**Title:** The importance of obtaining a sputum sample and how it can aid diagnosis and treatment

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Declaration of Interests

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**Abstract:** Respiratory disease has a major impact on the NHS and continues to be a growing problem as each year passes. However through improving diagnosis and management of respiratory disease the problem could be lessened. Sputum samples are common practice within respiratory medicine especially for chronic obstructive pulmonary disease (COPD) patients and helps to diagnose, confirm infection and offers correct treatment. It is important that the multidisciplinary team (MDT) are aware of how to appropriately obtain sputum samples and when to request them. It is important as a respiratory professional to understand the patients usual sputum history including colour, amount and viscosity. Antibiotic stewardship aims to reduce antibiotic resistance through offering the most appropriate antibiotics for those with a bacterial infection and to discourage antibiotic prescribing for those that have not. This should result in better patient outcomes and lower healthcare costs.

In the UK one in five people have been diagnosed with a respiratory disease (Public Health England (PHE), 2015) around 12 million people in total in 2013 (British Lung Foundation (BLF), 2016: 14). This figure is likely to be higher due to undiagnosed cases of respiratory diseases such as COPD (PHE, 2015). Subsequently lung disease is a major burden on UK health services resulting in over 700,000 hospital admissions each year. Improving diagnosis and disease management are important in the strategy to decrease both societal and personal burden borne by patients and carers (BLF, 2016; PHE, 2015; Kuprys-Lipinska and Kuna, 2014)*.*

**Key Points**

1. Respiratory disease particularly COPD impacts greatly on society and national and local policies are being implemented to help lessen the burden.
2. Sputum collection is very important to aid diagnosis and treatment.
3. There are various ways to collect sputum samples with the most used approach being the sputum pot, however there are advantages and disadvantages to each technique.
4. Antibiotic stewardship aims to improve antibiotic use meaning improved patient outcomes, decreased healthcare costs and reduced antibiotic resistance.

Key Words

* Sputum
* Sample
* Antibiotics
* Respiratory
* Patient
* COPD

Importance of Sputum Samples

The collection of sputum is one of the most common tests within respiratory medicine (Hickin, Renshaw and Williams, 2015). Sputum is (coughed up and spat out) salivary matter mixed with mucus or pus from the respiratory tract (British Dictionary, 2012). Mucus is naturally made by the cells in the trachea and bronchial tubes and lines the airways to prevent harmful substances entering the lungs by keeping the airways moist which prevents dust, viruses and bacteria from passing into the lungs (Preston and Kelly, 2017). If any substances do enter the lungs the cilia will attempt to remove them enabling the individual to swallow the mucus or cough it out (Preston and Kelly, 2017; Fahy and Dickey, 2010). In chronic respiratory disease too much mucus is often produced causing the cells that produce the mucus to expand, resulting in limited airflow, breathlessness and cough, often impacting on ventilation and causing infection (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2019; Preston and Kelly, 2017).

Sputum samples are important to confirm a respiratory tract infection and its sensitivities to antibiotics (Shepherd, 2017). Respiratory tract infections can be defined as any infectious disease involving the upper or lower respiratory tract, including a cold, tonsillitis/pharyngitis, laryngitis, acute rhinitis, acute bronchitis, bronchiolitis, pneumonia and tracheitis (National Institute for Health and Care Excellence (NICE), 2008). It can be difficult to diagnose respiratory infections particularly in COPD patients as symptoms are often longstanding meaning sputum samples are vital to determine if bacteria is present particularly if symptoms such as cough and sputum production is increased and purulent (NICE, 2018a; Cukic, 2013). Frequent and repeated cellular and airway inflammation driven by bacteria, has significant pathophysiological effects and thus worsens clinical outcomes for patients (Beasley, et al., 2012). As such, where lower tract respiratory infection is present sputum samples are important in guiding appropriate antibiotic therapy (Reychler, et al., 2016).

Understanding a patients usual sputum production (e.g. colour, viscosity, amount) is important in assessment of patient symptoms, as changes from this baseline may identify infection (Preston and Kelly, 2017; American Thoracic Society, 2015). It is important to note amount, colour, consistency and odour when reviewing sputum (Hickin, Renshaw and Williams, 2015). See figure 1.0 for different sputum colours (Murray, et al., 2009).

