Proposal to include an additional listing of oxygen for management of hypoxemia on the WHO Model List of Essential Medicines and List of Essential Medicines for Children

Application for submission to the 21st Expert Committee on the Selection and Use of Essential Medicines

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Contents

Acronyms and abbreviations v
1. Summary statement of the proposal for change 1
2. WHO technical department(s) and focal point(s) supporting the application 2
3. Organization(s) consulted and/or supporting the application 2
4. International Nonproprietary Name and Anatomical Therapeutic Chemical of the medicine 3
5. Formulation(s) and strength(s) proposed for inclusion, including adult and pediatric 3
6. Listing requested as an individual medicine 3
7. Treatment details (requirements for diagnosis, treatment, and monitoring) 5
    a. Dosage regimen 5
    b. Duration 6
    c. Reference to existing WHO and other clinical guidelines 7
    d. Need for special diagnostics, treatment or monitoring facilities, and skills 7
    e. Listing sought for the core list 8
8. Information supporting the public health relevance 8
    a. Epidemiological information on disease burden 8
    b. Assessment of current use 10
    c. Target population(s) 12
    d. Likely impact of treatment on the disease 12
9. Review of benefits: Summary of comparative effectiveness in a variety of clinical settings 13
    a. Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data) 13
    b. Summary of available data (appraisal of quality, outcome measures, summary of results) 14
10. Review of harms and toxicity: Summary of evidence on safety 16
    a. Estimate of total patient exposure to date 16
    b. Description of the adverse effects/reactions and estimates of their frequency 17
    c. Summary of available data on safety 17
    d. Summary of comparative safety against comparators 18
    e. Identification of variation in safety that may relate to health systems and patient factors 18
11. Summary of available data on comparative cost and cost-effectiveness 19
    a. Range of costs of the proposed medicine 19
    b. Resource use and comparative cost-effectiveness 20
12. Summary of regulatory status of the medicine in various countries 22
13. Availability of pharmacopoeial standards 23
14. References 25
Annex I. Normative guidance on the clinical use of oxygen for various conditions 33
Annex II. Listing of oxygen medicinal gas in the WHO Model Formulary (2008) and Model Formulary for Children (2010) 37
Annex III. Technical consensus meeting on increasing oxygen access through normative policy change 38
Annex IV. Sample listing of oxygen on national essential medicines lists 41
Annex V. Oxygen delivery methods in children and infants 45
Annex VI. Comparison of oxygen cylinders and concentrators as the basis for oxygen systems 47

Letters of support 49

Acronyms and abbreviations

AARC	American Association for Respiratory Care
AAGBI	Association of Anaesthetists of Great Britain and Ireland
BP	British Pharmacopoeia
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CRD	chronic respiratory disease
DALY	disability-adjusted life year
EML	Model List of Essential Medicines
EMLc	Model List of Essential Medicines for Children
FiO_2	fraction of inspired oxygen concentration
GMP	Good Manufacturing Practice
IMCI	integrated management of childhood illness
IP	Indian Pharmacopoeia
ISO	International Organization for Standardization
JP	Japanese Pharmacopoeia
LMIC	low- and middle-income country (as defined by the World Bank)
LPM	liters per minute
MERS	Middle East respiratory syndrome
NEML	national essential medicines lists
Ph. Eur	European Pharmacopoeia
Ph. Int	International Pharmacopoeia
ROP	retinopathy of prematurity
SpO_2	peripheral blood oxygen saturation
USP	United States Pharmacopeia
WHO	World Health Organization

1. Summary statement of the proposal for change

Oxygen is included on the current World Health Organization (WHO) Model List of Essential Medicines (EML) and List of Essential Medicines for Children (EMLc) because of its proven life-saving properties, safety, and cost-effectiveness.[1] Oxygen is currently listed in the anesthetics section of the WHO EML and EMLc. In addition, oxygen is one of 30 medicines included in the WHO *Priority life-saving medicines for women and children*, listed for treatment of pneumonia in children under five years of age.[2] Our proposal is to include an additional listing for oxygen as a medical gas to formalize and support its broad therapeutic use for the management of hypoxemia[i] outside of anesthetic settings. Furthermore, this proposed update would align the EML and EMLc with WHO treatment guidelines, with recently published WHO guidance for oxygen delivery and therapy, and with the oxygen monograph in the WHO Model Formulary (see Annexes I and II).[3]

Oxygen is a well-established therapeutic medical gas that has long been used as an often lifesaving intervention for the management of hypoxemia, a common complication of a number of serious illnesses and conditions affecting newborns, children, and adults globally. Common conditions for which medical oxygen may be needed to manage hypoxemia include respiratory complications of preterm birth (such as neonatal respiratory distress syndrome and birth asphyxia), acute respiratory infections (such as pneumonia, bronchiolitis, and those caused by pandemic and epidemic pathogens), severe infections (such as sepsis), chronic respiratory diseases (CRDs) (such as asthma and chronic obstructive pulmonary disorder), and emergency care (such as obstetric emergencies and trauma). Therapeutic intervention with oxygen is important in certain cases to achieve adequate tissue oxygenation to prevent serious damage of organs, therefore minimizing sequelae and saving life. Increased access to oxygen and pulse oximetry has been shown to reduce childhood pneumonia-related mortality by 35% in high-burden, low-resource settings.[4]

Despite the inherent risks of hypoxemia and the effectiveness of oxygen therapy, oxygen remains a scarce resource and access is unpredictable and limited in many developing countries today.[5] Surveys of low- and middle-income countries (LMICs) have found less than half of health facilities have uninterrupted access to oxygen.[6,7,8,9] Each year, lack of access to oxygen supplies contributes to preventable deaths; for example, an estimated 122,000 child pneumonia deaths could be averted globally each year if oxygen systems were strengthened.[10,11,12] Critical deficiencies in oxygen availability for patient care in LMICs has prompted review of the oxygen listings on the WHO EML and EMLc to ensure that it aligns with and complements efforts to improve global access to oxygen therapy for management of hypoxemia according to WHO standard-of-care guidelines and formularies (see Section 7c and Annexes I and II).

In order to satisfy a global public health need, we propose to include oxygen as a medical gas on the EML and EMLc to clarify its importance as an essential medicine for its clinical indications outside settings of anesthetic use.[13] The WHO EML and EMLc inform the structure, composition, and content of national essential medicines lists (NEMLs) and in this way impact decisions made by countries about procurement of oxygen and related equipment, financial support, and schemes that reimburse medicine costs, provider

[i] Hypoxemia is low levels of oxygen in the blood (low blood oxygen saturation or content). Hypoxemia has many causes and can cause tissue hypoxia (inadequate oxygenation for normal cell and organ function).

training, and equipment maintenance to address local disease burden and priority health concerns.[14,15] Updating the listing of oxygen on the WHO EML and EMLc to reflect its broad indications and achieve harmonization with existing and newly published standard treatment guidelines will support its broad clinical application and may increase coverage of oxygen therapy in LMICs where it is most urgently needed.

The expected benefits of creating an additional listing of oxygen on the EML and EMLc include:

- Increased recognition among policymakers and health care providers about the importance of oxygen as a therapeutic medical gas for hypoxemia, supporting the procurement, selection, and utilization of appropriate oxygen technologies in LMICs.
- Alignment of the WHO EML and EMLc with international drug classifications and other global normative guidance on oxygen, including clinical guidelines to improve safe administration of oxygen.
- Reducing the severe health consequences of respiratory infections and sepsis among children and adults by facilitating optimal clinical management and improved quality of care through increased availability of oxygen therapy.
- Increased readiness and capacity to respond to pandemics and epidemics of severe infectious diseases.

2. WHO technical department(s) and focal point(s) supporting the application

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- Management of Noncommunicable Diseases, Disability, Violence, and Injury Prevention—Nils Bilo, Medical Officer
- Pandemic and Epidemic Diseases—Yinzhong Shen, Medical Officer; and Nikki Shindo, Coordinator, Epidemic Clinical Management

3. Organization(s) consulted and/or supporting the application

The following organizations were consulted in relation to this application. Those with an asterisk also provided a letter of support for this application, included as an attachment. All organizations listed are partners of PATH. The Bill & Melinda Gates Foundation is a donor to PATH and provided financial support for the development of this application.

- The Aga Khan University*
- Association of Anaesthetists of Great Britain and Ireland (AAGBI) and the AAGBI Foundation*
- The Bill & Melinda Gates Foundation
- Clinton Health Access Initiative*
- GE Foundation*
- Gradian Health*
- International Centre for Diarrhoeal Disease Research, Bangladesh*
- Lifebox*

- Masimo*
- Pneumonia Innovations Team*
- The University of Melbourne*
- World Federation of Societies of Anaesthesiologists*

4. International Nonproprietary Name and Anatomical Therapeutic Chemical of the medicine

There is no International Nonproprietary Name for oxygen.[16] Oxygen is a member of the therapeutic category and drug class "medical gas." Its generic or chemical name is oxygen (English), oxygène (French), and oxígeno (Spanish).

The Anatomical Therapeutic Chemical code for oxygen is V03AN01, and it is categorized as V, Various; V03A, All Other Therapeutic Products; and V03AN, Medical Gases.[17] In addition to oxygen, other medical gases in this category include nitrogen, helium, medical air, and carbon dioxide.

5. Formulation(s) and strength(s) proposed for inclusion, including adult and pediatric

We recommend that the proposed additional listing of oxygen include the same formulation language as the original listing of oxygen (i.e., "inhalation, medicinal gas"). To increase the fraction of inspired oxygen concentration (FiO_2) available to a patient, oxygen medical gas with specific purity levels can be produced and administered by a variety of methods. Selection of medical grades of oxygen (see Section 13) and appropriate oxygen medical devices to serve adult and pediatric patients must be based on patient needs, the FiO_2 required to manage hypoxemia, and practicality of use. Medical oxygen can be supplied to patients from oxygen stored in cylinders or tanks; electrically powered oxygen concentrators; or central pipeline systems utilizing a compressed gas manifold, liquid oxygen storage system, or oxygen generator. Compressed gas tanks or liquid oxygen are procured and distributed from medical gas suppliers. Equipment for oxygen delivery often differs in its features and functions; therefore, it is important to consider what is practical in the intended setting. Selection of appropriate oxygen systems for a hospital or ward will depend on several factors, such as power supply and maintenance requirements.

6. Listing requested as an individual medicine

Oxygen is currently included on the 19th WHO EML under section 1. Anaesthetics, subsection 1.1 General anaesthetics and oxygen, and subsection 1.1.1 Inhalational medicines, as well as on the 5th WHO EMLc under the same section as on the adult list.

This proposal requests the additional inclusion of oxygen as an individual medicine under a new section for medical gases on the 20th WHO EML and 6th WHO EMLc to clarify its importance as an essential

medicine for broad indications and to reinforce its use for the management of hypoxemia as promoted by existing WHO normative policies and guidelines (see Table 1). The proposed language for an additional listing of oxygen was developed at a technical consensus meeting with WHO focal points in 2016 (see Annex III). This proposal is also in line with a 2010 call to action by many experts, including the Union Oxygen Systems Working Group, which noted that "oxygen has broad indications and should be in a class of its own [in the EML], perhaps the only drug with no alternative agent."[4] The inclusion of oxygen under a new medical gases section may contribute to overcoming inadequate and impaired access to oxygen therapy for all patients needing this lifesaving medicine and could stimulate increased coverage of oxygen medical gas in LMICs, where it can be particularly challenging to access. We have proposed an age restriction to this listing to ensure that oxygen is being delivered safely to preterm neonates (see Section 10 for more detail).

