Assessing the evidence base for medical procedures which create a higher risk of respiratory infection transmission from patient to healthcare worker

Version Final. 12th May, 2020.

Situation	A substantial number of enquiries have been received regarding the definition of aerosol generating procedures (AGPs) as they pertain to UK infection prevention and control guidance and the associated need for airborne precautions. This Situation, Background, Assessment and Recommendations (SBAR) document reflects the findings of a Health Protection Scotland led rapid review which aimed to assess the published scientific evidence and seek UK expert opinion to establish if the AGPs on the extant list continue to merit inclusion and whether additional procedures should be included. **The content and recommendations within the SBAR have been agreed in collaboration with experts from New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) and Public Health England (PHE).**
Background	The concept of an AGP arose following the study of Severe Acute Respiratory Syndrome (SARS) transmission events where it was observed that a pathogen, which was consistently associated with droplet or contact transmission, appeared to have the potential to infect healthcare workers via the airborne route during specific procedures. The World Health Organization (WHO) defines an AGP as those procedures which result in the production of airborne particles (aerosols).(1) Particles which they describe as being <5 micrometres (µm) in size and as such can remain suspended in the air, travel over a distance and have the potential to cause infection if inhaled. These particles are created by air currents moving over the surface of a film of liquid, the faster the air, the smaller the particles produced.(1) Using this definition there are potentially many medical or patient care procedures which could be classed as 'aerosol generating' but whether they lead to an increased risk of respiratory infection transmission is a different and important question. There is a lack of distinction in the literature between 'aerosol generating procedures' and 'high risk aerosol generating procedures'. High risk AGPs are

	theorised to pose a significantly greater transmission risk of patient-to-healthcare worker infection and require use of airborne transmission precautions. In the WHO 2014 guidance, AGPs are referred to as “any medical and patient care procedure that results in the production of airborne particles (aerosols)”.[1] On discussion of procedures listed as AGPs, this definition is frequently cited, however, if taken out of this context, it can be misinterpreted to suggest that all procedures or activities which create any level of aerosol require enhanced (airborne) infection control precautions. The frequently cited AGP definition lies within the WHO document section entitled ‘high-risk aerosol-generating procedures’ where the guidance specifically defines AGPs, in the context of the procedure i.e. “medical procedures that have been reported to be aerosol-generating and consistently associated with an increased risk of pathogen transmission”.[1] The published literature and expert opinion support the concept that any procedure or activity which causes bodily liquids to be expelled into the environment will lead to a range of differently sized airborne droplets and aerosols. Coughing, sneezing and even breathing will generate aerosols. However, what must be determined is which procedures, demonstrated through evidence, generate a significantly high number of respirable aerosols/droplets; and are associated with a higher incidence of healthcare worker acute respiratory infection.
Assessment	A rapid evidence appraisal was conducted to assess the risk of patient to healthcare worker infection transmission associated with a wide range of potential AGPs. Studies of clinical procedures were assessed for their association with historical transmission events and generation of aerosols/environmental contamination. The following search was conducted within academic databases. 1. aerosol generating procedure.tw 2. aerosol generating procedure*.mp 3. (aerosol adj3 procedure).mp 4. (aerosol or airborne).mp 5. Airborne infection.mp 6. Aerosol*.mp 7. Occupational exposure.mp 8. Infectious disease transmission.mp 9. Infection control.mp 10. Infection control, dental.mp 11. exp cross infection/ 12. Disease outbreaks.mp

	13. Disease transmission.mp 14. 1 or 2 or 3 or 4 or 5 or 6 15. 7 or 8 or 9 or 10 or 11 or 12 or 13 16. 14 and 15 17. limit 16 to English language 18. limit 17 to human 19. limit 18 to humans 20. limit 19 to yr="2000 – Current" Over 5000 results were screened with 367 relevant articles rapidly assessed. Please see Supplementary Document 1. The WHO (2014) states that there is only consistent evidence of an increased risk of aerosol transmission for the following procedures: tracheal intubation, tracheotomy procedures, non-invasive ventilation, and manual ventilation before intubation.(1) This was reflected in the findings of this rapid review which, based on the assessed studies, identified weak evidence for an increased risk of respiratory infection transmission associated with the following procedures: • open suctioning of the respiratory tract of mechanically ventilated patients (2-7) • dental procedures using high speed devices such as ultrasonic scalers and drills (8-12) • high speed cutting in surgery/post mortem procedures[1] (13-16) • manual ventilation (4,6,17) • non-invasive ventilation (4,18-20) • performing a tracheotomy (4) • performing tracheal intubation (2,4-7,20) No evidence of appropriate quality or strength was identified for the following procedures: • High frequency oscillating ventilation* (4, 20) • Bronchoscopy* (4,18,19,26,27) • Induction of sputum (associated with nebulisation of hypertonic saline)* • Tracheotomy removal* • High flow nasal oxygen therapy** (23, 24)