**Figure 1.0**



M = mucoid

MP = Mucopurulent

P = Purulent

Different types of sputum can indicate different conditions, for example in asthma sputum contains high levels of eosinophils and is often yellow in colour without any infection being present (Hickin, Renshaw and Williams, 2015). Carcinomas can produce mucoid sputum if at alveolar cell level, however all other bronchogenic carcinomas will not produce any (Hickin, Renshaw and Williams, 2015). Chronic bronchitis is associated with a chronic cough and sputum production (for majority of days over a 3 month period) so this is vital to be aware of to aid diagnosis (Mayo Clinic, 2018). Additionally the type of sputum can help identify the causes of pneumonia, tuberculosis, lung abscess, COPD, bronchiectasis, aspergillosis and cystic fibrosis (Doe, 2017; Hickin; Nall, 2012).

Sputum collection has helped improve understanding of chronic airways disease as it can identify the presence and type of bacteria, which can indicate the severity of airways disease aiding treatment and management options (Lacy, Lee and Vethanayagam, 2005). Frequent high neutrophils in sputum usually indicates advanced COPD (Hoenderdos and Condliffer, 2013; Kim and Nadel, 2004; O’Donnell, et al., 2004; Chung, 2001). Similar to asthma a third of COPD patients have raised eosinophils in sputum (Singh, et al., 2014).

Sputum Sample Collection

The most common type of sputum sample test is microscopy, culture and sensitivities (M, C and S). This type of test detects any presence of pathogenic bacteria and guides antibiotic treatment. It can also confirm the effectiveness of commenced treatment (Shepherd, 2017). A sputum sample should be requested if an individual has an increased cough with purulent sputum, pyrexia and/or signs of systemic infection (GOLD, 2019; Shepherd, 2017). A sputum sample should be placed in a clean sputum pot preferably first thing in the morning when the patient has cleared the mouth and throat of debris and taken a deep cough (Preston and Kelly, 2017; Shepherd, 2017). The sample can be collected at any point throughout the chest infection, however ideally it should be obtained prior to commencing antibiotic therapy (Centers for Disease Control and Prevention, 2017). It should be taken to the laboratory ideally within 1 to 2 hours of being produced (Nall, 2012). Therefore patients need to be aware to inform healthcare professionals as soon as sputum has been produced to allow this to happen within secondary care. In primary care ideally family members should take the sample to the surgery and if there is a delay then the sample should be kept in the fridge. Healthcare professionals also need to be aware of this guidance so samples are not delayed getting to the laboratory.

Additional strategies to support sputum collection include induced sputum through inhalation of nebulised hypertonic saline, transtracheal aspiration, bronchoscopy and bronchial washings, with the latter usually being used to confirm any malignancies (Hickin, Renshaw and Williams, 2015). It has been reported when completing bronchoscopies that at least 50% of COPD patients have high concentrations of bacteria in their lower airways during exacerbations (Sethi, et al., 2002). Nonetheless when completing bronchoscopies it has been noted that there can be contamination by bacteria in the upper airway if protocols are not followed vigorously meaning this statistic could be disputed (Segal, et al., 2013; Charlson, et al., 2011).

Induced sputum provides key information regarding the inflammatory process of the airways (Weiszhar and Horvath, 2013). This type of sputum collection is more accurate than spontaneous sputum as it provides greater cell viability and reproducibility of cell counts (Lacy, Lee and Vethanayagam, 2005). Consequently Tangedal, et al. (2014) found that although there were differences between spontaneous and induced sputum samples, there is scope for both types of samples in medicine as both can provide key information. The main differences were when measured during a COPD exacerbation tumornecrosis factor-alpha (TNF-a) was significantly higher in spontaneous samples. Furthermore in spontaneous samples interleukin 18 (IL-18) and monokine induced by gamma interferon (MIG) were significantly higher in ex-smokers compared to induced samples. Those spontaneous samples that were found to have haemophilus influenza (HI) in them were associated with lower levels of interleukin 6 (IL-6), not comparative with induced samples. Finally MIG levels were lower in spontaneous samples with HI, opposite to findings in induced samples (Tangedal, et al., 2014). It needs to be decided which sample technique is needed when requesting a sample, but practicality needs to be considered and in practice induced sputum collection is an infrequent procedure.