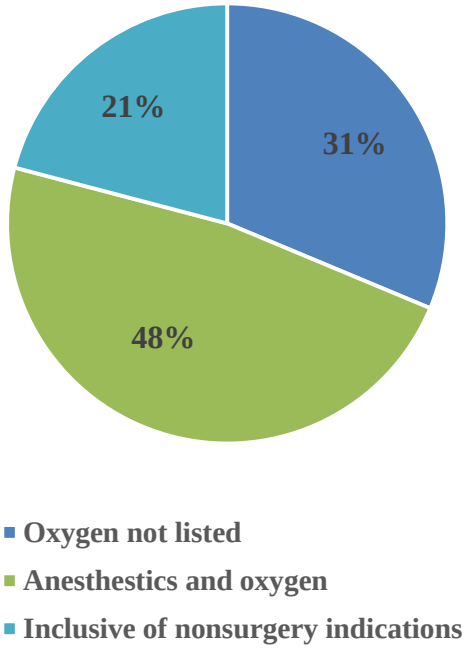
Table 1. Proposed additional inclusion of oxygen as a medical gas (new text in blue fields).

1. Anaesthetics	
1.1 General anaesthetics	
1.1.1 Inhalational medicines	
halothane	Inhalation.
Isoflurane	Inhalation.
nitrous oxide	Inhalation.
Oxygen	Inhalation (medicinal gas).
X. Medical gases	
oxygen*****	**Inhalation** (medicinal gas). Use for the management of hypoxemia. *No more than 30% oxygen should be used to initiate resuscitation of neonates ≤ 32 weeks of gestation.

Many countries develop and use their own NEML to support selection, procurement, and quality assurance of medicines and devices. The NEML from 131 countries were retrieved from an online database.[ii] Oxygen was not searchable for 26 countries due to a language barrier or because an online EML was unavailable. A review of 105 NEML, including those from the 49 LMICs with the highest child and maternal mortality burden, was conducted (see Annex IV). Based on this review of a subset of 105 NEML, most countries (48%) listed oxygen under the "anaesthetics and oxygen" section in alignment with the WHO EML and EMLc (see Figure 1). Despite this, oxygen is missing from the NEML in 31% of the countries. Notably, the remaining 21% of the countries included a listing of oxygen that supports its use for broader clinical indications. For example, alternative listings of oxygen on NEML include placement under a medical gases section, utilization of the Anatomical Therapeutic Chemical classification system, inclusion of nonsurgical indications (e.g., oxygen under "drugs for respiratory system" or "treatment of diseases of the respiratory system and allergy" sections), or as an independent, uncategorized listing.

[ii] National EML search is available at: http://www.cecinfo.org/emlsearch/.

Figure 1. Listing of oxygen in 105 National Essential Medicines Lists (NEML).



7. Treatment details (requirements for diagnosis, treatment, and monitoring)

a. Dosage regimen

Oxygen saves lives when used appropriately as a treatment for those who present with or are at risk of hypoxemia and is an essential component in resuscitation of critically ill patients. Oxygen is administered as a continuous flow of inhalation gas and can be delivered directly through oxygen tubing to the patient interface or in conjunction with ventilator support, continuous positive airway pressure (CPAP) devices, or nebulizer treatments. WHO has specific recommendations for the appropriate interface for oxygen delivery (see Annex V). Guidelines advocate that oxygen is administered within a target saturation range (see Table 2) and regularly monitored by pulse oximetry. Adult or pediatric doses to achieve target peripheral blood oxygen saturation (SpO_2) levels can be administered by adjusting the oxygen concentration percentage and flow rate in liters per minute (LPM), depending on standard clinical treatment practices in each country. Note that recommended flow rate and/or use of an air-oxygen blend is dependent on the patient, disease, and condition (see Table 3). For example, during newborn resuscitation, WHO recommends starting on room air and, if that is not effective, progressing to 30% oxygen.[13,18] In particular, safe use of oxygen among preterm infants requires monitoring with pulse oximetry to minimize damage from oxygen radicals to organs such as the eyes and lungs.[18] Flow rates used to treat severe hypoxemia are usually higher for adults than for children and vary by delivery devices

used (e.g., CPAP and ventilators require high flow of oxygen), so supply chain calculations need to account for the patient populations when making purchasing decisions and in epidemic and pandemic preparedness activities.

Table 2. Target SpO_2 levels for different patient populations.

Patient	Target SpO_2 level	
Newborns[19]	Resuscitation to be started using room air, progressing to 30% oxygen.[18]	
	Preterm neonates	Oxygen should be administered until SpO_2 is >88%, but no higher than 95%.
Children[19]	≤2,500 meters above sea level	Oxygen should be administered until SpO_2 is >90%. Oxygen should only be ceased when SpO_2 maintained above 90% for at least 15 minutes on room air.
	>2,500 meters above sea level	Oxygen should be administered until SpO_2 is >87%. Oxygen should only be ceased when SpO_2 maintained above 87% for at least 15 minutes on room air.
	Emergency signs*	Oxygen should be delivered to SpO_2 >94%.
Adults[20]	Nonpregnant	Oxygen should be delivered to SpO_2 >90%.
	Pregnant	Oxygen should be delivered to SpO_2 92%–95%.
	Risk of hypercapnic respiratory failure[21]	Oxygen should be administered until SpO_2 is >88%, but no higher than 92%.

* Emergency signs include obstructed or absent breathing, severe respiratory distress, central cyanosis, signs of shock, coma, or convulsion. SpO_2, peripheral blood oxygen saturation.

Table 3. Standard flow rates for different patient populations.

Patient	Standard flow rates* for oxygen through nasal prongs, catheters, or face masks	
Newborns[19]	Neonates	Initiated at 0.5–1.0 LPM and titrated to recommended SpO_2
	CPAP use in neonates	Initiated at 5–10 LPM and titrated to recommended SpO_2
Children[19]	Infants	Initiated at 1–2 LPM and titrated to recommended SpO_2
	Older children	Initiated at 1–4 LPM and titrated to recommended SpO_2
Adults[20]	Initiated at 5 LPM and titrated to recommended SpO_2, up to 15 LPM for patients with severe hypoxemia	

* Humidification is necessary when oxygen is delivered at a higher than standard flow rate (>4 LPM) through a nasal catheter or nasal prongs.[19]
CPAP, continuous positive airway pressure; LPM, liters per minute; SpO_2, peripheral blood oxygen saturation.

b. Duration

Oxygen can be used for the management of acute or chronic hypoxemia. Oxygen therapy used for the management of acute hypoxemia should be discontinued in a clinically stable patient when SpO_2 remains stable at greater than the recommended level (see Section 7a) for at least 15 minutes on room air.[19] The requirements and dependency on long-term administration (>15 hours per day) for patients with chronic hypoxemia vary by condition, and prescription decisions are based on a set of individual baseline assessments and regular monitoring.

c. Reference to existing WHO and other clinical guidelines

There are numerous normative guidance documents from national and international associations that recommend or include the use of oxygen for management of hypoxemia in various populations (Annex I). The following are recent WHO publications that include guidance on the safe use and delivery of oxygen:

- 2016 Standards for improving quality of maternal and newborn care in health facilities http://www.who.int/maternal_child_adolescent/documents/improving-maternal-newborn-care-quality/en/
- 2016 Oxygen therapy for children: A manual for health workers http://www.who.int/maternal_child_adolescent/documents/child-oxygen-therapy/en/
- 2016 Paediatric emergency triage, assessment and treatment: Care of critically ill children http://www.who.int/maternal_child_adolescent/documents/paediatric-emergency-triage-update/en/
- 2016 Technical specifications of neonatal resuscitation devices http://apps.who.int/iris/bitstream/10665/206540/1/9789241510264_eng.pdf
- 2016 Clinical management of patients with viral haemorrhagic fever
- http://apps.who.int/iris/bitstream/10665/205570/1/9789241549608_eng.pdf?ua=1
- 2015 Technical specifications for oxygen concentrators (WHO medical device technical series) http://www.who.int/medical_devices/publications/tech_specs_oxygen-concentrators/en/
- 2015 Recommendations on interventions to improve preterm birth outcomes http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/preterm-birth-guideline/en/
- 2015 Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected http://apps.who.int/iris/bitstream/10665/178529/1/WHO_MERS_Clinical_15.1_eng.pdf
- 2015 Safe childbirth checklist implementation guide http://www.who.int/patientsafety/implementation/checklists/childbirth/en/
- 2014 Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care
- http://who.int/csr/bioriskreduction/infection_control/publication/en/
- 2014 Hospital preparedness for epidemics http://apps.who.int/iris/bitstream/10665/151281/1/9789241548939_eng.pdf?ua=1&ua=1

d. Need for special diagnostics, treatment or monitoring facilities, and skills

Oxygen is a medical gas and hence should be treated as a drug—administered, titrated to reach target SpO_2, and closely monitored by trained staff. Administration of oxygen therapy requires the ability of the health worker to roughly determine the patient's age and to diagnose hypoxemia, signs of respiratory insufficiency, or severe respiratory distress. Hypoxemia or underlying respiratory disease are often underdiagnosed, and many patients are not diagnosed until the patient's condition is severe.

Pulse oximeters are a low-cost, portable, easy-to-use intervention that should be used to diagnose and monitor patients with hypoxemia. Pulse oximetry is recommended for the clinical determination of hypoxemia and for guiding administration of oxygen therapy. Even in high-income settings, hypoxemia can be difficult to establish with certainty unless pulse oximetry or arterial blood gas data are available.[10] Pulse oximetry has been shown to correctly diagnose hypoxemia in 20% to 30% more cases than with

clinical signs alone.[19] Nonetheless, in the absence of SpO_2, or arterial blood gas data, WHO guidelines support health workers identifying relevant clinical signs and erring on the side of overuse rather than underuse of oxygen.[22]

The need for skilled evaluation means that oxygen treatment requires a medical facility setting and is not currently recommended in community settings. Often, patients in need of oxygen treatment are referred to higher levels of facility care because of a lack of oxygen access at lower levels of care due to oxygen availability, training, or equipment deficiencies. If feasible, patients at risk of hypoxemia should receive oxygen during transfer to a higher level of facility. Generally, greater oxygen access, along with the ability of trained staff to monitor patients at lower levels of skilled care, may reduce the overall patient burden for specialized facilities by reducing, in some cases, the need for mechanical ventilation as well as intensive care admission.

Appropriate training and supplies for oxygen delivery also need to account for reprocessing equipment to avoid nosocomial infections.[23] Respiratory therapy equipment, including resuscitation equipment and other oxygen delivery systems, is classified as "semicritical" by the Spaulding Classification System describing the risk of infection transmission posed by medical devices and supplies. [24] This means that such equipment must be free from all microorganisms and undergo, at a minimum, high-level disinfection in order to be used safely with another patient. Health care providers should have access to personal protective equipment and follow established guidelines for infection control in health facilities.

e. Listing sought for the core list

Oxygen is currently on the **core list** of the WHO EML and EMLc due to its lifesaving properties, public health relevance, and cost-effectiveness. For the proposed additional listing of oxygen in a new medical gases section, we request to retain the listing of oxygen as an individual medicine and formulation (inhalation, medicinal gas) on the **core list** of the WHO EML and EMLc. Placement on the core list emphasizes that oxygen is a lifesaving commodity and should be available for the management of hypoxemia.

8. Information supporting the public health relevance

a. Epidemiological information on disease burden

From a public health perspective, it is clear that oxygen is a critical component of basic health services for its prescribed use in a wide range of clinical indications.[25] Oxygen is frequently needed for the management of hypoxemia during provision of safe surgery; treatment of acute and chronic respiratory conditions; use in disease epidemics and pandemics such as influenza, severe acute respiratory syndrome, and Middle East Respiratory Syndrome (MERS); emergency and critical care; and aiding overall improvement of quality of care within health systems. Below is an overview of the disease burden of various medical conditions for which medical oxygen for the management of hypoxemia might be needed

outside of a surgical setting, supporting the need for an additional listing of oxygen in a medical gases section.