[1] In relation to increased **respiratory** infection transmission risk this refers to surgical procedures involving the respiratory tract or paranasal sinuses

	• Administration of nebulised saline, medication or drugs [4,7,18,19] • Chest compressions [4,6] • Chest physiotherapy [2,4,18,21,22] • Defibrillation [4,6] • Administration of oxygen therapy [4,18,25] • Abdominal suctioning • Airway Suctioning of newborn infants • Amputation with open arterial surgery • Bone drilling • Chest drains with activate air leak (pneumothorax or following cardiothoracic surgery) • Colonography • Dental procedures not involving high speed devices, e.g. scaling by hand • Diathermy (smoke generated) • Harvesting split thickness skin grafts • Heavy exhalation during labour • Hydro surgical debridement • Inhalation sedation, Entonox use or other inhaled gases (not nebulised) • Irrigation during surgery • Laparoscopy/Laparotomy • Laryngectomy care including surgical voice restoration (stoma inspection; voice prosthesis changes) • Lower GI endoscopy • Manual saw during surgery • Nasendoscopy • Nasogastric tube insertion • Needle decompression of a tension pneumothorax • Nose and throat swabbing • Peak flow device meter use • Percutaneous lung biopsy • Phaecoemulsification • Pulsed lavage during surgery • Supraglottic airway insertion • Surgical procedures in head and neck area not involving the respiratory tract, paranasal sinuses or oral cavity • Swallowing assessments (SALT)

	• Thoracoscopy • Tracheostomy care and management without suctioning procedures, with and without connection to mechanical ventilator • Trans Oesophgeal Echo (TOE) • Upper GI endoscopy • VAC dressing application • Vitrectomy * Those procedures for which no or very weak evidence was found, but are currently included in the HPS AGP list, are based on historic expert opinion and have not been removed, as absence of evidence for transmission may be influenced by the effect of healthcare workers currently wearing respirators for these procedures. These procedures are bronchoscopy [4, 18, 19, 26, 27], high frequency oscillating ventilation [4, 20], induction of sputum (associated with nebulisation of hypertonic saline) and removal of tracheostomy. Some historic case studies involving respiratory pathogens such as SARS-CoV and MERS-CoV show that certain procedures are associated with patient to healthcare worker transmission. However, some procedures are often conducted together, for example, in a resuscitation scenario, and so it is often challenging to implicate a specific single procedure as being the definitive cause of airborne infection transmission. **Further Detailed Analysis** ****High flow nasal oxygen** High flow nasal oxygen therapy (HFNO) [23, 24] has recently been added to the list of high risk AGPs. High Flow Nasal Oxygen, sometimes referred to as High Flow Nasal Cannula Therapy, is the process by which warmed and humidified respiratory gases are delivered to a patient through a nasal cannula via a specifically designed nasal cannula interface. These devices can be set to deliver oxygen at specific concentrations and flow rates (typically 40-60L/min-1 for adults). As previously outlined, WHO explain that *"aerosols are produced when an air current moves across the surface of a film of liquid"* and that "*the greater the force of the air the smaller the particles that are produced*".[1] With HFNO flow

	rates being much higher than conventional oxygen therapy, one may expect a greater proportion of smaller aerosolised particles to be generated. The decision to include HFNO was based on clinical expert opinion and consensus (Table 1). **Airway suctioning and Open suctioning** It appears that the definition of 'open suctioning', in the context of a high risk AGP, has become distorted over time through unclear descriptions within the literature and a misinterpretation of what specific aspect of the process generates significant aerosols and increases airborne transmission risk. Open suctioning has been defined as *"clearing the airways of a mechanically ventilated patient with a suction catheter inserted into the endotracheal tube after the patient has been disconnected from the ventilator circuit."*[28] Evidence that 'airway suctioning' is associated with an infection risk almost always describes suctioning that is associated with either intubation or mechanically ventilated patients.[2-7] No evidence exists to implicate more routine oropharyngeal suctioning. It is likely that the risk associated with 'open suctioning' relates to disconnection of the ventilator circuit and not the suctioning procedure itself as described by Chung et al in 2015[2].[3] In 2009, the WHO referred to *"aspiration or open suctioning of the respiratory tract including for the collection of lower respiratory tract specimens, intubation, resuscitation, bronchoscopy, autopsy"* as being a high risk AGP.[29] In the 2019 HPS AGP literature review, the following procedure is listed as a high risk AGP; "Intubation, extubation and related procedures e.g. manual ventilation and open suctioning".[30] In line with a precautionary approach, suctioning of the respiratory tract, regardless of association with ventilation, has been incorporated into the recommended list[3] (Table 1).

