximately 7 days time a RCSI pharmacy researcher will contact the patient for a follow up telephone interview. This will take between 5-10 minutes and the patient is asked about their sore throat.

4. Data Collection and Record Keeping

4.1 Creating a Patient ID

Each pharmacy has been assigned a pharmacy code for the study. In order to ensure the lead researcher is blinded to the code for each pharmacy the unique code for each pharmacy will be emailed directly to the pharmacy team. The pharmacy code will be used to create a patient ID for every patient enrolled in the study. The patient ID will be made up of the pharmacy code followed by the order in which they enroll in the study. For example store if pharmacy 1711 has a pharmacy code of B1 then the first patient to be recruited to the study in 1711 would be given the Patient ID B1_01.

Please note: All patient forms for the study, except the Patient Consent Form, must have the relevant patient ID clearly marked.

4.2 Data Collection

The following forms should be completed, in full, for the study:

6. The Patient Consent Form
7. The Patient Survey*
8. The Patient Identifier List. This contains patient contact data which will enable the pharmacy researcher in RCSI to contact the patient. This information is obtained from the first page of the patient survey and inputted into the Patient Identifier List excel file, which will be sent back to RCSI via secure email through HEAnet to protect patient confidential information (see point 4.3 for details of transfer).

9. The Patient Refusal form (for those excluded or refused to join the study)

*The patient ID should be filled out on every page of the patient survey. In order to have accurate data collection the pharmacist should check that every question has been answered.

4.3 Forwarding information electronically to RCSI

Information to enable telephone follow up should be inputted into the Patient Identifier List excel file and sent to Dr Gráinne Cousins in RCSI, every Monday and Thursday by 5pm as per Step by Step Guide 1 Sore Throat Service: Electronic Data Transfer. This information includes:

- Patient ID
- Patient name
- Date of birth
- Gender
- Contact number
- Date joined study
- Convenient time for follow up.

The Patient Identifier List excel file, will be sent to the pharmacy via email. This Patient Identifier List excel file should be saved to the desktop on the pharmacy computer. As the patients are enrolled in the study, the patient details should be inputted into the Patient Identifier List excel file. Before sending the Patient Identifier List excel file to RCSI, the file must be encrypted. In order to do this, use the AxCrypt encryption software, which has been sent to your master PC in your dispensary. If the AxCrypt software is not visible on your master PC please contact the lead researcher Claire O’Neill for further assistance. In the event that Claire is not available please contact the
Pharmacy Office. The Patient Identifier List Excel file will be encrypted using this software and then sent to RCSI via a secure email network called HEAnet (https://filesender.heanet.ie). The full process for this is found in “Step by Step Guide 1 Sore Throat Study: Electronic Transfer” Appendix 2. This will be sent to RCSI twice weekly, so that follow up with the patient can be carried out on time.

4.4 Forwarding paperwork to Park West

All paperwork relating to the study must be returned to The Superintendent Pharmacist Parkwest as soon as the patient has completed it. This will be done through the Boots Internal Recorded Delivery System, as described in Appendix 3 Step by Step Guide 2 STS: Document Transfer.

The paperwork to be returned to The Superintendent Pharmacist is as follows:

- Patient Survey (with page 1 removed*)
- Patient Consent Form x 1 copy (other copy to be provided to the patient as their record)

**NB Page 1 MUST be removed to protect patient confidentiality.**

So as to protect patient confidentiality the Patient Survey and the Patient Consent Form must be sent separately. The relevant form should be placed in an envelope and addressed to:

The Superintendent Pharmacist
Boots Ireland
Unit 2F, Block 71A,
Park West Business Park
Nangor Road,
Dublin 12
Once received in Park West this information will be gathered and provided to Claire O’Neill and Dr Gráinne Cousins in the Royal College of Surgeons, Stephens Green, Dublin 2 to support analysis. All information will be kept strictly confidential and will not be shared with any other third parties.