- **Neonatal infections and complications of preterm birth.** Neonatal deaths accounted for 45% of the 5.9 million child deaths in 2015.[26] The majority (85%) of causes of neonatal deaths are due to conditions that can lead to hypoxemia: complications of preterm birth, intrapartum-related mortality (including birth asphyxia), and neonatal infections (including sepsis and pneumonia).[26,27,28] More than 50% of preterm babies born at 31 weeks of gestation or less will develop respiratory distress syndrome.[29] Severe respiratory distress syndrome (a common and serious complication of preterm birth), neonatal pneumonia,[30] and neonatal sepsis[31] together account for more than half of all neonatal deaths globally.[32]
- **Treatable infectious diseases in children.** Every year, more than 5.9 million children die, mostly from preventable or easily treatable diseases, and more than 95% of those deaths occur in LMICs. Many of the diseases with the highest mortality burden require oxygen for effective treatment, including conditions such as pneumonia, bronchiolitis, severe acute asthma,[33] acute sepsis, meningitis, malaria, gastroenteritis, and severe malnutrition. In particular, pneumonia is the leading infectious cause of death in children younger than five years old, responsible for at least 15% of all deaths in this age category.[34,35,36] Hypoxemia is the major fatal complication of pneumonia, increasing the risk of death multifold.[37] It is estimated that at least 13% of children with pneumonia develop hypoxemia, corresponding to between 1.5 and 2.7 million cases of hypoxemic pneumonia each year.[38] Bronchiolitis and influenza also contribute to the burden of acute respiratory infections in children that may require oxygen treatment for severe cases.
- **Obstetric care interventions.** Approximately 300,000 women were estimated to have died during and following pregnancy and childbirth in 2015.[39] Improving access to oxygen could help avert many of those deaths. Around 15% of all pregnant women develop a potentially life-threatening complication that may require emergency obstetrical intervention—including oxygen—to survive.[40] The use of oxygen has been recommended during many obstetric emergencies, including hemorrhage, pulmonary embolism, eclampsia, sepsis, and heart failure.[4] Studies conducted in low-income countries have found that emergency obstetric procedures represent a high proportion of the total surgical and trauma care volume.[41]
- **Emergency and critical care.** It is crucial to provide emergency oxygen supplementation for immediate care to ensure adequate ventilation during severe respiratory distress, sepsis, obstructed or absent breathing, prolonged convulsions, airway compromise (such as aspiration), respiratory or cardiac compromise, trauma, shock (including septic shock), brain injury, and many other emergency and critical conditions. Oxygen is the most commonly used drug in emergency, critical, and intensive care medicine in some high-income countries. In fact, 34% of ambulance patients receive oxygen during transit, and 15% to 17% of hospital inpatients receive oxygen at any given time.[42] In some cases of trauma, respiratory distress and hypoxemia may be secondary to injuries or dysfunction and often require oxygen treatment. Trauma ranks as the leading cause of global disability and death, accounting for more than 1.24 million deaths annually, with the majority of trauma-related deaths (91%) occurring in the poorest countries.[43]
- **Noncommunicable diseases.** Disability and mortality due to noncommunicable diseases are growing global concerns, among which the steady increase in incidence of CRDs—including asthma and chronic obstructive pulmonary disease (COPD)—now constitutes a serious public health problem.

Many of these illnesses require regular oxygen therapy for effective case management. For instance, COPD is predicted to be the third most common cause of global mortality by 2020 and access to oxygen is an important piece of the management plan for many COPD patients.[11] Notably, not only is the prevalence of COPD rising, but it is also one of the few chronic diseases with rising mortality rates.[44] In settings where domiciliary oxygen is available, the use of oxygen for COPD management is pervasive with as many as 79% of patients with COPD receiving long-term oxygen therapy.[45] There is evidence that in many high-resource settings, oxygen may be overprescribed; nonetheless, the burden of CRD requiring oxygen is significant.[46]

- **Pandemic and epidemic infectious diseases.** Preparedness for emerging infections includes planning for pandemic and epidemic severe acute respiratory infections. Influenza viruses (such as H1N1, H5N1, and H7N9) and MERS can cause severe pneumonia and acute respiratory distress syndrome, which need oxygen treatment. For example, the 2009 influenza A (H1N1) virus led to an estimated range of between 151,700 and 575,400 deaths in the first year of the pandemic. The majority of global deaths occurred in Africa and Southeast Asia where access to treatment, including oxygen, was limited.[47] The number of cases often overwhelmed the health system and many facilities were not able to deliver lifesaving oxygen treatment as recommended by WHO treatment guidelines for management of patients with hypoxemia.[48] More recently, the emerging H7N9 avian influenza A strain was first reported in 2013 and has led to a total of 798 laboratory-confirmed cases reported to the WHO through August 11, 2016.[49] Most patients with H7N9 become severely ill, often developing acute respiratory distress syndrome, and over one-third of reported cases have died.[50]

b. Assessment of current use

Medical oxygen is often missing in a majority of surgical settings in LMICs, and its availability is especially lacking for management of patients with hypoxemia (see Table 4).[7] In the last decade, those surveying and routinely assessing oxygen availability for essential surgery have documented approximately 35% of facilities in most low-resource settings had a complete absence of oxygen supplies.[6] The WHO Service Availability and Readiness Assessment and the Tool for Situational Analysis to Assess Emergency and Essential Surgical Care are instruments that include indicators on oxygen availability and have been used to collect data that are comparable across regions.[51] The latter has been used in more than 53 countries as part of the largest effort to assess availability of oxygen in health facilities.[52] Results show that oxygen availability highly varies from country to country and between regions. Additionally, oxygen survey questions were sometimes contextualized only for anesthesia and surgical care, so the availability of oxygen therapy for other clinical indications was often not determined and is therefore not well understood. Not all surveys of oxygen availability have assessed pulse oximetry, but a systematic literature review of anesthesia capacity in 22 LMICs found that of 394 hospitals which reported on pulse oximetry availability, 51% had functional pulse oximeters.[9]

Table 4. Examples of multicountry assessments of oxygen availability.

Study	Country	Setting	Oxygen availability
Assessment of oxygen availability for surgery			
Kusher et al. 2010[53]	8 LMICs	Essential surgery and anesthesia in 132 facilities	Oxygen was sometimes available in 33% of facilities, and never available in 46%.
LeBrun et al. 2014[54]	7 LMICs	Essential surgery and safe anesthesia in 78 district hospitals	Availability of pulse oximetry, essential medicines, and key infrastructure (water, electricity, oxygen) varied widely between and within countries.
Ologunde et al. 2014[55]	26 LMICs	Cesarean delivery availability in 719 facilities	Of facilities performing cesarean delivery, 21.3% did not have a consistent supply of oxygen; in the 54 health facilities that reported referring cesarean deliveries due to nonfunctioning equipment, 26.4% had no access to oxygen supply, and an additional 34% had access to oxygen only intermittently.
Vo et al. 2012[6]	22 LMICs	Anesthesia capacity in 590 health facilities	Thirty-five percent reported no access to oxygen; 45.2% of facilities had consistent access to oxygen supplies either via cylinder or oxygen concentrator.
Assessment of oxygen availability for settings outside of anesthetic use			
Nolan et al. 2001[7]	7 countries in Africa and Asia	Quality of hospital care for children in 21 hospitals	More than half of children were undertreated or inappropriately treated with antibiotics, fluids, feeding, or oxygen.
Belle et al. 2010[56]	12 countries in Africa	Influenza preparedness in 231 hospitals and health centers	Roughly 43% of facilities had uninterrupted access to oxygen; 29% of first-level health facilities possessed a fully functioning oxygen concentrator.
Manasyan et al. 2013[8]	7 sites in Africa, Asia, and Latin America	Emergency obstetric/neonatal care in 136 hospitals and 228 health clinics	Oxygen was not available in 40% of African hospitals, 17% of Asian hospitals, 91% of African clinics, and 69% of Asian clinics.

LMIC, low- and middle-income country.

Despite the substantial public health need to reduce inequities in oxygen access, the integration of oxygen within the quality-of-care continuum has been neglected in international as well as national programs aimed at decreasing maternal, child, and newborn mortality. There is evidence that hospital care for children is deficient in many countries, including recent data from a number of hospital assessment exercises on the quality of pediatric hospital care delivery in countries including Angola, Brazil, Cambodia, Indonesia, Kazakhstan, Kenya, Russia, Solomon Islands, and Timor-Leste.[57] Based on current evidence, it is estimated that about 10% to 20% of sick children presenting for primary care may require referral to a first-referral or district hospital.[58] Many of these health facilities, however, lack functioning oxygen supplies and adequate oxygen delivery equipment for management of hypoxemia. Common barriers include lack of infrastructure or effective procurement and distribution systems to install and maintain reliable supply of medical oxygen, lack of locally adapted operating procedures, competition for use, insufficient training, and perceived high cost.[3,59] Many of the barriers to access may be addressed by better integration of oxygen therapy into quality-of-care efforts.[60,61] The additional listing of oxygen in the EML and EMLc may stimulate a shift in thinking and increase prioritization of increased access to safe oxygen as part of activities to improve the quality of health care for newborns, children, and women.

c. Target population(s)

Evidence points to the need to advocate for integration and improved awareness of appropriate use of oxygen and pulse oximetry as lifesaving commodities within health systems to ensure vulnerable patients receive oxygen safely. Target populations that would particularly benefit from safe use of oxygen for the management of hypoxemia include preterm infants, children with severe respiratory disease, children and adults with septic shock, and patients during emergency and critical care—including women with delivery complications, practitioners in preparedness efforts against respiratory infection pandemics, and people living with CRD. While access to oxygen remains a global problem, LMICs with limited coverage and limited resources are of particular concern. For many first-level hospitals in LMICs, access to supplemental oxygen remains unpredictable and limited.[5] Ensuring global endorsement and normative guidance for the broader applications of oxygen may foster a more enabling environment for oxygen delivery at the national level.

d. Likely impact of treatment on the disease

When left untreated, hypoxemia leads to physiological damage and mortality that results from decreased oxygen perfusion to metabolically active tissues. Because all the functions of the human body require oxygen, oxygen deprivation can have severe adverse effects. Lack of oxygen leads very quickly to the termination of biological processes, dysfunction of vital organ systems, and death. Therefore, hypoxemia is a life-threatening condition that requires early detection and treatment with essential oxygen medicine. Capabilities for the safe administration of oxygen to patients in respiratory distress are essential at all hospital facilities and would be useful at all levels of the health system with trained medical staff.[62]

Strengthening availability of and access to oxygen should be a component of universal health coverage. In addition to uses of oxygen in essential surgical care and anesthesia, oxygen is also an essential component of integrated strategies to reduce the burden of neonatal and child mortality caused by leading causes of death: pneumonia, preterm birth complications, and neonatal infections resulting in conditions that can lead to hypoxemia.[63] The Lives Saved Tool model calculates that if full supportive care for severe neonatal infection were available globally, including oxygen, intravenous antibiotics and fluids, blood transfusion, and phototherapy,[64] a total of 409,877 neonatal deaths would be averted each year.[63] Full supportive care—including oxygen therapy—ranks third for most deaths averted among 54 interventions included in the Lives Saved Tool model. Based on a systematic literature review, the evidence suggests that pulse oximeter use combined with improved oxygen administration in children can reduce mortality rates.[65] Table 5 below highlights the large impact of oxygen treatment on reducing childhood mortality as observed in two studies in Papua New Guinea and Malawi. In Ethiopia, improved access to oxygen has the potential to benefit 20% of the estimated 4 million cases of child pneumonia each year.[66] The use of oxygen and pulse oximetry has been shown to reduce the length of emergency department stays, increase admission of children with previously unrecognized hypoxemia, and inform decisions on illness severity, diagnosis, and treatment. Furthermore, if pulse oximetry and oxygen therapy were both available, it has been estimated that up to 148,000 child deaths could be averted each year in the 15 countries with the highest pneumonia burden.[67]

Table 5. Studies evaluating impact of oxygen-related interventions.