[2] *"Before performing open suctioning, the endotracheal tube must be disconnected from a ventilator circuit. A few phenomena are observable while the endotracheal tube of the patient is discontinued from a mechanical ventilator. First, the thoracic pressure of the patient becomes negative to the atmosphere, creating a risk of inhalation of airborne pathogens. Second, the mechanical ventilator provides a much higher flow to compensate for the low pressure in the ventilator circuit, and the condensates in the ventilator circuit may then be aerosolized from the forceful gas flow. This results in contamination of the air in the room."* (3)

[3] Does not include suctioning as part of a closed system circuit

	<u>High speed cutting in surgery/post mortem procedures</u> The evidence that exists shows that the generation of infectious aerosols leading to transmission events arises from the respiratory tract. This is consistent with what is known about where viral replication occurs. Current evidence suggests that SARS-CoV-2 RNA can be found within blood, faeces and lacrimal fluid. There is currently no evidence to support the infectivity of this detected viral material, or to suggest that inhaling aerosolised versions of these fluids would result in infection.[31] Currently, no studies report the detection of SARS-CoV-2 in ascetic fluid or cerebrospinal fluid. One study failed to detect SARS-CoV-2 in semen.[32] Furthermore, exposure to such fluids was not shown to be a risk for HCWs in the SARS outbreak of 2003.[33] **<u>Induction of sputum</u>** Inclusion of 'induction of sputum' has led to significant debate over whether induced and forceful coughing should be considered a high risk AGP, but with no scientific studies to support this, and an absence of explanation as to why 'induction of sputum' was included by UK experts in 2007[30] (specifically what aspect of the procedure was hypothesised to significantly increase transmission risk), one should not associate its inclusion as presenting the concept that close proximity to a coughing patient is an AGP. The current 'induction of sputum' evidence base is not supportive of inclusion in the high risk AGP list but, as previously outlined, it is currently included based on historic expert opinion and a decision not to remove any procedure from the high risk AGP list where absence of evidence for transmission may be influenced by the effect of healthcare workers currently wearing respirators for these procedures. **<u>Coughing</u>** Coughing in itself does not constitute an AGP. Coughing does create aerosols, as does talking and breathing, but it is not a medical procedure.[34, 35] Current infection prevention and

	control guidelines do not recommend AGP level PPE for contact with patients who are coughing. A challenge arises however, because it is likely that a continuum exists for the amount of infectious aerosol that is released in certain settings. A simple cough may lie at one end of a spectrum, whilst aerosol creation from tracheal intubation lies at the other. The significance of infection transmission from 'natural' aerosols is unknown but it is likely that a higher risk comes from the various medical procedures described in this SBAR. **Nebulisation** Nebulisation is not considered to be an AGP. There is published evidence that nebulisation does not result in an increased risk of patient generated aerosols.[18] Nebulisers do however, produce profuse sterile aerosols. Patients with respiratory virus infections can produce aerosols which may contain virus, but these are distinct from the aerosol particles originating from the nebuliser. Patients may cough during administration of a nebuliser. However, two case-control cohort studies that assessed the risk of infection transmission to HCWs present during nebuliser administration to SARS patients.[21, 22] did not report a significant risk. To limit coughing, a precautionary measure would be to limit nebuliser administration to patients with COVID. Wherever possible, nebulisation should be deferred in favour of metered dose inhaler (MDI) and spacer use, depending on patient tolerance and severity of exacerbation. This has been shown to be an effective alternative.[36] **Cardiopulmonary Resuscitation** Published evidence quality on CPR is extremely weak and heavily confounded by inability to separate out specific procedures performed as part of CPR, e.g. chest compression, defibrillation, manual ventilation and intubation. A systematic review found that chest compressions and defibrillation were not significantly associated with an increased risk of SARS infection.[4]