### Appendix 1: Refusal Form

#### Sore Throat Study Refusal Form

Store number:

*If a patient refuses to participate in the study, please mark the date and the reason why, in the order they present to the pharmacy.*

<table>
<thead>
<tr>
<th>Patient Refused</th>
<th>Date</th>
<th>Why?</th>
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<td>17</td>
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</tbody>
</table>
Appendix 2: Step by Step Guide 1 Sore Throat Study (STS): Electronic Data Transfer

Please note: If your pharmacy has an intern, please follow Step by Step Guide 1 STS: Electronic Data Transfer A. If your pharmacy has no intern please follow Step by Step Guide 1 STS: Electronic Data Transfer B.

A. Step by Step Guide 1 STS: Electronic Data Transfer A – with Intern

1. This Step by Step Guide is to be completed by the Pharmacy Intern
2. Open the Excel file sent to you via email on the pharmacy computer.
3. For each study participant input the following under the correct headings:
   a. Patient ID
   b. Patient name
   c. Gender
   d. Date of birth
   e. Contact number
   f. Date joined study.
4. Save the excel file on the desktop with the pharmacy code (Appendix 1) and the date e.g. B1_02092016.
5. Every Monday and Thursday send this saved file to Dr Gráinne Cousins via the HEAnet.
6. Create a zipped folder. Right click on the file, go to ‘Send to’ and then click on ‘Compressed (zipped) folder.

7. Open AxCrypt2Go software. Select the Patient ID file. Right click on the file and select ‘Encrypt’.

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8. Logon to https://filesender.heanet.ie using your RCSI username/password

**Step 1**

![HEAnet FileSender](image)

**Step 2**

![Choose your home organisation to login to HEAnet Filesender](image)

**Step 3**

![Royal College of Surgeons in Ireland](image)
9. Send the encrypted Excel file to gcousins@rcsi.ie
   
a. Please put Pharmacy Study ID (e.g. B1) in the subject heading.

   a. Please enter your name and pharmacy study ID number in the message and any additional information you wish to include

   b. Expiry date (click in this box and tick the last day available – last day will be one month from the day you are sending the message – e.g. today is January 20th, latest expiry date available is 19th February)

   c. Click on browse, and upload the encrypted Excel file you saved & send.

   d. Once the lead applicant has received and verified the data transfer, instructions will be sent to delete the patient information.
**Step by Step Guide 1 STS: Electronic Data Transfer B – no Intern**

1. This Step by Step Guide is to be completed by the Pharmacist.
2. Open the Excel file sent to you via email on the pharmacy computer.
3. For each study participant input the following under the correct headings:
   a. Patient ID
   b. Patient name
   c. Gender
   d. Date of birth
   e. Contact number
   f. Date joined study.
4. Save the excel file on the desktop with the pharmacy code and the date e.g. B1_02092016.
5. Every Monday and Thursday send this saved file to Dr Gráinne Cousins via the HEAnet.
6. Create a zipped folder. Right click on the file, go to ‘Send to’ and then click on ‘Compressed (zipped) folder.
7. Open AxCrypt2Go encryption software. Select the Patient ID file. Right click on the file and select ‘Encrypt’.
8. A separate email will be received from Dr Gráinne Cousins. This contains a link to the HEAnet, a secure website for sending electronic files. Note that this can only be used once. When you are ready to transfer the data, please click the link (see below). If you have not yet received an email with an invite please email gcousins@rcsi.ie to obtain one.

When you click on the link you will be brought to the following page:

9. Send your Excel file to gcousins@rcsi.ie
a. Please put Pharmacy Study ID (e.g. B1) in the subject heading

b. Please enter your name and pharmacy study ID in the message and any additional information in relation to the interviews you wish to include.

c. Expiry date (click in this box and tick the last day available – last day will be one month from the day you are sending the message – e.g. today is January 13th, latest expiry date available is 12th February).

d. Click Choose File, and upload the encrypted zipped file you saved and click Send.

e. Once the lead applicant has received and verified the data transfer, instructions will be sent to delete the patient information.
Appendix 3: Step by Step Guide 2 Sore Throat Study: Document Transfer

1. This Step by Step Guide is to be completed by a pharmacy team member and checked by the pharmacist.

2. The following information is to be sent via BIRD as described in section 4.4 of the Study Guidance Pack:
   a. Patient Consent Form
   b. Patient Survey (Page 1 of document removed)
   c. Refusal Form (sent at end of study period)