Study	Country	Patients	Intervention	Impact
Duke et al. 2008[68]	Papua New Guinea	11,000 children with pneumonia	Improved oxygen systems, including oxygen concentrators and pulse oximeters	Overall reduction in case-fatality rate of 35.2% (from 4.97% to 3.22%) over 27 months
Enarson et al. 2009[69]	Malawi	40,000 children with pneumonia	Improved case management of pneumonia, which included introduction of oxygen concentrator equipment, training, maintenance, and program monitoring and evaluation	Reduction of 54.8% in the proportion of children dying from pneumonia over baseline (from 18.6% to 8.4%) over 62 months

Similarly, acute and chronic respiratory conditions, including severe acute respiratory infections (e.g., pneumonia, influenza) and noncommunicable diseases such as asthma and COPD, continue to have a significant impact on worldwide health because of their prevalence, high disease burden, and enormous cost to the health care system. There are also unmeasured, indirect economic costs due to loss of productivity, morbidity, or mortality. Even with advances in understanding of the prevention, detection, and treatment of respiratory diseases and the effectiveness of interventions such as oxygen and pulse oximetry, the high prevalence of conditions resulting in hypoxemia underscores the need to better prioritize the availability and integration of oxygen therapy as part of national and subnational health care systems in LMICs.

9. Review of benefits: Summary of comparative effectiveness in a variety of clinical settings

a. Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

During the preparation of WHO treatment guidelines and other guidance documents, multiple systematic literature reviews for various indications are undertaken. The findings are carefully assessed by the technical review teams and are often published in a Grading of Recommendations Assessment, Development and Evaluation table as part of the document publication. As oxygen use is extensively covered in existing WHO guidelines, additional systematic reviews were not conducted for this application. In addition, discussions with WHO focal points included the recommendation not to conduct additional systematic reviews. Instead, Grading of Recommendations Assessment, Development and Evaluation tables were reviewed from existing WHO guidance documents (see Annex I) and any pertaining to the indication, contraindication, administration, or monitoring of oxygen use were noted.

b. Summary of available data (appraisal of quality, outcome measures, summary of results)

There is technical consensus among experts on the need to detect hypoxemia with pulse oximetry and to treat hypoxemic patients with oxygen. There is a lack of randomized, controlled trials comparing oxygen intervention to a control (e.g., room air) in an acute care setting, as it would be unethical to deny patients oxygen, the standard practice for a century, and have them suffer severe consequences. There is no debate about whether oxygen is needed to sustain life, but many of the specifics for administration of oxygen have not been rigorously studied to date. Upon review by a WHO steering committee and a guidelines development group of experts, the evidence reviewed for the recent publication of WHO's *Oxygen Therapy for Children* was determined to be of "low quality" overall. Nonetheless, WHO's expert review panel was able to issue a weight of "strong recommendation" for all but one of the recommendations in the manual (see Table 6). A similar strength of recommendation despite low quality of evidence is reflected in recommendations from other WHO treatment guidelines, including those for treatment in adults. Despite the quality of data on exactly how much oxygen to deliver to which specific patient populations via various delivery mechanisms, it is understood that oxygen is essential for the management of hypoxemia.

Table 6. Quality of evidence for WHO recommendations on oxygen use.[18,19,70,71]

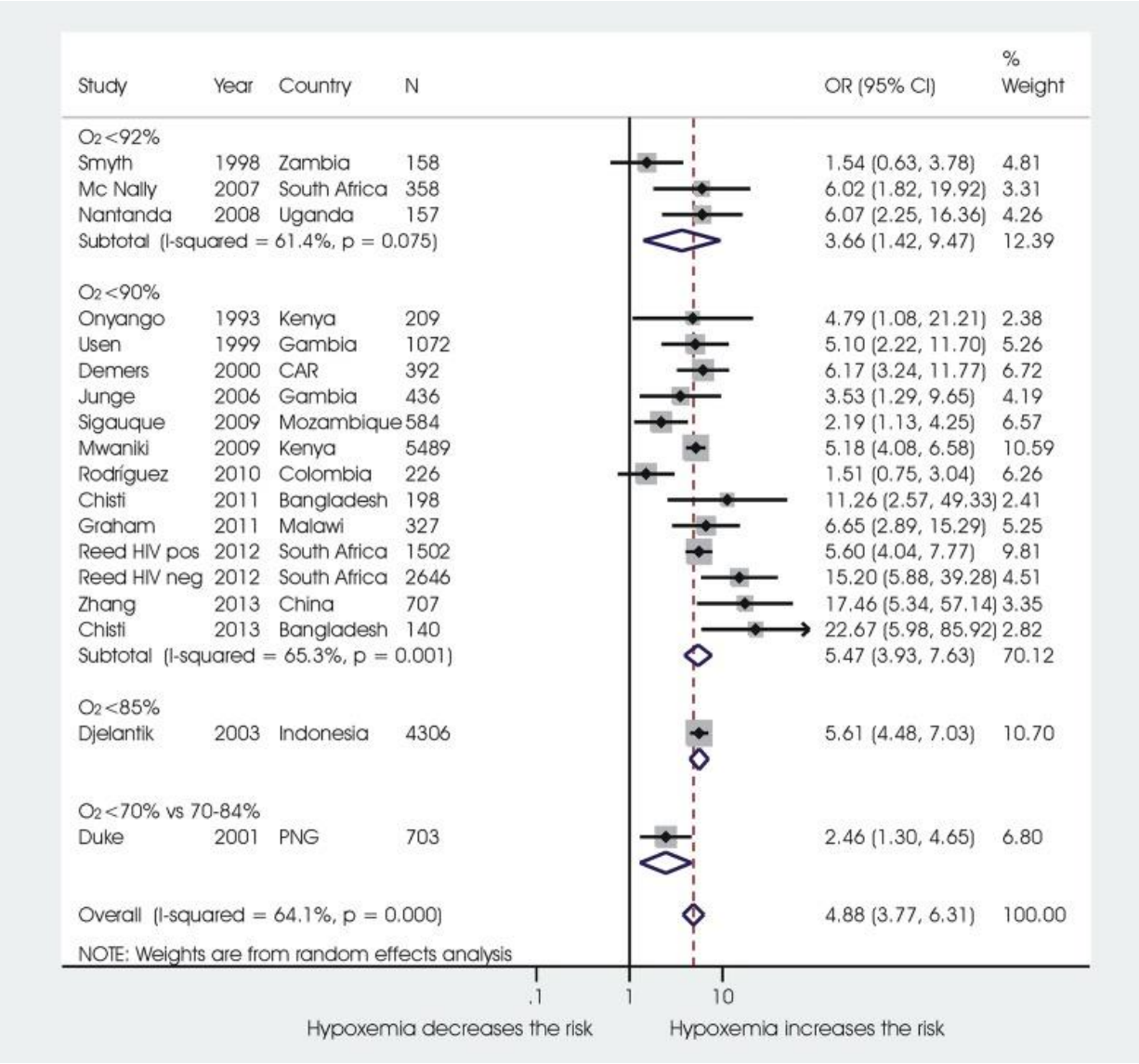
Recommendation	Strength	Quality of evidence
Administration of oxygen therapy should be guided by pulse oximetry when available.	Strong recommendation	Very low
Effective oxygen delivery systems should be a universal standard of care and should be made more widely available.	Strong recommendation	Expert opinion
Pulse oximetry is recommended for determining the presence of hypoxemia and for guiding administration of oxygen therapy to infants and children.	Strong recommendation	Low
Use pulse oximetry whenever possible for the detection of hypoxemia in children with severe lower respiratory tract infections. If oximetry is not available, the following clinical signs could be used to determine use of oxygen therapy: central cyanosis, nasal flaring, inability to drink or feed (when due to respiratory distress), grunting with every breath, depressed mental state (e.g., drowsy, lethargic).	Strong recommendation	Low
Children with hypoxemia should receive appropriate oxygen therapy.	Strong recommendation	Very low
Children with respiratory disease living at ≤2,500 meters above sea level should receive oxygen therapy if their oxygen saturation is ≤90%, as measured by pulse oximetry.	Strong recommendation	Very low
Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, signs of shock, coma, or convulsion) should receive oxygen therapy during the resuscitation phase if their SpO_2 is <94%.	Strong recommendation	Very low
In children living at high altitude (>2,500 meters above sea level), the normal oxygen saturation is lower than in those living at sea level. At high altitude, a lower level of saturation, such as SpO_2 ≤87%, could be used as a threshold for giving oxygen.	Recommendation	Very low
In newly born term or preterm (>32 weeks of gestation) babies requiring positive-pressure ventilation, ventilation should be initiated with air. For preterm babies born at or before 32 weeks of gestation, it is preferable to start	Strong recommendation	Moderate

Recommendation	Strength	Quality of evidence
ventilation with 30% rather than 100% oxygen.		
For exacerbation of COPD, oxygen should be administered by a device that controls concentration between 24% and 28%.	Strong recommendation	Very low
Oxygen should be administered to patients with acute severe asthma, where the decision to use oxygen is based on low saturation readings.	Strong recommendation	Very low

COPD, chronic obstructive pulmonary disease; SpO_2, blood oxygen saturation.

The benefit of oxygen therapy in hypoxemia management for newborns, children, and adults is supported by several systematic reviews.[72,73] Moreover, the need for diagnosing and treating hypoxemia is very clear, as a meta-analysis of 17 studies from around the world showed a fivefold increased risk of mortality associated with hypoxemia among children with acute lower respiratory infections (Figure 2). This large effect on mortality highlights the importance of oxygen interventions to prevent and treat hypoxemia in children.

Figure 2. A meta-analysis of 17 studies showing the association between hypoxemia and death among children younger than five years old with acute lower respiratory infection in LMICs.[74]



10. Review of harms and toxicity: Summary of evidence on safety

a. Estimate of total patient exposure to date

Published literature supports the safety and effectiveness of oxygen administration dating back more than 100 years.[75,76] Oxygen has been used as a therapeutic medicine since 1885.[75] In York, Pennsylvania, the first recorded use of medical oxygen was on a patient during treatment of acute bacterial pneumonia, and the use of supplemental oxygen in clinical practice for treatment of patients with respiratory conditions

resulting in hypoxemia was quickly established.[77] Since then, medical oxygen has been a commonly used drug in clinical settings to treat countless patients and has been shown to be a safe and effective medicine if administered correctly.

b. Description of the adverse effects/reactions and estimates of their frequency

Oxygen can be administered and titrated to the appropriate SpO_2 with no adverse effects. The contraindications of oxygen therapy relate to the dangers of hyperoxia,[iii] which can result in relatively rare adverse effects, including oxygen toxicity.[iv,78] Patients who are particularly vulnerable to the risks of oxygen toxicity and subsequent organ damage include preterm infants and patients who are sensitive to hypercapnic respiratory failure.[21] However, evidence also shows that targeting lower blood oxygen saturations can lead to higher incidence of neurological damage and mortality.[79] Therefore, it is important that oxygen therapy is administered to achieve adequate tissue oxygenation using the lowest possible FiO_2 and monitoring with pulse oximetry.

Special caution should be observed when treating preterm infants. Preterm infants who have reduced antioxidant defenses are particularly sensitive to the toxic effects of oxygen. The concentration of therapeutic oxygen should be titrated to the appropriate target SpO_2 for newborn preterm infants in order to minimize the risk of bronchopulmonary dysplasia, retinopathy of prematurity (ROP) and subsequent blindness, or other potential adverse effects.[79] Retinal damage may also occur in adults exposed to 100% oxygen for extended periods (24 to 48 hours) or at greater than atmospheric pressure, particularly in individuals whose retinal circulation has been previously compromised.[80]

ROP is one of the leading causes of potentially avoidable childhood blindness globally, with systematic reviews and meta-analyses undertaken estimating that annually 184,700 (uncertainty range: 169,600–214,500) preterm babies developed any stage of ROP in 2010, 20,000 (15,500–27,200) of whom became blind or severely visually impaired from ROP and a further 12,300 (8,300–18,400) having mild/moderate visual impairment.[81] These adverse events may be prevented by careful titration and monitoring of oxygen concentrations, emphasizing the importance of pulse oximetry.