It is noted microscopy of sputum is inexpensive and simple (Nall, 2012). The only disadvantages found were some chest discomfort when obtaining the sample due to deep coughing. Certain tests, such as tuberculosis, are different as they require expensive equipment and specially trained professionals making them more expensive than general microscopic tests (TBFACTS, 2017). They also require large amounts of sputum to detect a positive sample as sensitivity is low and often take several weeks to confirm (Doe, 2017; Acharya, 2013).

Bathoorn, et al., (2017) confirm that a low number of sputum samples are requested in primary care. This could be the result of patients not supplying the sample if left with a sputum pot and/or access to transportation to drop the sample at the surgery (Alves, et al., 2016). COPD guidelines state sputum collection is not routinely recommended in primary care for the routine management of an exacerbation, however if an individual is admitted into hospital and/or sputum is purulent then a sample should be sent for M,C and S (NICE, 2018a). Nonethesless it could be argued if more sputum samples were taken in primary care then this may prevent hospital admissions as correct antibiotic prescriptions could be made sooner (Bathoorn, et al., 2017)..

Under use of sputum sampling is likely to contribute to high levels of inefficiencies through health care expenditure, including prolonged and potentially unnecessary hospital admission, whilst also prolonging and worsening clinical outcomes for patients (Bathoorn, et al., 2017). This may be due to a breakdown in communication between healthcare professionals (e.g. presuming others have already requested one), a lack of knowledge regarding antibiotic policy or doctors using old sputum cultures to guide antibiotic therapy especially in high risk patients that have previously grown pathogens (Bathoorn, et al., 2017). Over use and inappropriate use of antibiotics are driving worldwide antibiotic resistance (Shallcross and Davies, 2014). Therefore it is critically important that antibiotic prescriptions are based on sputum culture results, especially in cases of recurrent COPD exacerbations (Bathoorn, et al., 2017; NICE, 2015).

A study undertaken by Bathoorn, et al. (2017) found in 3,638 sputum samples 50% of them showed no potential pathogen and therefore would not require antibiotics. Hickin, Renshaw and Williams (2015) claim bacteria found in sputum are often resistant to common antibiotics and therefore it is important to request an antibiotic sensitivity test through M, C and S testing. Consequently this would help towards antibiotic resistance as over prescribing can cause antibiotics to lose effectiveness (NHS Choices, 2016). Brusse-Keizer et al. (2009) and Laue et al. (2015) argue that treating all exacerbations of COPD based only on purulent sputum would result in over treatment of antibiotics. NICE (2018b) state antibiotics should be considered if sputum colour has changed and there is an increase in thickness or volume out of the ordinary for the patient.

Antibiotic Stewardship

Antibiotic stewardship includes coordinated strategies which aim to improve antibiotic use resulting in enhanced patient outcomes, reduced antibiotic resistance and decreased healthcare costs (World Health Organisation (WHO), 2018; The Society for Healthcare Epidemiology of America, 2018). Antibiotic stewardship aims to offer the most appropriate antibiotic to patients with a bacterial infection and avoid using antibiotics in those cases where no bacteria is present (Bathoorn, et al., 2017). It is recommended stewardship programs are undertaken by employers to monitor individual prescribing practices and to ensure guidelines are being followed (NICE, 2015).

Antibiotics should only be considered for COPD patients if in addition to a positive sputum culture there are symptoms of dyspnoea, cough and increased sputum volume and change in sputum colour (GOLD, 2019; NICE, 2018a; O’Donnell, et al., 2007; Celli, et al., 2004; Pauwels, et al., 2001). Bathoorn et al. (2017) further states in the COPD patient, antibiotic prescribing should be withheld unless there is clinical indication of infection, a temperature (38 degrees and above) or no response to treatment after 2 to 4 days, however sepsis must not be ruled out in the presence of these symptoms. Nonetheless GOLD (2019) claim, when indicated, antibiotics should be given for 5-7 days to decrease recovery time and hospital length of stay and the risk of early relapse. The antibiotic needed will be influenced by the pathogen grown (Cukic, 2013). Bathoorn et al. (2017) believe sputum gram stains can provide helpful information regarding the need for an antibiotic prescription. If a sample shows no indication of a single microorganism or copious potential pathogenic organisms then it is highly likely to be non-bacterial (Van der Valk, et al., 2004).