3. Complete a BIRD Duo label with the full delivery address to The Superintendent Pharmacist in Park West and place attach it to the envelope. (Item code 99 03 607)

4. Complete the BIRD dispatch list with the following information: (Item code 99 03 631)
   a. The delivery details
   b. Your shop number in the 'FROM' box
   c. Your name in the 'CONSIGNEE BY' box
   d. The serial number from the Duo label in the 'BIRD No' box
   e. The type of UOD in the 'CARTON ETC' box
   f. The name or shop number of who it's being sent to in the 'CONSIGNEE TO' box

5. Ask the driver to sign the dispatch list and give him the top copy.

6. Obtain the driver’s signature on the bottom of the dispatch list and give them the top (pink) copy.


8. Fill in the number of BIRD UODs being dispatched on the GIT note.

9. If you wish to enquire about any BIRD items please:
   a. Contact the recipient to check if they have received the item, if not:
      • Contact mailing services, D6 Beeston (telephone (0044) 115 968 9234) and advise them of the BIRD serial number and the dispatch date

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• If there is no trace of the item; D6 will inform loss prevention immediately.

Appendix 4: FAQs Control Group

Why participate in research?

In order for the pharmacy profession to expand their role in Ireland scientific evidence is required which shows that pharmacists are delivering services which are having a positive impact on patient care and the healthcare system. It is hypothesised that the Sore Throat Test and Treat Service has the potential to support a reduction in the number of patients visiting a GP and/or taking an antibiotic for their sore throat. The purpose of the study is to determine if that hypothesis is correct.

Do I have to record if the patient is not eligible for the study or they do not want to participate in the study?

Yes. A refusal form is included in the study pack. Patient details are not required for this form. The date, the order in which they present to the pharmacy and the reason why (if they give it) are recorded on the form.

How many patients do I have to recruit?

Every pharmacy taking part in the study has a target of 25 patients to recruit. Patients must be recruited consecutively. This means that every patient as they approach the healthcare counter that is eligible for the study must be invited to join the study. If patients are not recruited consecutively it results in selection bias in the study, which could result in the study population differing from the general population. This could result in an inaccurate study.

When do I have to recruit patients by?

We would like to recruit patients and gather data as quickly as possible to ensure this study is not part of an ongoing workload for the pharmacy team and to ensure that those pharmacies which part of the control group can implement the service in those stores as soon as possible. This type of infection tends to be in low circulation during the Spring and Summer months. Therefore, we would aim to have all patients recruited by the end of April however, the study will run until the required number of patients have been recruited.

At what point do I recruit patients?

The patient is invited to join the study when the OTC consultation is closing. The OTC consultation with the patient has been carried out as normal, the SOMP has been followed, and if necessary the pharmacist has spoken to the patient. The patient may have been referred to their doctor, received OTC treatment or lifestyle advice. As you are closing the consultation you inform the patient that a university, the Royal College of Surgeons is carrying out a study on sore throats in the community and ask them would they like to take part.
Who can provide information to patients and obtain informed consent?

The pharmacist or the trained Sore Throat Test and Treat healthcare team member can go through the patient information leaflet with the patient and obtain informed consent. However the pharmacist must be confident that anyone who is carrying out the study in the pharmacy is fully competent in obtaining informed consent.

Do I have to read the full patient information leaflet each time with the patient, or can I just give the rough details to the patient about what the study involves?

In order to obtain informed consent and for informed consent to be valid, the patient must fully understand the study. Therefore you must read through the patient information leaflet in full with every patient.

Why can only a healthcare team member carry out the patient survey with the patient?

All pharmacists will have been trained on the Sore Throat Test and Treat Service, therefore for ethical reasons the patient must only go through the patient survey with an appropriately trained healthcare team member.

Contact Details

Study Supervisor:

Dr. Gráinne Cousins
Address: School of Pharmacy, Royal College of Surgeons in Ireland, Dublin 2.
Phone No: 01-402 2551 (Mon-Fri 9am -5pm)

Pharmacy Researcher

Claire O’ Neill
Phone No: 01-4969700
Email: claireoneill@rcsi.ie

References


Sore Throat Test and Treat Service – Consultation Record Form

1. Pre-screening Consultation

To be completed by an authorized Pharmacist or healthcare team member

Team name: ________________________

Time: ________________________

Patient's reason for choosing the service:

Self-referral

Referral by Doctor

Referral by Pharmacist

Pharmacy team recommendation


Data of Birth: _______________

Gender: Male Female

In May

Are there any medications or allergies to which the patient is sensitive?