Nosocomial infections are a risk if oxygen delivery devices and supplies are contaminated with pathogenic microorganisms and used with other patients without appropriate reprocessing or storage. In neonatal intensive care units, nosocomial infections have been observed to be spread via neonatal resuscitation equipment.[82,83] In general, the application of oxygen therapy and use of oxygen equipment is safe when used as recommended.

c. Summary of available data on safety

The general safety profile and reported adverse events of supplemental oxygen therapy represent a long history of use in clinical medicine, which has been studied and communicated to date.[84] Because of its

[iii] Hyperoxia is an excess supply or concentration of oxygen to tissues and organs.
[iv] Oxygen toxicity is a condition resulting from the harmful effects of breathing molecular oxygen at elevated partial pressures.

proven efficacy and safety, oxygen medical gas continues to be widely used for management of patients with hypoxemia because of its favorable therapeutic index and benefits that outweigh the risks.[iv] The majority of studies that have explored the relationship between hyperoxia and mortality in critically ill patients are retrospective observational investigations with highly heterogeneous characteristics and inconsistent results.[85] Additional clinical research is warranted to determine whether supplemental oxygen in medical emergencies causes more harm than benefit in certain patient populations. Nonetheless, numerous WHO recommendations on the clinical use of oxygen have been published based on observational evidence and strong expert consensus that oxygen is beneficial (see Section 9b and Annex I).

Understanding the particular risk of hyperoxia in newborn preterm infants, several studies have compared the effect of resuscitation using air with the use of higher concentrations of oxygen on mortality. Following a review of the available evidence, a group of experts on the development of WHO guidelines made a strong recommendation that it is preferable to start ventilation with 30% rather than 100% oxygen in preterm (≤32 weeks of gestation) babies to avoid potentially harmful extremes of hyperoxia or hypoxemia.[18,86] This recommendation was made on the basis of "moderate quality" evidence on the benefits of oxygen on mortality and no evidence for significant harms (Table 6).[18] Recognition of the risks of oxygen therapy has resulted in continuous improvements in safety and protocols for clinical use and strengthened initiatives to improve the availability and coordinated use of pulse oximetry for oxygen delivery and monitoring. Pulse oximetry is strongly recommended to monitor the needed concentration of oxygen and ensure that the maximal benefits of oxygen therapy are achieved while reducing the potential for harm due to hyperoxia.[87,88,89]

d. Summary of comparative safety against comparators

Oxygen is the only therapeutic drug class effective in improving oxygen saturation that has been extensively studied and recommended by WHO and other guidelines. There is no known medicine for the management of hypoxemia that currently substitutes for medical oxygen.

e. Identification of variation in safety that may relate to health systems and patient factors

Delivery of oxygen therapy should be guided and monitored by the use of pulse oximetry, if available. Insufficient education and training; lack of familiarity with oxygen delivery devices; lack of understanding of the effects, benefits, and dangers of oxygen therapy; and differing levels of health care practitioner experience and skills, as well as patient factors and varying baseline risks, workforce constraints, and the practical issues regarding overall quality of care, may relate to variations in safety of oxygen administration that differ from country to country.[46] Variations in safety could also be due to using devices that were neither designed nor manufactured to global specifications or using unclean equipment. The safety and quality of oxygen supply and delivery equipment are dependent on quality assurance processes, including Good Manufacturing Practice (GMP) and International Organization for Standardization (ISO) standards.

11. Summary of available data on comparative cost and cost-effectiveness

a. Range of costs of the proposed medicine

Oxygen is an internationally available and relatively affordable medicine with options for selecting from several common sources including cylinders, concentrators, and pipelines (see Annex VI). Reliable provision of oxygen therapy also requires systems and resources to ensure appropriate and sustained use. Trained technicians, device warranties, patient circuit consumables, service components, and adequate health budgeting and supply chain management are often key to improving oxygen availability and access. The cost range of a robust oxygen system for a health facility is difficult to narrow down due to the various options for commodities (both static and consumable), additional costs for training and maintenance, and a lack of reliable oxygen-pricing data.

For many LMICs, pressurized oxygen cylinders are more widely available than concentrators or generators for oxygen delivery because they are initially less expensive to purchase than concentrators and have lower installation costs than centralized, piped oxygen systems. Cylinders do not require an electrical supply, but they need refilling at a supplier, which adds recurring costs to the price of use. Some key suppliers of oxygen cylinders include Air Liquide (France), Air Products and Chemicals, Inc. (United States of America), Airgas, Inc. (United States of America), Atlas Copco (Sweden), GCE Holding AB (Sweden), The Linde Group (Germany), Messer Group (Germany), Oxygas (Uganda), Praxair, Inc. (United States of America), SOL-SpA (Italy), and Taiyo Nippon Sanso Corporation (Japan).[90,91,92]

It is challenging to demonstrate global price ranges for oxygen. The Management Sciences for Health *International Drug Price Indicator Guide*, published with WHO, is commonly used to identify current prices for a range of health commodities; however, price information for oxygen is not available in the present guide (2014 edition)[93] and only data on the prices for filled oxygen cylinders in Uganda were available in an earlier version (2010 edition; see Table 7).

Table 7. Buyer prices for oxygen cylinders in Uganda.[94]

Country	Package	Price (US$)	Price/liter of treatment (US$)
Uganda National Medical Stores	1 bottle (6.8 cubic meters)	11.00	1.62
Uganda National Medical Stores	1 bottle (8.5 cubic meters)	14.96	1.76

Oxygen concentrators can be an effective, low-cost solution to oxygen shortages in developing countries. Concentrators offer a consistent source of oxygen by concentrating oxygen from ambient air; however, oxygen concentrators require a reliable power supply, regular maintenance, and training for users. In an assessment of oxygen systems for treatment of childhood pneumonia, many good-quality concentrators delivering 5 to 10 LPM were identified to be suitable for LMICs, currently costing between US$650 and US$1,500.[3] A PATH landscape analysis found the cost of commercially available oxygen concentrators ranged from US$315 to US$3,995 (see Table 8).[95]

Table 8. Supplier prices for oxygen concentrators.

Source	Product	Model details	Price (US$)	Liters per minute
PATH Technology landscape: oxygen concentrators (Global)[95]	1 stationary concentrator	Specifications	315.00–3,995.00	5
Missionpharma (Denmark)[96]	1 stationary concentrator	Specifications	1,150.00	5
United Nations Population Fund (Denmark)[97]	1 stationary concentrator	Specifications	416.49	5
United Nations Children's Fund (Denmark)[98]	1 stationary concentrator	Specifications	765.31	5

Oxygen concentrators have numerous advantages, including sustainability and low cost, compared with oxygen cylinders and piped oxygen supply systems. Two studies, one in Malawi[99] and another in Papua New Guinea,[100] showed that with adequate planning, training, and repairs, oxygen systems utilizing oxygen concentrators could be sustainably implemented in district hospitals at an overall cost per unit of US$3,670 over 5 years and US$6,320 over 2 years, respectively. [10] The actual purchase price of the concentrators was a low proportion of the total cost of implementing an oxygen system, with the costs split between equipment and human resources at approximately 55% and 45%, respectively. Furthermore, an assessment of concentrator functioning in pediatric wards in Mongolia and Malawi demonstrates that concentrators can remain functional with up to 30,000 hours of use, which is equivalent to more than 40 months of continuous utilization.[101] Some models of oxygen concentrators are designed for continuous operation and can produce oxygen 24 hours per day, seven days per week, for up to five years or more with minimal preventive maintenance. WHO generally recommends that oxygen concentrators be used as the primary oxygen supply in LMICs.[102]

When evaluating oxygen concentrator models for settings where mechanical ventilator devices or air-oxygen blenders are required, it is important to determine whether the oxygen concentrator can deliver oxygen at the necessary concentration and outlet pressure. High-pressure oxygen is available from cylinders and piped oxygen systems, but not from most oxygen concentrators (<140 kPa).

b. Resource use and comparative cost-effectiveness

Oxygen concentrators are ideal for use in LMIC and pandemic settings given advantages in cost and efficiency of oxygen delivery (per patient) over oxygen cylinders (see Table 9). The average cost of ownership of an oxygen concentrator and yearly maintenance is about half as much as the cost associated with cylinder use in LMIC, with a return on investment reported to be achieved within one to two years.[103]

Table 9. Examples of studies evaluating comparative cost between oxygen cylinders and concentrators.

Study	Country	Setting	Cost of cylinders	Cost of concentrators	Comparative cost analysis
Mokuolu and Ayayi 2002[104]	Nigeria	Neonatal unit	US$2,320 for one patient per year based on cost of refilling cylinders at US$8 per cylinder)	US$630 for one patient per year (initial capital outlay of US$2,000 for life span of four years)	Cost of one patient on the concentrator for one year is 27% of the cost of using cylinders; for four patients using the concentrator at once, the relative cost is 7% of the cost of using cylinders.
Howie et al. 2009[105]	The Gambia	Hospitals having at least 20 hours of national grid access per day	Annual facility cost of US$152,747	Annual facility cost of US$18,742	Concentrators provided oxygen at a less expensive rate than cylinders, at a cost of US$0.84 per 1,000 liters from concentrators compared to $4.80 to $6.56 per 1,000 liters from cylinders.
		Average-sized pediatric ward	Best-case scenario average annual cost of US$5,000	Average annual cost of US$1,500	Annual cost-savings for an oxygen concentrator system with 24 hours of electricity per day and a five-year lifespan is 70% of the cost of using cylinders.
Duke et al. 2010[100]	Papua New Guinea	District hospital consuming 17,000 L of oxygen per day	PGK 333,000 over two years	PGK 33,000 over two years	Cost of oxygen concentrator to a district hospital for two years is 10% of the cost of using cylinders.

PGK, Papua New Guinea Kina.

The cost-benefit ratio for improvements in access to oxygen therapy is likely to be highly favorable, given the high volume of patients for whom supplemental oxygen could be lifesaving. Increased availability and use of noninvasive measurements of SpO_2 by pulse oximetry in developing countries to improve effective detection of hypoxemia and rational use of oxygen could further lower cost and reinforce evidence of benefit. Pulse oximetry supports rational use of oxygen by guiding decisions on initiation, titration, and discontinuation of oxygen in specific patients. Table 10 below provides examples of studies to illustrate the cost per outcome (i.e., cost per treatment, cost per additional life saved, and cost per disability-

adjusted life year [DALY] averted) of improved oxygen systems for the management of hypoxemia that results as a complication from childhood pneumonia. These studies suggest that the cost-effectiveness of oxygen is comparable to other interventions that are widely recommended to reduce mortality from pneumonia, including vaccines (pneumococcal conjugate vaccines are estimated at US$100 per DALY averted and US$4,500 per life saved in moderate- and high-mortality countries).[106] Additionally, innovations are underway to develop oxygen concentrators that would reliably deliver oxygen cheaply without relying on consistent electricity, pointing to potential future reductions in overall cost of oxygen delivery systems.[107]

Table 10. Examples of studies reporting cost per outcome for oxygen when used for the management of hypoxemia in children with pneumonia.