Once the sputum has been analysed in the laboratory the bacteria or fungi can be confirmed and the appropriate antibiotics can be prescribed by either a doctor or nurse prescriber (Nall, 2012). Microbiologists and pharmacists also often play a part in the guidance and prescription of antibiotics following sputum collection.

Conclusion

This paper has demonstrated the importance of sputum samples to aid diagnosis and treatment and how there is a need for larger samples to be taken. Several ways of obtaining samples have been presented and discussed. All health care professionals have a duty to ensure antibiotic prescribing is a safe and effective treatment for the benefit of patient care, embracing the principles of antibiotic stewardship.

CPD reflective Question

* What do you consider the main reasons for the rising number of respiratory disease?
* What areas of your practice could you change to ensure guidelines are followed in regards to sputum collection?
* Considering the four themes, which can you identify as being one in which you could further reflect and consider with your wider team?

Reference List

Acharya, T., 2013. *Advantage, Disadvantage and limitations of Microscopy to detect Acid Fast Bacilli (AFB)*. [online] Available at: <<https://microbeonline.com/advantage-disadvantage-limitations-microscopy-detect-acid-fast-bacilli-afb/>> [Accessed 1 March 2018].

Alves, J., Paulo, Z., Dos Santos, N., Pinto, E. and Davim, R., 2016. Socioeconomic-cultural barriers delaying the tuberculosis diagnosis. *Journal of Nursing*, 10(11), pp.4021-4027.

American Thoracic Society, 2015. *What Are the Signs and Symptoms of COPD.* [online] Available at: <<https://www.thoracic.org/patients/patient-resources/resources/signs-symptoms-of-COPD.pdf>> [Accessed 28 February 2018].

Bathoorn, E., Groenhof, F., Hendrix, R., Van der Molen, T., Sinha, B., Kerstjens, H., Friedrich, A. and Kocks, J, 2017. Real-life data on antibiotic prescription and sputum culture diagnostics in acute exacerbations of COPD in primary care. *International Journal of COPD*, 12, pp. 285-290.

Beasley, V., Joshi, P., Singanayagam, A., Molyneaux, P., Johnston, S. and Mallia, P., 2012. Lung microbiology and exacerbations in COPD. *International Journal of COPD*, 7, pp.555-569.

British Dictionary, 2012. *Sputum.* [online] Available at: <<http://www.dictionary.com/browse/sputum>> [Accessed 28 February 2018].

British Lung Foundation (BLF), 2016. *The Battle for Breath: The impact of lung disease in the UK*. London: British Lung Foundation.

Brusse-Keizer, M., Grotenhuis, A., Kerstjens, H., Telgen, M., Van der Palen, J., Hendrix, M. and Van der Valk, P., 2009. Relation of sputum colour to bacterial load in acute exacerbations of COPD. *Respiratory Medicine*, 103(4), pp.601-606.

Celli, B., MacNee, W., Agusti, A., Anzueto, A., Berg, B., Buist, A., Calverley, P., Chavannes, N., Dillard, T., Fahy, B., Fein, A., Heffner, J., Lareau, S., Meek, P., Martinez, F., McNicholas, W., Muris, J., Austegard, E., Pauwels, R., Rennard, S., Rossi, A., Siafakas, N., Tiep, B., Vestbo, J., Wouters, E. and ZuWallack, R., 2004. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *European Respiratory Journal*, 23, pp.923-946.

Centers for Disease Control and Prevention, 2017. *Specimen Collection Guidelines.* [online] Available at: <<https://www.cdc.gov/urdo/downloads/speccollectionguidelines.pdf>> [Accessed 28 February 2018].

Charlson, E., Bittinger, K., Haas, A., Fitzgerald, A., Frank, I., Yadav, A., Bushman, F. and Collman, R., 2011. Topographical continuity of bacterial populations in the healthy human respiratory tract. *American Journal of Respiratory and Critical Care Medicine,* 184(8), pp.957-963.

Chung, K., 2001. Cytokines in chronic obstructive pulmonary disease. *The European Respiratory Journal*, 34, pp.50-59.