	It is biologically plausible that chest compressions could generate an aerosol, but only in the same way that an exhalation breath would do. No other mechanism exists to generate an aerosol other than compressing the chest, and an expiration breath, much like a cough, is not recognised as a high risk event. Defibrillation is not likely to cause any significant breath exhalation. Airway intubation and manual ventilation consistently come out as the highest risk procedures that take place during CPR. **<u>Infection Control</u>** In the hierarchy of control measures within the care environment, PPE, including RPE, is often considered the last line of protection because: it only protects the wearer (i.e. not all those in the area); if PPE is used incorrectly or is badly maintained, the wearer is unlikely to receive adequate protection; it can be uncomfortable to wear; it may interfere with physical work activities; and it may not be compatible with other types of PPE (i.e. face masks and safety goggles). Under COSHH regulations/guidance, where it is not reasonably practicable to prevent exposure to a substance hazardous to health via elimination or substitution (as is the case where HCWs are caring for individuals/patients with suspected or known airborne micro-organisms), the hazard must be adequately controlled by 'applying protection measures appropriate to the activity and consistent with the risk assessment'.[37] This includes the following controls listed in order of priority: 1. The design and use of appropriate work processes, systems and engineering controls, and the provision and use of suitable work equipment and materials; 2. The control of exposure at source, including adequate ventilation systems and appropriate organizational measures; and 3. Where adequate control of exposure cannot be achieved by other means, the provision of suitable PPE. In the healthcare setting where workers are caring for patients who may have infectious diseases, the way of adequately

	controlling HCW exposure to potentially infectious biological agents that is most reasonably practicable is via the use of PPE. For the control of infectious agents that may be transmissible via the airborne route, and where AGPs are undertaken, the use of PPE would include RPE. Organisations and Healthcare Professionals should conduct their own risk assessments when considering infection control precautions, and discussion with their infection control team as required. This responsibility extends to include the appropriate selection and use of PPE.
Recommendations	Previously listed AGPs, even if recently reassessed as not supported by published evidence, should not be removed from the list at this time. Table 1 has been created with consideration of all procedures referenced in this SBAR. Evidence regarding high risk AGPs is continually being assessed and the list presented in Table 1 may change as new evidence emerges. Final recommendations agreed in collaboration with experts from New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) and Public Health England (PHE). **Table 1: Procedures which are currently considered to create an increased risk of respiratory infection transmission and therefore require airborne precautions:** Respiratory tract suctioning Bronchoscopy Dental procedures (using high speed devices such as ultrasonic scalers and high speed drills) High flow nasal oxygen (HFNO) High Frequency Oscillatory Ventilation (HFOV) High speed cutting in surgery/post mortem procedures if this involves the respiratory tract or paranasal sinuses Induction of sputum using nebulised saline Manual ventilation Non-invasive ventilation (NIV); Bi-level Positive Airway Pressure Ventilation (BiPAP) and Continuous Positive Airway Pressure Ventilation (CPAP) Tracheal intubation and extubation Tracheotomy or tracheostomy procedures (insertion or removal) Upper ENT airway procedures that involve suctioning

	Upper gastro-intestinal endoscopy where there is open suctioning of the upper respiratory tract