Study	Country	Type	Intervention	Cost per outcome
Duke et al. 2008[68]	Papua New Guinea	Prospective observational study with retrospective comparison	Improved oxygen systems, including oxygen concentrators and pulse oximeters	US$51 per pneumonia patient treated, US$1,673 per additional life saved, and US$50 per DALY averted
Enarson et al. 2009[69]	Malawi	Prospective observational study	Improved case management of pneumonia, including introduction of oxygen concentrator equipment, training, maintenance, and monitoring	US$136 per treatment for a hospitalized case of pneumonia
Floyd et al. 2015[67]	15 highest burden of pneumonia countries	Deterministic compartmental model	Pulse oximetry combined with WHO IMCI guidelines (at least 60% of hospitals must have oxygen available in order for pulse oximetry to offer any mortality benefit)	Median estimates ranging from US$3 to US$53 per DALY averted
Zhang et al. 2016[108]	24 published studies supplemented with data from 10 unpublished studies	Systematic review	Management of severe pneumonia, including interventions as detailed in the WHO pocketbook for community- and facility-based management	Total cost of treatment per episode of severe pneumonia is US$243 in different levels of hospital inpatient settings in LMICs

DALY, disability-adjusted life year; IMCI, integrated management of childhood illness; LMIC, low- and middle-income country; WHO, World Health Organization.

Oxygen is a therapeutic drug that can be used to treat any form of hypoxemia, regardless of its underlying cause. While we present the data on its particular effectiveness in treating acute respiratory diseases and hypoxemic conditions found in children as an example, oxygen systems are cost-effective and could have the added benefit of strengthening existing health facilities to improve health outcomes globally.[35]

12. Summary of regulatory status of the medicine in various countries

Oxygen medical gas is registered and approved for use by regulatory agencies for numerous indications in virtually all WHO Member States that have medicines regulatory authorities.[109]

Oxygen medical gas is classified as a medicinal product and regulated as a finished pharmaceutical. Stringent regulatory bodies, such as the US Food and Drug Administration, European Medicines Agency, and the Japanese Pharmaceuticals and Medical Devices Agency, have guidelines on the classification of oxygen medical devices and GMP manufacture of medical gases and multiple accredited suppliers.[110,111,112,113]

Medical sources of oxygen must be manufactured in conformance with current industry practice to ensure drug safety, identity, strength, quality, and purity.[114] This standard includes following GMP for all manufacturing steps, such as processing, filling, transfilling, mixing, purifying, separating, cascading, transferring, packaging, labeling, and distributing oxygen cylinders.

Oxygen supply systems and some of the associated equipment are regulated as a medical device when used to administer oxygen medical gas. For example, oxygen concentrators that meet ISO standards (ISO 80601-2-69) and oxygen generator supply systems (ISO 10083) for use with a medical gas piping distribution system (ISO 7396-1) are registered medical devices in numerous countries around the world. Medical devices carrying a CE marking indicate that the manufacturer or importer declares product compliance with the requirements of the applicable Medical Devices Directive.

Medical device classification may determine the type of premarketing submission required for clearance to market. For example, oxygen concentrators are regulated as Class II medical devices in the United States. The device shall comply with regulatory requirements for appropriate national regulatory clearance (e.g., Australia: Therapeutic Goods Administration device license; Canada: Health Canada medical device license; European Union: CE or Medical Devices Directive Mark; Japan: Pharmaceuticals and Medical Devices Agency device license; United States: 510(k) market clearance) or have an equivalent internationally recognized regulatory approval.

13. Availability of pharmacopoeial standards

Oxygen is listed in all major pharmacopeias (with most including monographs for both Oxygen 99 percent and Oxygen 93 percent):

- The British Pharmacopoeia (BP) 2016[115]
  - Oxygen
  - Oxygen 93 percent
- The European Pharmacopoeia (Ph. Eur) 8th Edition (Version 8.8) 2016[116]
  - Oxygen—Monograph 0417
  - Oxygen 93 percent—Monograph 02455
- The Indian Pharmacopoeia (IP) 7th Edition 2014, Addendum 2016[117]
  - Oxygen
  - Oxygen 93 percent
- The International Pharmacopoeia (Ph. Int) 5th Edition 2015[118]
  - Oxygen (Oxygenium)
- The Japanese Pharmacopoeia (JP) 17th Edition 2016[119]
  - Medical Oxygen
- The United States Pharmacopeia (USP 39)—National Formulary (NF 34) 2016[120]
  - Medical Oxygen—Monograph 7782-44-7
  - Oxygen 93 percent—Monograph 5231

Compressed medical gas supplies generally delivering Oxygen 99 percent (pharmacopoeial standards BP 2016, Ph. Int 5, USP 39, Ph. Eur 8, JP XVII, IP 2014) can be classified as being within one of two broad categories: (1) transfillers that manufacture oxygen medical gas by transferring oxygen, either in a gaseous or liquid (cryogenic) form, from a larger container into storage in smaller containers, customarily high-pressure cylinders or cryogenic vessels; or (2) air separation units that separate atmospheric air into constituent oxygen gas through a process of precleaning, compression, cooling, and fractional distillation of liquefied air.

Oxygen concentrators are medical devices that extract nitrogen from atmospheric air to deliver a continuous flow of concentrated Oxygen 93 percent (pharmacopoeial standards: BP 2016, USP 39, Ph. Eur 8, IP 2014) to patients or to supply central hospital pipeline systems.

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Annex I. Normative guidance on the clinical use of oxygen for various conditions

Table A-1. WHO normative guidance documents on oxygen use.

Year	Title	Resource link
2016	Oxygen therapy for children: A manual for health workers	http://www.who.int/maternal_child_adolescent/documents/child-oxygen-therapy/en/
2016	Paediatric emergency triage, assessment and treatment: Care of critically ill children	http://www.who.int/maternal_child_adolescent/documents/paediatric-emergency-triage-update/en/
2016	Clinical management of viral haemorrhagic fever	http://apps.who.int/iris/bitstream/10665/205570/1/9789241549608_eng.pdf?ua=1
2016	Technical specifications of neonatal resuscitation devices (WHO medical device technical series)	http://apps.who.int/iris/bitstream/10665/206540/1/9789241510264_eng.pdf
2016	Clinical management of patients with viral haemorrhagic fever	http://apps.who.int/iris/bitstream/10665/205570/1/9789241549608_eng.pdf?ua=1
2015	Technical specifications for oxygen concentrators (WHO medical device technical series)	http://www.who.int/medical_devices/publications/tech_specs_oxygen-concentrators/en/
2015	Safe childbirth checklist: Improving the quality of facility-based delivery	http://apps.who.int/iris/bitstream/10665/199177/1/9789241549455_eng.pdf?ua=1
2015	Recommendations on interventions to improve preterm birth outcomes	http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/preterm-birth-guideline/en/
2015	Clinical management of severe acute respiratory infection	http://apps.who.int/iris/bitstream/10665/178529/1/WHO_MERS_Clinical_15.1_eng.pdf
2015	Improving paediatric quality of care at first-level referral hospitals: Final meeting on the WHO-Russian Federation paediatric quality of care improvement initiative	http://apps.who.int/iris/bitstream/10665/197628/1/9789241509800_eng.pdf?ua=1
2015	Interagency list of medical devices for essential interventions for reproductive, maternal, newborn and child health	http://apps.who.int/medicinedocs/en/m/abstract/Js22018en/
2015	Safe childbirth checklist implementation guide	http://www.who.int/patientsafety/implementation/checklists/childbirth/en/
2014	Hospital preparedness for epidemics	http://apps.who.int/iris/bitstream/10665/151281/1/9789241548939_eng.pdf?ua=1&ua=1
2014	Guidelines on infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care	http://apps.who.int/iris/bitstream/10665/112656/1/9789241507134_eng.pdf?ua=1
2014	Integrated management of childhood illness chart booklet	http://www.who.int/maternal_child_adolescent/documents/IMCI_chartbooklet/en/
2014	Global Alliance against Chronic Respiratory Diseases: 9th general meeting report	http://www.who.int/gard/GARDGMreport2014_web.pdf
2014	Revised WHO classification and treatment of childhood pneumonia at health facilities	http://worldpneumoniaday.org/wp-content/uploads/2014/10/WHO_Quick-reference-guide_Pneumonia_Sept-2014.pdf
2013	Pocket book of hospital care for children	http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/
2013	Ending preventable child deaths from pneumonia and diarrhoea by 2025: The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD)	http://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en/

Year	Title	Resource link
2013	Pandemic influenza risk management interim guidance	http://www.who.int/influenza/preparedness/pandemic/GIP_PandemicInfluenzaRiskManagementInterimGuidance_Jun2013.pdf?ua=1
2013	Interim guidance document—Clinical management of severe acute respiratory infections when novel coronavirus is suspected: What to do and what not to do	http://www.who.int/csr/disease/coronavirus_infections/InterimGuidance_ClinicalManagement_NovelCoronavirus_11Feb13u.pdf
2013	Guideline: Updates on the management of severe acute malnutrition in infants and children	http://apps.who.int/iris/bitstream/10665/95584/1/9789241506328_eng.pdf
2013	Compilation of WHO recommendations on maternal, newborn, child and adolescent health	http://www.who.int/maternal_child_adolescent/documents/mnca-recommendations/en/
2012	Generic essential emergency equipment list	http://www.who.int/surgery/publications/s15982e.pdf
2012	Guide to anaesthetic infrastructure and supplies at various levels of health care facilities	http://www.who.int/surgery/publications/GuideAnaestheticInfrastructureSupplies_revAug2012.pdf
2012	Guidelines on basic newborn resuscitation	http://www.who.int/maternal_child_adolescent/documents/basic_newborn_resuscitation/en/
2012	Priority life-saving medicines for women and children	http://www.who.int/medicines/publications/emp_mar2012.1/en/
2012	Guidelines for primary health care in low-resource settings: Cancer, diabetes, heart disease and stroke, chronic respiratory disease	http://www.who.int/nmh/publications/phc2012/en/
2011	Pulse oximetry training manual	http://www.who.int/patientsafety/safesurgery/pulse_oximetry/who_ps_pulse_oxymetry_training_manual_en.pdf
2011	Integrated Management of Adolescent and Adult Illness (IMAI) district clinician manual: Hospital care for adolescents and adults—Guidelines for the management of common illnesses with limited resources	http://www.who.int/hiv/pub/imai/imai2011/en/
2010	Model formulary for children	http://apps.who.int/medicinedocs/en/m/abstract/Js17151e/
2010	Packages of interventions for family planning, safe abortion care, maternal, newborn and child health	http://apps.who.int/iris/bitstream/10665/70428/1/WHO_FCH_10.06_eng.pdf
2010	Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings	http://www.who.int/nmh/publications/essential_ncd_interventions_lr_settings.pdf
2009	Guidelines for safe surgery	http://apps.who.int/iris/bitstream/10665/44185/1/9789241598552_eng.pdf
2009	Pandemic influenza preparedness and response: WHO guidance document	http://www.who.int/influenza/resources/documents/pandemic_guidance_04_2009/en/
2008	Model formulary	http://apps.who.int/medicinedocs/en/m/abstract/Js16879e/
2008	Practical approach to lung health (PAL): Manual on initiating PAL implementation	http://apps.who.int/iris/bitstream/10665/69937/1/WHO_HTM_TB_2008.410_eng.pdf
2007	Managing complications in pregnancy and childbirth: A guide for midwives and doctors	http://apps.who.int/iris/bitstream/10665/43972/1/9241545879_eng.pdf
2007	Global surveillance, prevention and control of chronic respiratory diseases: A comprehensive approach	http://apps.who.int/iris/bitstream/10665/43776/1/9789241563468_eng.pdf
2007	Tuberculosis care with TB-HIV co-management: Integrated Management of Adolescent and Adult Illness (IMAI)	http://apps.who.int/iris/bitstream/10665/43668/1/9789241595452_eng.pdf

Year	Title	Resource link
2006	Guide to anaesthetic infrastructure and supplies at various levels of health care facilities emergency and essential surgical procedures	http://apps.who.int/medicinedocs/en/m/abstract/Js15329e/
2005	Prevention and control of chronic respiratory diseases at country level	http://www.who.int/respiratory/publications/WHO_NMH_CHP_CPM_CRA_05.1.pdf
2004	Guidelines for essential trauma care	http://www.who.int/violence_injury_prevention/publications/services/en/guidelines_traumacare.pdf
2003	Surgical care at the district hospital	http://www.who.int/entity/surgery/publications/en/SCDH.pdf?ua=1
2003	Managing newborn problems: A guide for doctors, nurses and midwives	http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9241546220/en/
2003	Informal consultation on clinical use of oxygen	http://www.who.int/surgery/collaborations/Oxygen_Meeting_Report_Geneva_2003.pdf

Table A-2. National and international associations' guidelines for oxygen use.