Cukic, V., 2013. The Most Common Detected Bacteria in Sputum of Patients with the Acute Exacerbation of COPD. *Journal of the Academy of Medical Sciences*, 25(4), pp.226-229.

Doe, S., 2017. Respiratory Investigations. In: V.Gibson., and D., Waters, ed. 2017. *Respiratory Care*. Boca Raton: CRC Press. Ch.3.

Fahy, J. and Dickey, B., 2010. Airway Mucus Function and Dysfunction. *The New England Journal of Medicine*, 363, pp.2233-2247.

Global Initiative for Chronic Obstructive Lung Disease (GOLD)., 2019. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. [online] Available at: <<https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf>> [Accessed 26 February 2019].

Hickin, S., Renshaw, J. and Williams, R., 2015. *Respiratory System*. Edinburgh: Elsevier.

Hoenderdos, K. and Condliffer, A., 2013. The neutrophil in chronic obstructive pulmonary disease. *American Journal of Respiratory Cell and Molecular Biology*, 48(5), pp.531-539.

Kim, S. and Nadel, J., 2004. Role of neutrophils in mucus hypersecretion in COPD and implications for therapy. *Treatments in Respiratory Medicine*, 3(3), pp.147-159.

Kuprys-Lipinska, I. and Kuna, P., 2014. *Impact of chronic obstructive pulmonary disease (COPD) on patients life and his family*. [online] Available at: <<https://www.ncbi.nlm.nih.gov/pubmed/24615192>> [Accessed 24 February 2018].

Lacy, P., Lee, J. and Vethanayagam, D., 2005. Sputum analysis in diagnosis and management of obstructive airway diseases. *Therapeutics and Clinical Risk Management*, 1(3), pp.169-179.

Laue, J., Reierth, E. and Melbye, H., 2015. When should acute exacerbations of COPD be treated with systemic corticosteroids and antibiotics in primary care: A systematic review of current COPD guidelines. *NPJ Primary Care Respiratory Medicine*, 25, pp.1-8.

Mayo Clinic, 2018. *Bronchitis*.[online] Available at: <<https://www.mayoclinic.org/diseases-conditions/bronchitis/symptoms-causes/syc-20355566>> [Accessed 27 July 2018].

Murray, M., Pentland, J., Turnball, K., MacQuarrie, S. and Hill, A., 2009. Sputum colour: a useful clinical tool in non-cystic fibrosis bronchiectasis. *European Respiratory Journal*, 34(2), pp.361-364.

Nall, R., 2012. *Routine Sputum Culture*. [online] Available at: <<https://www.healthline.com/health/routine-sputum-culture>> [Accessed 1 March 2018].

National Health Service (NHS) Choices, 2016. *Antibiotics Resistance: Antibiotics.* [online] Available at: <https://www.nhs.uk/conditions/antibiotics/antibiotic-antimicrobial-resistance/> [Accessed 26 February 2019].

National Institute for Health and Care Excellence (NICE), 2015. *Antimicrobial stewardship: Systems and processes for effective antimicrobial medicine use*. [online] Available at: <<https://www.nice.org.uk/guidance/ng15/resources/antimicrobial-stewardship-systems-and-processes-for-effective-antimicrobial-medicine-use-pdf-1837273110469>> [Accessed 11 April 2018].

National Institute for Health and Care Excellence (NICE), 2018a. *Chronic Obstructive Pulmonary Disease in over 16s: diagnosis and management*. [online] Available at: <<https://www.nice.org.uk/guidance/ng115/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-pdf-66141600098245>> [Accessed 26 February 2019].

National Institute for Health and Care Excellence (NICE), 2018b. *Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing*. [online] Available at: <<https://www.nice.org.uk/guidance/ng114/resources/chronic-obstructive-pulmonary-disease-acute-exacerbation-antimicrobial-prescribing-pdf-66141598418629>> [Accessed 27 February].

National Institute for Health and Care Excellence (NICE),2008. *Respiratory Tract Infections – Antibiotic Prescribing*. [online] Available at: <<https://www.nice.org.uk/guidance/CG69>> [Accessed 27 July 2018].