Yes No

Signature: ________________________

Date: ________________________

Pharmacist consultation


2. Clinical Consultation

Part I

1.1 Patient's History

Date of Birth: _______________

Age: _______________

Sex: Male Female

Past medical history:

Date of Admission: _______________

Date of Discharge: _______________

Hospital: ________________________

2.1 Clinical Examination

(a) General appearance:

(b) Physical examination:

(c) Laboratory investigations:

(d) Radiological investigations:

(e) Clinical diagnoses:

(f) Treatment plan:

(g) Follow-up:

3. Consultation Outcome

Self-management advice given:

Yes No

OTC products recommended:

Yes No

Referred to Doctor:

Yes No

Appendix 5: Consultation Record Form
Sore Throat Test and Treat Service at Boots Pharmacy

Boots Ireland are providing a Sore Throat Test and Treat Service to help patients determine the best treatment options for their sore throat. The service involves a pre-screen to determine eligibility for the service followed by an assessment using the Centor Criteria. This involves scoring against the following criteria:

- Absence of cough
- History of fever
- Tonsillar exudate
- Tender anterior cervical lymph nodes

With one point scored for each symptom present. If the patient has a Centor Score of 3 or greater, they are offered the option of having a Throat Swab* designed to detect the presence of Group A Streptococcus. For patients with a Centor score of greater than or equal to 3, and who has tested positive for Group A Streptococcus, antibiotics may be recommended.

A consultation summary for patient ________________________________ is provided opposite.

Please don’t hesitate to contact me if you have any questions.

Yours sincerely,

______________________________
Pharmacist

*The throat swab used is the Opsona Sore A Rapid Antigen Test manufactured by Salixs Diagnostics UK Ltd. (96% sensitivity and 97% specificity)

Consultation Summary

Patient information

First name: ___________________________
Address: ____________________________
Date of birth: _______________________

Patient Assessment

Pre-screen completed? Yes No
Throat swab test completed? Yes No
Centor Score: A/A
Test result: Positive Negative

Consultation Conducted by:
Pharmacist Name: __________________
PSI Number: __________________

About Antibiotics

This service has been developed to help reduce the use of antibiotics in situations where they might not be needed.

- Bacteria can become ‘antibiotic-resistant’ by adapting to, and finding ways of surviving the effects of antibiotics
- The likelihood of this happening increases the more we use antibiotics
- Antibiotic-resistant bacteria don’t just put you at risk, they spread to those in close contact as well

We all need to cut down the use of antibiotics to help slow down bacterial resistance, as resistance to antibiotics is one of the biggest threats facing us today. Routine treatments like setting broken bones, basic operations and even chemotherapy become increasingly dangerous without effective antibiotics.

If we have identified that your sore throat is not likely to have been caused by a Strep A infection, then antibiotics are not recommended as it is most likely your sore throat is caused by a virus. The good news is that such infections usually get better without the need for medications such as antibiotics.
Appendix 7a: Patient Survey – Intervention Group

Note: This form should be filled out prior to an authorised Sore Throat Test and Treat Service (STTTS) pharmacist conducting the physical examination of the patient as part of the STTTS. It should be completed by a pharmacist or pharmacy team member who has successfully completed training in conducting the Sore Throat Test and Treat Service Study and is authorised to conduct any study related procedures.

Convenient time to contact: ________________
Patient ID: ____________________________
Date completed survey: ________
Form completed by: ____________________
Store number: _________________________

Section 1 - Eligibility Criteria Checklist – Interviewer to fill out
Please note: The patient must be eligible for the Sore Throat Test and Treat Service and be OVER 18 YEARS of age, in order to be eligible for the STUDY. If the patient is under 18 but 16 years or over they are still eligible for the service, however they cannot take part in the study. Please ensure all information has been obtained from section 1.1 in the Consultation Record Form before proceeding to section 2.