Association: Title	Resource link
American Association for Respiratory Care (AARC): Evidence-based clinical practice guidelines and expert panel reference-based guidelines	http://www.rcjournal.com/cpgs/#evidence
AARC: Clinical practice guideline: Neonatal and pediatric O_2 delivery (2002)	http://www.rcjournal.com/cpgs/pdf/06.02.707.pdf
AARC: Clinical practice guideline: Oxygen therapy for adults in the acute care facility (2002)	http://www.rcjournal.com/cpgs/pdf/06.02.717.pdf
American College of Emergency Physicians: Guidelines for care for children in the emergency department (2009)	https://www.acep.org/Clinical---Practice-Management/Guidelines-for-Care-of-Children-in-the-Emergency-Department/
American Thoracic Society: Statements, guidelines & reports	http://www.thoracic.org/statements/index.php
British Thoracic Society (BTS): Guideline for emergency oxygen use in adult patients (2008)	https://www.brit-thoracic.org.uk/document-library/clinical-information/oxygen/emergency-oxygen-use-in-adult-patients-guideline/emergency-oxygen-use-in-adult-patients-guideline/
British Thoracic Society: BTS guidelines for home oxygen in children (2009)	http://thorax.bmj.com/content/64/Suppl_2/ii1.full
College of Respiratory Therapists of Ontario: Oxygen therapy clinical best practice guideline (2013)	http://www.crto.on.ca/pdf/PPG/Oxygen_Therapy_CBPG.pdf
European Respiratory Society: Guidelines for respiratory medicine	http://www.ers-education.org/guidelines.aspx
Federation of Gynecology and Obstetrics: Committee and working group publications	http://www.figo.org/figo-committee-and-working-group-publications
Global Initiative for Asthma (GINA): GINA reports	http://ginasthma.org/gina-reports/
Global Alliance Against Respiratory Diseases (GARD) Basket: A package of information, surveillance tools and guidelines, to be offered as a service to countries	http://www.who.int/gard/publications/GARD_Basket_web.pdf?ua=1
Global Initiative for Chronic Obstructive Lung Disease (GOLD): GOLD reports	http://goldcopd.org/gold-reports/
International Pediatric Association: Child survival resource materials	http://ipa-world.org/child-survival-hiv-malaria.php
Médecins Sans Frontières: Clinical guidelines: Diagnosis and treatment manual	http://refbooks.msf.org/msf_docs/en/clinical_guide/cg_en.pdf
Pre-Hospital Emergency Care Council: Medication	http://www.phecit.ie/Images/PHECC/Clinical%20

Association: Title	Resource link
formulary	Practice%20Guidelines/Medication%20Formulary/EMT%20Medication%20Formulary%202012%20Version.pdf
The Royal Children's Hospital Melbourne: Clinical guidelines (nursing): Oxygen delivery	http://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Oxygen_delivery/
Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock	http://www.survivingsepsis.org/sitecollectiondocuments/implement-pocketguide.pdf
World Association of Perinatal Medicine: Guidelines page	http://www.wapm.info/guidelines.php

Annex II. Listing of oxygen medicinal gas in the WHO Model Formulary (2008) and Model Formulary for Children (2010)

WHO Model Formulary (2008)

- Adult formulary only includes oxygen use during inhalational anesthesia.

Oxygen

Inhalation (medicinal gas).

Uses: to maintain an adequate oxygen tension in inhalational anaesthesia.

FIRE HAZARD. Avoid use of cautery when oxygen is used with ether; reducing valves on oxygen cylinders must not be greased (risk of explosion).

Precautions: interactions: Appendix 1.

Dose:

Concentration of oxygen in inspired anaesthetic gases should never be less than 21%.

Adverse effects: concentrations greater than 80% have a toxic effect on the lungs leading to pulmonary congestion, exudation and atelectasis.

WHO Model Formulary for Children (2010)

- Pediatric formulary includes supplemental oxygen for use during resuscitation and in the treatment of respiratory problems.

Oxygen

ATC code: V03AN01

Inhalation (medicinal gas)

Fire hazard. Avoid use of cautery when oxygen is used with ether; reducing valves on oxygen cylinders must not be greased (risk of explosion).

Special Notes: Inhalation gas.

Indications: Maintain adequate tissue oxygenation in inhalational anaesthesia and other indications for use in neonates and children. Used during resuscitation and in the treatment of respiratory problems requiring supplemental oxygen.

Dose:

Concentration of oxygen in inspired anaesthetic gases should never be less than 21%, and preferably 30% or above.

The concentration required depends on the condition being treated.

Renal impairment: No dosage adjustment necessary.

Hepatic impairment: No dosage adjustment necessary.

Adverse effects: Long-term use of concentrations greater than 80% have a toxic effect on the lungs leading to pulmonary congestion, exudation and atelectasis. Short-term use of 100% is not associated with these toxic effects.

The concentration required depends on the condition being treated; if available, monitoring of the oxygen delivered is strongly recommended, as inappropriate concentration may have serious or even lethal effects. Risks include morbidity, brain damage, and especially in pre-term neonates can cause retinopathy with blindness and chronic lung disease.

Use of 100% oxygen should not be withheld in an emergency situation.

Annex III. Technical consensus meeting on increasing oxygen access through normative policy change

Wednesday, August 10, 2016 | 8:30 a.m.–12:00 p.m. Central European Time | PATH Geneva office | Elevating Oxygen project

PATH organized a technical consensus meeting on August 10, 2016, to bring together focal points from the World Health Organization (WHO) to discuss the critical issues regarding access to oxygen and approach for the WHO Model List of Essential Medicines (EML) and List of Essential Medicines for Children (EMLc) application. The aim of the meeting was to reach consensus on the contents of the current application to update the listing for oxygen on the WHO EML/EMLc. This also included the type of EML/EMLc change to propose and how to ensure the listing of oxygen reflects and supports strengthened availability for surgery as well as for a variety of other clinical indications for the management of hypoxemia in infants, children, and adults.

PREREAD MATERIALS

- A draft application to update the WHO EML/EMLc, including literature summaries of the evidence on oxygen, will be shared for peer review prior to the meeting (required reading).
- Fact sheet for PATH Elevating Oxygen project, which includes a list of recent WHO guidance documents and tools on oxygen (optional reading).

AGENDA

Schedule	Agenda topic
8:30 – 8:50	• Welcome and introductions • Review meeting purpose and objectives
8:50 – 9:30	• Present the Elevating Oxygen project and discuss the potential opportunities afforded by normative global policy change
9:30 – 9:45	• Discuss existing policies and guidelines on oxygen and deficiencies in oxygen availability in low-resource settings
9:45 – 10:30	• Review evidence in the draft proposal to update oxygen on the WHO EML and EMLc
10:30 – 10:45	Break
10:45 – 11:30	• Continue discussion re: evidence in the EML and EMLc application
11:30 – 12:00	• Determine next steps regarding quality of the evidence and evidence gaps deemed essential for application submission

PARTICIPANTS

- Bernadette Cappello, Essential Medicines and Health Products, WHO
- Adriana Velazquez Berumen, Essential Medicines and Health Products, WHO
- Shamim Qazi, Maternal, Newborn, Child and Adolescent Health, WHO
- Nils Bilo, Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention, WHO
- Yinzhong Shen, Pandemic and Epidemic

Diseases, WHO
- Karin von Eije, Pandemic and Epidemic Diseases, WHO
- Bonnie Keith, Advocacy and Public Policy, PATH
- Darin Zehrung, Devices and Tools, PATH
- Jaclyn Delarosa, Devices and Tools, PATH
- Manjari Quintanar-Solares, Devices and Tools, PATH
- Gwen Ambler, Drug Development, PATH

DISCUSSION HIGHLIGHTS

- Listing of oxygen for expanded indications on the WHO EML/EMLc is an important and influential first step toward improving access to oxygen at country level.
- Achieved consensus on draft language for the proposed listing of oxygen on the WHO EML/EMLc.
- Confirmed next steps for revising the EML/EMLc application.
- Opportunities to leverage the EML/EMLc update to advocate for integration and improved efforts to ensure sustainable access to oxygen.
- Advocacy opportunities identified during the discussion.

ABRIDGED MEETING MINUTES

- **Listing of oxygen for expanded indications on the WHO EML/EMLc is an important and influential first step toward improving access to oxygen at the country level**—but ultimately, the WHO EML/EMLc is a recommendation.
  - Must create a link between global EML and national EMLs.
  - Essential Medicines and Health Products department works with regional and country offices and uses the WHO EML/EMLc as a guide for countries to create their national list; however, compliance is not mandatory.
  - WHO EML/EMLc often informs national health policy, including national EML.
  - Clearly an access issue—oxygen is often not thought of as a drug outside of surgery, and there is need to improve recognition of the essential indications for oxygen, particularly for newborn and children's health.
  - Application should include evidence from priority diseases to support the use of oxygen therapy for management of hypoxemia in both adults and children:
    - Adults:
      - Emergency: trauma and obstetric care.
      - Noncommunicable diseases such as chronic obstructive pulmonary disease, asthma exacerbations, heart disease.
      - Respiratory infectious diseases including pneumonia, Middle East respiratory syndrome, H71/H51.
    - Children:
      - Neonatal deaths from preterm complications.
      - Pneumonia and other common childhood illnesses.

- **Achieved consensus on draft language for the proposed listing of oxygen on the WHO EML/EMLc**—preserve the anaesthetic indication for oxygen and add a new section on medical gases.
  - Do not want the process of editing the EML/EMLc to reduce oxygen availability in surgery; leave current listing in the "Anaesthesia" section as-is.
  - Propose a second listing for oxygen under a new "Medical Gases" section (see Table A-3).
    - Opportunity to leverage a new, additional listing for oxygen for advocacy.
    - Draw out age restriction to highlight safety requirements for oxygen administration.
  - Consensus to keep the listing simple:
    - Oxygen as an inhalation (medical gas).
    - Use for management of hypoxemia.

- No more than 30% oxygen should be used during resuscitation of neonates ≤32-weeks of gestation.

- Do not include on the EML/EMLc application:
  - Oxygen purity (already included in monographs and pharmacopeia).
  - Reference to medical devices or pulse oximetry (already included in other guidance documents, and not necessarily appropriate for the EML/EMLc).

Table A-3. Consensus on proposal for inclusion of oxygen as a medical gas on the WHO Model List of Essential Medicines (new text in blue fields).

1. Anaesthetics	
1.1 General anaesthetics and oxygen	
1.1.1 Inhalational medicines	
Halothane	**Inhalation.**
Isoflurane	**Inhalation.**
nitrous oxide	**Inhalation.**
oxygen	**Inhalation** (medicinal gas).
X. Medical gases	
oxygen*	**Inhalation** (medicinal gas). Use for the management of hypoxemia. *****No more than 30% oxygen should be used during resuscitation of neonates ≤32weeks of gestation.

Note: The proposed text in Section 6 was altered from the text above developed at the technical consensus meeting, replacing "during resuscitation" with "to initiate resuscitation" to more accurately reflect current WHO guidelines for neonatal resuscitation.

Annex IV. Sample listing of oxygen on national essential medicines lists

The national essential medicines lists (NEML) from 131 countries are included in an electronic database available at: http://www.cecinfo.org/EMLSearch/. A review of the 105 searchable NEML, including those from the 49 low- and middle-income countries with the highest child and maternal mortality burden, was conducted. The results for the listing of oxygen for this subset of 105 countries are provided in Table A-4 below. Table A-5 highlights examples of NEMLs that have referenced nonsurgical inclusions of oxygen medical gas.