References

1. World Health Organization. Infection prevention and control of epidemic-and pandemic prone acute respiratory infections in health care. WHO guidelines. 2014.
2. Thompson KA, Pappachan JV, Bennett AM, Mittal H, Macken S, Dove BK, Nguyen-Van-Tam JS, Copley VR, O'Brien S, Hoffman P, Parks S, Bentley A, Isalska B, Thomson G, on behalf of the EASE Study Consortium. 2013. Influenza Aerosols in UK Hospitals during the H1N1 (2009) Pandemic – The Risk of Aerosol Generation during Medical Procedures. PLOS ONE. Volume 8, Issue 2, e56278
3. Chung F, Lin H, Liu H, Lien AS, Hsiao H, Chou L, and Wan G. 2015. Aerosol Distribution During Open Suctioning and Long-Term Surveillance of Air Quality in a Respiratory Care Center Within a Medical Center RESPIRATORY CARE, VOL 60, NO 1
4. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. 2012. Aerosol Generating Procedures and Risk of Transmission of Acute Respiratory Infections to Healthcare Workers: A Systematic Review. PLOs One 7(4), e35797
5. Moon J, Lee H, Jeon JH, Kwon Y, Kim H, Wang EB, Seo CW, Sung SA, Kim S, Seok H, Choi WS, Choi W and Park DW. 2019. Aerosol transmission of severe fever with thrombocytopenia syndrome virus during resuscitation. Infection Control & Hospital Epidemiology 40, 238–241
6. Nam H, Yeon M, Park JW, Hong J and Son JW. 2017. Healthcare worker infected with Middle East Respiratory Syndrome during cardiopulmonary resuscitation in Korea, 2015. Epidemiology and Health. Volume: 39
7. Pshenichnaya Y and Nenadskaya SA. 2015. Probable Crimean-Congo hemorrhagic fever virus transmission occurred after aerosol-generating medical procedures in Russia: nosocomial cluster Natalia International Journal of Infectious Diseases 33 120–122
8. Yamada H, Ishihama K, Yasuda K, Hasumi-Nakayama Y, Shimoji S, Furusawa K. Aerial dispersal of blood-contaminated aerosols during dental procedures. Quintessence International 42(5), 2011.
9. Rautemaa R, Nordberg A, Wuolijoki-Saaristo K, Meurman JH. 2006. Bacterial aerosols in dental practice - a potential hospital infection problem? Journal of Hospital Infection 64, 76e81.
10. Singh A, Shiva Manjunath R G, Singla D, Bhattacharya HS, Sarkar A, Chandra N. 2016. Aerosol, a health hazard during ultrasonic scaling: A clinico-microbiological study. Indian J Dent Res 27:160-2
11. Veena HR, Mahantesha S, Joseph PA, Patil SR, Patil SH. 2015. Dissemination of aerosol and splatter during ultrasonic scaling: a pilot study. Journal of infection and public health. 8(3):260-5.

12. Bennett AM, Fulford MR, Walker JT, Bradshaw DJ, Martin MV, Marsh PD. 2000. Microbial aerosols in general dental practice. British dental journal. 189(12):664-7.

13. Pluim JME, Jimenez-Boua L, Gerretsen RRR, Loeve AJ. 2018 Aerosol production during autopsies: The risk of sawing in bone. Forensic Science International 289: 260–267

14. Nogler M, Lass-Florl, C, Wimmer C, Mayr E, Bach M, Ogon M. 2003. Contamination during removal of cement in revision hip arthroplasty. A cadaver study using ultrasound and high-speed cutters. J Bone Joint Surg [Br] 2003;85-B:436-9.

15. Nogler M, Lass-Florl C, Ogon M, Mayr E,Bach C, Wimmer C. Environmental and Body Contamination Through Aerosols Produced by High-Speed Cutters in Lumbar Spine Surgery. Spine 2001; Volume 26, Number 19, pp 2156–2159.

16. Nogler M, Lass-Florl C, Wimmer C,Bach C, Kaufmann C, Ogon M. 2001. Aerosols produced by high-speed cutters in cervical spine surgery: extent of environmental contamination. Eur Spine J 10 :274–277, DOI 10.1007/s005860100310

17. Christian MD, Loutfy M, McDonald LC, Martinez KF, Ofner M, Wong T, Wallington T, Gold WL, Mederski B, Green K, Low DE and on behalf of the SARS Investigation Team. 2004. Possible SARS Coronavirus Transmission during Cardiopulmonary Resuscitation. Emerging Infectious Diseases 10: 287-293

18. Simonds AK, Hanak A, Chatwin M, Morrell MJ, Hall A, Parker KH, Siggers JH and Dickson RJ. 2010. Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebulizer treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. Health Technology Assessment; vol. 14: No. 46, 131-172.

19. O'Neil CA, Li J, Leavey A, Wang Y, Hink M, Wallace M, Biswas P, Burnham CD and Babcock HM; for the Centers for Disease Control and Prevention Epicenters Program. 2017. Characterization of Aerosols Generated During Patient Care Activities. Clinical Infectious Diseases, Vol 65(8):1342–8

20. Fowler RA, Guest CB, Lapinsky SE, Sibbald WS, Louie M, Tang P, Simor AE and Stewart TE. 2004. Transmission of severe acute respiratory syndrome during intubation and mechanical ventilation. American Journal of Respiratory and Critical Care Medicine. 169, 11.