O’Donnell, R., Peebles, C., Ward, J., Daraker, A., Angco, G., Broberg, P., Pierrou, S., Lund, J., Holgate, S., Davies, D., Delany, D., Wilson, S. and Djukanovic, R., 2004. Relationship between peripheral airway dysfunction, airway obstruction and neutrophilic inflammation in COPD. *Thorax*, 59(10), pp.837-842.

O’Donnell, D., Aaron, S., Bourbeau, J., Hernandez, P., Marciniuk, D., Balter, M., Ford, G., Gervais, A., Goldstein, R., Hodder, R., Kaplan, A., Keenan, S., Lacasse, Y., Maltais, F., Road, J., Rocker, G., Sin, D., Sinuff, T. and Voduc, N., 2007. Canadian Thoracic Society Recommendations for management of chronic obstructive pulmonary disease 2007 – update. *Canadian Respiratory Journal*, 14, pp.5-32.

Pauwels, R., Buist, A., Carverley, P., Jenkins, C., Hurd, S. and Gold Scientific Committee., 2001. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) Workshop summary. *American Journal of Respiratory and Critical Care Medicine*, 163(5), pp.1256-1276.

Preston, W. and Kelly, C., 2017. *Respiratory Nursing at a Glance*. Chichester: Wiley Blackwell.

Public Health England (PHE), 2015. *Respiratory disease: applying All Our Health*. [online] Available at: <<https://www.gov.uk/government/publications/respiratory-disease-applying-all-our-health/respiratory-disease-applying-all-our-health>> [Accessed 11 March 2018].

Reychler, G., Andre, E., Couturiaux, L., Hohenwarter, K., Liistro, G., Pieters, T. and Robert, A., 2016. Reproducibility of the Sputum Colour Evaluation Depends on the Category of Caregivers. *Respiratory Care*, 61(7), pp.936-942.

Segal, L., Alekseyenko, A., Clemente, J., Kulkami, R., Wu, B., Gao, Z., Chen, H., Berger, K., Goldring, R., Rom, W., Blaser, M. and Weiden, M., 2013. Enrichment of lung microbiome with supraglottic taxa is associated with increased pulmonary inflammation. *Microbiome*, 1(1), pp.1-12.

Sethi, S., Evans, N., Grant, B. and Murphy, T., 2002. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *The New England Journal of Medicine*, 347(7), pp.465-471.

Shallcross, L. and Davies, S., 2014. Antibiotic overuse: a key driver of antimicrobial resistance. *British Journal of General Practice*, 64(629), pp.604-605.

Shepherd, E., 2017. Specimen Collection 4: procedure for obtaining a sputum specimen. *Nursing Times*, 113(10), pp.49-51.

Singh, D., Kolsum, U., Brightling, C., Locantore, N., Agusti, A. and Tal-Singer, R., 2014. Eosinophilic inflammation in COPD prevalence and clinical characteristics. *European Respiratory Journal*, 44, pp.1697-1700.

Tangedal, S., Aanerud, M., Persson, L., Brokstad, K., Bakke, P. and Eagan, T., 2014. Comparison of inflammatory markers in induced and spontaneous sputum in a cohort of COPD patients. *Respiratory Research*, 15(138), pp.1-8.

TBFACTS., 2017. TB Tests – For diagnosing TB and for resistance testing. [online] Available at: <<https://www.tbfacts.org/tb-tests/>> [Accessed 31 July 2018].

The Society for Healthcare Epidemiology of America, 2018. *Antimicrobial Stewardship*. [online] Available at: <<https://www.shea-online.org/index.php/practice-resources/priority-topics/antimicrobial-stewardship>> [Accessed 11 April 2018].

Van der Valk, P., Monninkhof, E., Van der Palen, J., Kielhuis, G., Van Herwaarden, C. and Hendrix, R., 2004. Clinical predictors of bacterial involvement in exacerbations of chronic obstructive pulmonary disease. *Clinical Infectious Diseases*, 39(7), pp. 980-986.

Weiszhar, Z. and Horvath, I., 2013. Induced sputum analysis: step by step. *European Respiratory Society*, 9, pp.300-306.

World Health Organisation (WHO), 2018. *Stewardship*. [online] Available at: <<http://www.who.int/healthsystems/stewardship/en/>> [Accessed 17 March 2018].