Is the patient under 18 years old? [ ] Yes [ ] No

Interviewer: Thank you for agreeing to take part in the study. Before we continue with the rest of the Sore Throat Service I am going to ask you a few questions about your sore throat. Answer as best you can, if you are unsure or do not understand please feel free to ask any questions.

1. Do you have a temperature? [ ] Yes [ ] No
2. Did you take a reading of your temperature with a thermometer? [ ] Yes [ ] No
3. If yes, do you remember what the reading of the temperature was and when you took it? ___ <sup>°</sup>C ___
   Date patient recorded this temperature: ____________________
4. Did you take any medication in the last 8 hours? [ ] Yes [ ] No
5. If yes, what did you take? __________________________

6. What dose did you take? __________________________

7. How long have you been taking this dose? __________________________

8. Do you have a cough? Yes ☐ No ☐

9. Is your throat sore to touch on the outside? Yes ☐ No ☐

10. If yes, can you mark on the picture on the following page the location of where it is sore to touch? (Image 1) Yes ☐ No ☐

11. Have you looked into your mouth to check your throat or tonsils? Yes ☐ No ☐

12. If yes, what did you notice? __________________________

13. Please tick as appropriate, if patient mentions any of the following:

- Puss, white spots ☐
- Redness ☐
- Swelling ☐

Image 1
Patient Details:

1. Do you have a medical card? Yes ☐ No ☐
2. Do you have a GP visit card? Yes ☐ No ☐

If female:
3. Are you pregnant? Yes ☐ No ☐
4. Are you breastfeeding? Yes ☐ No ☐

Pharmacy - team member: We have come to the end of the questions for the study, thank you very much for taking the time to help us with our study. We will contact you by phone in approximately 7 days time to follow up with you, to see how your throat is. This follow-up will take between 5 to 10 minutes. If you have any further questions about your sore throat or concerns about the study, please phone or come into the pharmacy to speak with us.

You will now continue to the Sore Throat Test and Treat Service. Thank you for your time.
Appendix 7b: Patient Survey – Control Group

Note: This form should be completed by a pharmacist or pharmacy team member who has successfully completed training in conducting the Sore Throat Test and Treat Service Study and is authorised to conduct any study related procedures.

To be completed by a pharmacy team member

Date survey completed: _________________

Patient Information

First Name: ___________________________
Surname: ___________________________
Date of Birth: _________________________
Gender: Male [ ] Female [ ]
Contact number: _______________________
Convenient time to contact: _______________

Patient ID: ___________________________ Yes [ ] No [ ]
Are you currently taking any medication or diagnosed with a medical condition?
If yes, please detail:

1. Have you had symptoms for 10 days or more? Yes ☐ No ☐
2. Have you had symptoms for less than 3 days? Yes ☐ No ☐
3. Are you under 18 years old? Yes ☐ No ☐
4. Have you already taken antibiotics for this sore throat? Yes ☐ No ☐
5. Are your symptoms improving? Yes ☐ No ☐

Note any symptoms or additional information in the space below:

For Pharmacy team member attention: Please note red flag symptoms that may indicate referral include: skin rash, dysphagia (difficulty swallowing, drooling, noisy breathing, difficulty breathing, stridor [a loud, harsh, high-pitched respiratory sound] muffled voice, severe pain and/or other severe symptoms, symptoms that worsen very quickly (If patient has mentioned any of the above, please refer to pharmacist)

Section 2 - Sore Throat Symptoms
Pharmacy healthcare team member: I am going to ask you a few questions about your sore throat. Answer as best you can, if you are unsure or do not understand please feel free to ask any questions.