21. Raboud J, Shigayeva A, McGeer A, Bontovics E, Chapman M, Gravel D, Henry B, Lapinsky S, Loeb M, McDonald LC, Ofner M. 2010. Risk factors for SARS transmission from patients requiring intubation: a multicentre investigation in Toronto, Canada. PLoS One. 5(5).

22. Loeb M, McGeer A, Henry B, Ofner M, Rose D, Hlywka T, Levie J, McQueen J, Smith S, Moss L, Smith A, Green K, Walter SD. 2004. SARS among critical care nurses. Toronto. Emerg Infect Dis 10: 251–255.

23. Leung CCH, Joynt GM, Gomersall CD, Wong WT, Lee A, Ling L, Chan PKS, Lui PCW, Tsoi PCY, Ling CM, Hui M. 2019. Comparison of high-flow nasal cannula versus oxygen face mask for environmental bacterial contamination in critically ill pneumonia patients: a randomized controlled crossover trial. Journal of Hospital Infection 101: 84e87.

24. Roberts S, Kabaliuk N, Spence C, O'Donnell J, Zulkhairi Abidin Z, Dougherty R, Roberts S, Jiang Y and Jermy Mc. 2015. Nasal high-flow therapy and dispersion of nasal aerosols in an experimental setting. Journal of Critical Care. Vol 30 (4) p842.

25. Yu IT, Xie ZH, Tsoi KK, Chiu YL, Lok SW, Tang XP, Hui DS, Lee N, Li YM, Huang ZT, Liu T, Wong TW, Zhong NS and Sung JJ. 2007. Why Did Outbreaks of Severe Acute Respiratory Syndrome Occur in Some Hospital Wards but Not in Others? Clinical Infectious Diseases, Vol 44 (8) p1017–102.

26. Marchand G, Duchaine C, Lavoie J, Veillette M, Cloutier Y. 2016. Bacteria emitted in ambient air during bronchoscopy—a risk to health care workers? American Journal of Infection Control 44: 1634-8.

27. Zietsman M, Phan LT & Jones RM (2019) Potential for occupational exposures to pathogens during bronchoscopy procedures, Journal of Occupational and Environmental Hygiene, 16:10, 707-716.

28. The Free Dictionary's Medical dictionary. Available online at https://medical-dictionary.thefreedictionary.com/

29. World Health Organization. 2009. Infection prevention and control in health care for confirmed or suspected cases of pandemic (H1N1) 2009 and influenza-like illnesses. Available online at https://www.who.int/csr/resources/publications/swineflu/swineinfinfcont/en/

30. Health Protection Scotland. 2019. Aerosol Generating Procedures (AGPs) Literature Review. Available online at http://www.nipcm.hps.scot.nhs.uk/resources/literature-reviews/transmission-based-precautions-literature-reviews/

31. Rapid Review of the literature: Assessing the infection prevention and control measures for the prevention and management of COVID-19 in healthcare settings. Version 1.1, 3 April 2020. Health Protection Scotland, 2020

32. Song C, Wang Y, Li W, Hu B, Chen G, Xia P, Wang W, Li C, Sha J, Hu Z, Yang X, Yao B and Liu Y. 2020. Detection of 2019 novel coronavirus in semen and testicular biopsy specimen of COVID-19 patients. medRxiv doi: https://doi.org/10.1101/2020.03.31.20042333.

33. Liu W, Tang F, Fang L-Q, De Vlas SJ, Ma H-J, Zhou JP, Looman CWN, Richardus JH and Cao WC. 2009. Risk factors for SARS infection among hospital healthcare workers in Beijing: A case control study. Trop Med Int Health.14: 52–59.

34. Huynh KN, Oliver BG, Stelzer S, Rawlinson WD, Tovey ER. A new method for sampling and detection of exhaled respiratory virus aerosols. Clinical Infectious Diseases. 2008;46(1):93-5.

35. Lindsley WG, Blachere FM, Thewlis RE, Vishnu A, Davis KA, Cao G, et al. Measurements of airborne influenza virus in aerosol particles from human coughs. PloS one. 2010;5(11).

36. van Geffen WH, Douma WR, Slebos DJ, Kerstjens HA. Bronchodilators delivered by nebuliser versus pMDI with spacer or DPI for exacerbations of COPD. 2016. Cochrane Database Syst Rev (8).

37. UK Health and Safety Executive. Control of substances hazardous to health (fifth edition); The Control of Substances Hazardous to Health Regulations 2002 (as amended). Approved code of practice and guidance. London: UK Health and Safety Executive; 2005.