Table A-4. Summary of oxygen listing on 105 national essential medicines lists.

Oxygen not listed	Oxygen listed under "Anesthetics and oxygen"	Listing of oxygen includes support for its use in nonsurgery indications
1. Algeria 2. Angola 3. Barbados 4. Burundi 5. Cambodia 6. Cameroon 7. China 8. Colombia 9. Côte d'Ivoire 10. Ecuador 11. El Salvador 12. Fiji 13. Gabon 14. Guinea 15. Guyana 16. Honduras 17. Iran 18. Iraq 19. Jordan 20. Lebanon 21. Madagascar 22. Marshall Islands 23. Morocco 24. Myanmar 25. Niue 26. Oman 27. Palau 28. Somalia 29. Thailand 30. Trinidad and Tobago 31. Tunisia	1. Armenia 2. Bahrain 3. Bhutan 4. Botswana 5. Brazil 6. Burkina Faso 7. Cape Verde 8. Central African Republic 9. Chad 10. Cook Islands 11. Democratic Republic of the Congo 12. Djibouti 13. Dominican Republic 14. Egypt 15. Eritrea 16. Ethiopia 17. Georgia 18. Ghana 19. Haiti 20. India 21. Indonesia 22. Kenya 23. Kiribati 24. Lesotho 25. Malawi 26. Malaysia 27. Maldives 28. Mali 29. Namibia 30. Nauru 31. Nepal	1. Afghanistan 2. Argentina 3. Bangladesh 4. Belize 5. Bolivia 6. Chile 7. Republic of the Congo 8. Croatia 9. Jamaica 10. Malta 11. Mauritania 12. Mexico 13. Papua New Guinea 14. Paraguay 15. Senegal 16. South Africa 17. Tanzania 18. Togo 19. Tonga 20. Vietnam 21. Zambia 22. Zimbabwe

Oxygen not listed	Oxygen listed under "Anesthetics and oxygen"	Listing of oxygen includes support for its use in nonsurgery indications
32. Uruguay 33. Venezuela	32. North Korea 33. Nigeria 34. Pakistan 35. Peru 36. Philippines 37. Republic of Moldova 38. Rwanda 39. Saint Vincent and the Grenadines 40. Seychelles 41. Solomon Islands 42. Sri Lanka 43. Sudan 44. Syria 45. Timor-Leste 46. Tuvalu 47. Togo 48. Uganda 49. Vanuatu 50. Yemen	

Table A-5. Sample language for listing of oxygen on national essential medicines lists that supports its use in nonsurgery indications.

Country	Essential Medicines List	Edition/Year	Section and description
Afghanistan	National Essential Drugs List	2007	Essential Drugs List Anatomo Therapeutic Chemical Classification V: Various V03: All other therapeutic products Oxygen cubmt per bottle, inhalation gas [V03AN01]
Argentina	Formulario Terapeutico Nacional	10th Edition/ 2005	26.11. Intoxication con gases 26.11.01. Intoxication con monoxido De carbono 26.11.01.01. Oxigeno (100%) (*)
Bangladesh	List of Essential Drugs	2008	134. Oxygen Dosage form: Inhalation
Belize	Belize Drug Formulary and Therapeutics Manual	9th Edition/ 2009–2011	Treatment of poisoning Inhaled poisons: 3) Oxygen
Bolivia	Listado Nacional de Medicamentos Esenciales LINAME	2011–2013	Codigo: V 03 10 Medicamento: Oxigeno Concentracion: 99% Forma Farmaceutica: Gas M. Res.: Classific A.T.Q.: V03AN01

Country	Essential Medicines List	Edition/Year	Section and description
Chile	Formulario nacional de medicamentos	2005	Grupo 1 01.0 Medicamentos usados en anestesia y gases medicinales 01.01.03 Gases Medicinales Oxigeno
Republic of the Congo	Liste Nationale des Medicaments Essentiels	6th/2013	No. 242: Oxygene
Croatia	OSNOVNA LISTA LIJEKOVA HRVATSKOG ZAVODA ZA ZDRAVSTVENO OSIGURANJE	2010	R Drugs for respiratory system (Lijekovi s djelovanjem na sustav disnih organa) R03 Antiasthmatics (Antiastmatici) R03CB04 952 oxygen (kisik)
Jamaica	List of Vital Essential and Necessary Drugs and Medical Sundries for Public Health Institutions	2008	13. Drugs used in treatment of disorders of the respiratory system 13.8 Oxygen
Malta	Malta Medicines List	2008	Medicinal Oxygen Medicinal oxygen – Multigas Ltd./ Medicinal Oxygen – Polygas Ltd.
Mauritania	Liste Nationale des Medicaments Essentiels par Niveau	2007	II-Anesthesique II-1-Anesthesiques generaux et Gaz medicaux 135. Oxygene
Mexico	Cuadro Basico y Catalogo de Medicamentos	2009	Multiple occurrence of oxygen
Papua New Guinea	Papua New Guinea Department of Health Medical and Dental Catalogue	9th/2002	Section 5: Hospital sundries Catheter, nasal, oxygen Cylinder, gas, medical: 5157. oxygen (440L) (C) 5158. oxygen (3,800L) (E) 5159. oxygen (7,600L) (G)
Paraguay	Lista de Mediamentos Esenciales	2009	01. Todo el resto de los productos terapéuticos V.03.06. Oxigeno
Senegal	Liste Nationale de Medicaments et Produits Essentiels du Senegal	2008	II-Anesthesiques II-1 Anesthesiques generaux et Gaz medicaux Oxygene
South Africa	Standard Treatment Guidelines and Essential Drugs List	2008	Multiple occurrences of oxygen
Tanzania	Standard Treatment Guidelines and Essential Medicines List	4th/2013	Multiple occurrence of oxygen
Togo	Liste Nationale des Medicament Essentiels sous DCI pour les adultes	2012	1. Anesthesiques et oxygene 1.4 Oxygene 20 Oxygene*; inhalation *Niveau 3, usage reserve a la maternite
Tonga	Standard Treatment Guidelines and Essential Drugs List for the Ministry of Health, Tonga	2007	Multiple occurrence of oxygen

Country	Essential Medicines List	Edition/Year	Section and description
Vietnam	Danh muc thuốc tân dược	2008	13 Oxy dược dụng Đường hô hấp; bình khí lỏng hoặc nén
Zambia	Zambia Essential Medicine List (ZEML), 03	2013	6. Drugs used in the treatment of diseases of the respiratory system and allergy 6.5 Oxygen 6.5.1 Oxygen; medicinal gas
Zimbabwe	6th Essential Medicines List and Standard Treatment Guidelines for Zimbabwe	2011	Multiple occurrence of oxygen

Annex V. Oxygen delivery methods in children and infants

Patient delivery consumables (oxygen tubing and a delivery device such as nasal prongs, nasal catheters, or oxygen masks) are needed to deliver therapeutic levels of oxygen to the patient. The following recommendations on oxygen delivery methods in children and infants are taken from the World Health Organization's (WHO) *Technical specifications for oxygen concentrators*. Table A-6 is adapted from the WHO's *Oxygen therapy for children* manual.

"In children with hypoxic respiratory illness, it is recommended that nasal prongs are used. The distal prong diameter should fit well into the nostril (1 mm for preterm infants; 2 mm for neonates up to 10 kg). Nasal prongs and nasal catheters are consumables that are not recommended for reuse between patients by the manufacturer. If nasal prongs are to be reused, cleaning and disinfection protocols must be followed. Nasal prongs are preferred, however, nasal catheters can also be used. If nasal catheters are used, French size 6 or 8 can be used in neonates and infants (pp. 20–21)."

"Humidification may be required for high-flow oxygen needs greater than 2 LPM or if oxygen bypasses the nose, such as when nasopharyngeal catheters or tracheal tubes are used (p. 18)."

"Due to their relative inefficiency and low patient acceptance, oxygen masks are not ideal in locations where oxygen is scarce or for patients that require prolonged oxygen therapy. Oxygen masks require higher flows than nasal prongs or catheters to achieve similar inspired oxygen concentrations (p. 22)."

Source: World Health Organization (WHO). *Technical specifications for oxygen concentrators*. WHO medical device technical series. Geneva: WHO; 2015.

Table A-6. Oxygen delivery methods in children and infants.

Method	Maximum O_2 flow (l/min)[a]	Actual inspired O_2 fraction (%) from 1 L/min by a 5-kg infant	PEEP	Humidification	Risk for hypercapnea	Risk for airway obstruction	Equipment required	Nursing demand
Nasal prongs	Neonates: 0.5–1							
	Infants: 2							
	Preschool: 4							
	School: 6	45	Minimal	Not required	No	Minimal	Nasal prongs	+
Nasal catheter	Neonates: 0.5							
	Infants: 1	50	+	Not required	No	+	8-F catheter	++
Nasopharyngeal catheter	Neonates: 0.5							
	Infants: 1	55	++	Required	No	++	8-F catheter, humidifier	+++

Method	Maximum O_2 flow (l/min)[a]	Actual inspired O_2 fraction (%) from 1 L/ min by a 5-kg infant	PEEP	Humidi-fication	Risk for hyper-capnea	Risk for airway obstruction	Equipment required	Nursing demand
Head box, face mask, incubator, tent Not recommend-ed, as oxygen is used inefficiently	Head box: 2–3 L/kg per min		Nil	Not required	Yes	No	Head box, face mask	+++

F, French; PEEP, positive end expiratory pressure.

[a] Higher flow rates without effective humidification may cause drying of nasal mucosa, with associated bleeding and airway obstruction.

Source: World Health Organization (WHO). *Oxygen therapy for children*. Geneva: WHO; 2016.

Annex VI. Comparison of oxygen cylinders and concentrators as the basis for oxygen systems

The following table comparing oxygen cylinders and concentrators as the basis for oxygen systems is taken from the World Health Organization's *Technical specifications for oxygen concentrators*.

Table A-7. Comparison of oxygen cylinders and concentrators as the basis for oxygen systems.

System	Central oxygen (pipeline system)	Oxygen cylinders	Oxygen concentrators
Power source required	No	No	Yes, continuously (100–600 W, depending on model)
Transport requirement	Those associated with cylinders	Regularly: heavy and costly to transport	Only at time of installation
Exhaustible supply	Yes, if pipes are refilled from an offsite supply facility	Yes, depending on size, storage pressure, and patient needs	No, continuous supply as long as power remains uninterrupted
Initial costs	Significant: generator and cylinders (US$20,000), piping system (US$10,000+), installation, commissioning, and training	Moderate: cylinder, oxygen flow meter, and regulator per cylinder (~US$200)	Moderate: concentrator (US$300–US$3,400), spares, installation, commissioning, and training
Operational costs	Small to moderate: maintenance, continuous refill of pipeline by bank or tanks	High: cylinder refills and transport from refilling station to hospital	Small: electricity and maintenance
User care	Minimal	Minimal: regular checking, minimizes fire hazard (no grease or flammables)	Moderate: cleaning of filters and device exterior, minimizes fire hazard
Maintenance	Moderate: check for pressure leaks with manometer Maintenance of oxygen pipelines to prevent leaks and oxygen wastage Significant: if supply facility is onsite	Moderate: check for pressure leaks with gauge	Moderate: check for low oxygen output with analyzer

System	Central oxygen (pipeline system)	Oxygen cylinders	Oxygen concentrators
Cost per 1,000 liters of oxygen	Data not available	US$10–US$30/kiloliter, varying with estimated oxygen requirement and power availability	US$2–US$8/kiloliter (greater depending on cost of power source), varying with estimated oxygen requirement and power availability

Note: All costs are approximations and not guaranteed.

Source: World Health Organization (WHO). *Technical specifications for oxygen concentrators*. WHO medical device technical series. Geneva: WHO; 2015.

Letters of support