6. Do you have a temperature? Yes ☐ No ☐
7. Did you take a reading of your temperature with a thermometer? Yes ☐ No ☐
8. If yes, do you remember what the reading of the temperature was and when you took it? ☑ °C

9. Date patient recorded this temperature: ____________________

10. If no, do you mind if I take a reading of your temperature? Yes ☐ No ☐

Patient’s temperature: ☑ °C
11. Did you take any medication in the last 8 hours?  
   Yes  [ ]  No  [ ]

12. If yes, what did you take?  
   ____________________________________________________________

13. What dose of medication did you take, i.e., how many tablets?  
   ____________________________________________________________

14. How long have you been taking this medication for?  
   ____________________________________________________________

15. Do you have a cough?  
   Yes  [ ]  No  [ ]

16. Is your throat sore to touch on the outside?  
   Yes  [ ]  No  [ ]

17. If yes, can you mark on the picture on the following page the location of where it is sore to touch? (Image 1)  
   Yes  [ ]  No  [ ]

18. Have you looked into your mouth to check your throat or tonsils?  
   Yes  [ ]  No  [ ]

19. If yes, what did you notice?  
   ____________________________________________________________

20. Please tick as appropriate, if patient mentions any of the following:
   - Puss, white spots  [ ]
   - Redness  [ ]
   - Swelling  [ ]
Patient Details:

21. Do you have a medical card? 
   Yes [ ] No [ ]

22. Do you have a GP visit card? 
   Yes [ ] No [ ]

If female:

23. Are you pregnant? 
   Yes [ ] No [ ]

24. Are you breastfeeding? 
   Yes [ ] No [ ]

Pharmacy healthcare team member: We have come to the end of the questions, thank you very much for taking the time to help us with our study. We will contact you by phone in approximately 7 days time to follow up with you, to see how your throat is. This follow-up will take between 5 to 10 minutes. If you have any further questions about your sore throat or concerns about the study, please phone or come into the pharmacy to speak with us.

Section 3 - Pharmacy team member to fill out

Please note: This section is to be completed in consultation with the pharmacist
### Outcome of OTC consultation:

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTC treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self care advice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Referred to doctor</td>
<td></td>
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</tr>
</tbody>
</table>

**Reason:**

________________________________________
Appendix 7c: Patient Satisfaction Survey – Intervention Group

Thank you for taking part in the study. The following questions are about your experience of the service. This is completely confidential. Mark the appropriate answer with an X. After you are finished answering the questions, please place this form in the envelope provided and seal the envelope. By doing this no one in the pharmacy will have access to your answers and it will be directly forwarded to Dr Gráinne Cousins and Claire O’Neill, researchers in the Royal College of Surgeons in Ireland, Stephen’s Green, Dublin 2.

Patient ID: _________________________

1. How satisfied were you with the service?

   Very satisfied □ Satisfied □ Neither satisfied or dissatisfied □ Dissatisfied □ Strongly dissatisfied □

2. How satisfied were you that all your symptoms were addressed in the pharmacy?

   Very satisfied □ Satisfied □ Neither satisfied or dissatisfied □ Dissatisfied □ Strongly dissatisfied □

3. How satisfied were you that the pharmacist answered any questions you had?

   Very satisfied □ Satisfied □ Neither satisfied or dissatisfied □ Dissatisfied □ Strongly dissatisfied □

4. During the Sore Throat Test and Treat Service did the pharmacist explain things in a way that was easy to understand?

   No, definitely not □ Yes, somewhat □ Yes, definitely □

5. How confident are you that you can manage your sore throat symptoms with the advice you were given today?

   Very confident □ Confident □ Neutral □ Uncertain □ Very uncertain □
6. How satisfied were you with the level of privacy you received?

Very satisfied □  Satisfied □  Neither satisfied or dissatisfied □  Dissatisfied □  Strongly dissatisfied □

7. How long did you wait in the pharmacy for the service?

0 minutes □
less than 5 minutes □
less than 10 minutes □
more than 10 minutes □
I called back at a later stage □

8. Did you make an appointment for the service, before coming in to the pharmacy?

Yes □  No □

9. Why did you choose the Sore Throat Treat and Test Service?

Convenience □
Trust in pharmacist □
Did not want to pay to see GP □
I wanted to know if it was viral before seeing GP □

10. Would you choose to use this service in the future for a sore throat?

Yes □  Maybe □  No □
11. How did you find out about the service?

In the pharmacy     Referred from another Boots

Advertising     Online

Friend / Relative     Other

12. Would you recommend the service to a friend?

Yes     Maybe     No

Additional comments

Have you any additional comments or suggestions you would like to make? If yes please fill out details here: