1. Introduction

The past 15 years have been marked by intensive research efforts on pulmonary drug delivery (PDD) not only for local therapy but for systemic therapy as well as diagnostic purposes, primarily due to the several advantages the pulmonary route offers over other routes of drug administration. Drugs that undergo extensive first-pass metabolism or gastrointestinal degradation (such as proteins and peptides) are ideal candidates for pulmonary delivery. Even though the lung is enzymatically active, examples abound where these drugs have shown improved bioavailability after pulmonary administration [1, 2]. Pulmonary administration is less invasive and will lead to increased patient compliance. Lower incidence of side effects, especially for local therapies, is often observed due to localized drug deposition and reduced systemic and generalized exposure.

Targeted drug delivery to the lungs has evolved to be one of the most widely investigated systemic or local drug delivery approaches. The use of drug delivery systems (DDS) for the treatment of pulmonary diseases is increasing because of their potential for localized topical therapy in the lungs. This route also makes it possible to deposit drugs more site-specific at high concentrations within the diseased lung thereby reducing the overall amount of drug given to patients (10–20 % of the peroral quantity), as well as increasing local drug activity while reducing systemic side effects and first-pass metabolism.

To further exploit the other advantages presented by the lungs, as well as to overcome some challenges encountered, scientists developed interests in particulate DDS for pulmonary administration. These systems can be broadly classified into immediate release [e.g. lactose-drug mixtures for dry powder inhaler (DPI) application] and controlled release systems (such as liposomes, micelles, nano- and microparticles based on polymers).

Particulate drug carriers such as liposomes, microparticles and nanoparticles can be/have been used to improve the therapeutic index of new or established drugs by modifying drug absorption, reducing metabolism, prolonging biological half-life or reducing toxicity. Drug distribution is then controlled primarily by properties of the carrier and no longer by physico-chemical characteristics of the drug substance.
only. A careful design of such DDS, based on a thorough understanding of the clinical requirements for the disease conditions to be treated, lung architecture/physiology, appropriate selection of the carrier materials, production process and device, are key to successful delivery using advanced DDS such as liposomes and microparticles.

2. Limitations of PDD and how particulate DDS can be used to overcome current challenges

The respiratory tract, being in direct contact with the external environment, possesses a series of defenses against inhaled materials. The mucociliary escalator, coughing, and alveolar clearance are the 3 major physical ways of removing deposited particles. In the conducting airways deposited particles are rapidly cleared by the mucociliary clearance (MCC) into the pharynx. In the terminal airways (alveoli), absorptive or non-absorptive processes remove deposited particles. The absorptive process may involve either direct penetration into the epithelial cells or uptake and clearance by the alveolar macrophages (AM). The non-absorptive process involves transport of particles to the ciliated region (conducting airways) followed by clearance by the mucociliary escalator. The MCC consists of the coordinated interaction between the approximately 7 µm thick mucus blanket and the underlying cilia. The coordinated beating of the cilia propels the mucus blanket together with the deposited foreign particles very rapidly towards the pharynx where they are swallowed. The MCC in a healthy trachea transports the overlying mucus at the speed of about 10 mm/min [3]. This makes therapy of diseases such as asthma and COPD to require more frequent drug administration with the increased potential for systemic side effects. Liposomes and microspheres can be engineered to adhere to the mucus for prolonged time thereby decreasing the frequency of administration.

Human cilia are about 6 µm long in the large airways and decreases to about 5 µm or less in the bronchioles (4), and are about 5 µm in diameter (see also Chapter 1). Cilia are distributed differently along the respiratory tract: 53 % in the trachea, 45 % in the 1st generation airways, 23 % in the 3rd generation airways and 15 % in the 5th (5). MCC can be measured indirectly by measuring the ciliary beat frequency (CBF) [6, 7], or directly by monitoring the rate of removal of marker materials [8]. A triphasic clearance from the alveoli has been recorded, with half-life values of 1, 20 and 300 days corresponding to mucociliary escalator, macrophages and transepithelial penetration, respectively. In one of these studies 27 % of the total clearance was attributed to the macrophages, with a half-life of 30 days. The macrophages also play an important role in releasing chemotactic factors to attract polymorphonuclear neutrophils from the vascular bed to the sites of inflammation. AM are 15–50 µm in diameter and lie in contact with the surfactant lining in the alveoli [5]. Attachments of AM to foreign particles occur by electrostatic or receptor-mediated interaction. Following adhesion, macrophages ingest particles by pseudopod formation, interiorization of vacuoles or surface cavitations and subsequently digest them. Thereafter AM migrate to the ciliated epithelium for clearance via the bronchioles or to a lesser extent traverse the epithelium.
Both the particle size and surface properties of materials influence their efficiency of uptake and clearance. With respect to the particle size, efficiency of microspheres clearance was $3 \, \mu m > 6 \, \mu m > 0.66 \, \mu m$. This observation is being exploited in designing particulate drug targeting to the lung either for the purpose of targeting or evading the AM. Unless macrophages are the primary target, uptake, degradation and clearance by macrophages should be taken into account in designing the pulmonary delivery system. On the other hand, where the drug is intended to act within a short time (1–7 days), macrophage clearance may not be a very serious problem, unless on the occasion that due to mobilization/repopulation following the first administration, subsequent doses will be cleared much faster than initial doses.

Materials administered into the lung come in contact with an active metabolic barrier at every region. These enzymes are present both intracellularly and in extracellular secretions, or even membrane bound. Macrophages, lymphocytes, neutrophils and mast cells can release proteases and peptidases upon appropriate stimulation. A broad classification of the various hydrolases found in the lung is shown in Fig. 1.

Drug delivery in the forms of microparticles and liposomes have been used to reduce drug metabolism due to (i) reduced contact time between the drug and enzyme before absorption, (ii) co-administration of enzyme inhibitors and (iii) avoidance of sites of enzymatic degradation such as macrophages, neutrophils etc.

It is our opinion that the above challenges (MCC, AM, enzymatic metabolism, low permeability) can, to various degrees, be overcome by employing particulate DDS as further elaborated below. The duration of action of many inhaled drugs currently on the market is very short, to the extent that administration up to 3–4 times per day may be required [9]. Such high frequency of administration is very inconvenient and leads to poor patient compliance as well as increased incidence of side effects. A reduction in dosing frequency will clearly be beneficial to the patients. This is especially true for $\beta_2$-agonists used as bronchodilators due to their cardiovascular side effects. When

![Fig. 1: Broad classification of the various hydrolases found in the lung.](image)
formulated as controlled release dosage form, lower side effects will be the result (due to reduced amount of drug eventually administered), as well as increased therapeutic benefits. When properly designed, the circadian rhythm of the illness can be targeted, such that relief can be obtained from midnight to early morning when the lung function of most patients is reduced [10].

It will not be possible to achieve this desired prolonged release following drug administration to the conducting airways, the target region of the lungs in asthma therapy due to the MCC activity there. Having recognized this problem, several research groups have been investigating the use of mucoadhesive polymers to counter the effect of MCC in order to prolong drug residence time locally, thereby allowing sustained drug release. Although the concept of mucoadhesion at the upper respiratory tract has been broadly studied, application to the lower respiratory tract has been less extensive. Sagakami et al. [11] elegantly demonstrated with application of formulation techniques (mucoadhesion and drug crystallinity) the potential benefits of mucoadhesive drug delivery. Using the asthmatic guinea pig model to monitor the asthmatic pharmacodynamic parameter, eosinophil infiltration, it was demonstrated that crystalline beclomethasone dipropionate powder (1.37 mg/kg) significantly inhibited eosinophil infiltration for 1–6 h, while encapsulating the drug in hydroxypropylcellulose (HPC) polymer at a much lower dose (0.25 mg/kg) maintained a similar inhibitory effect for 24 h. Should this be reproduced in patients, an ideal formulation may be the result due to once daily administration as recently proposed by Cook et al. [12].

Sagakami et al. [13] investigated several hydroxypropylcellulose grades (differing in viscosity) and found that high viscosity hydroxypropylcellulose increases the bioavailability of fluorescein up to 85% due to its increased dissolution and causes a reduced MCC rate. Surendrakumar et al. [14] improved the pharmacokinetics profile of insulin when encapsulated in hyaluronic acid by spray drying. The result was an extended mean residence time (MRT, 91 min), terminal T1/2 (63 min), and T_max (25 min) compared to non-encapsulated insulin (29, 20 and 15 min, respectively). The effect was potentiated even further when HPC was used to improve the mucoadhesive property of the formulation to the extent that the MRT was 180–213 min, terminal T_1/2, 125–148 min and T_max, 40–50 min depending on the dose administered. Yamamoto et al. [15] improved the bioavailability of eel calcitonin by encapsulating the drug in PLGA [poly(lactic acid co-glycolic acid)] and subsequently coating the nanospheres with chitosan. In vivo experiments in guinea pigs showed that the elimination rate constants of chitosan-coated PLGA nanospheres from various regions of the lung were reduced compared to non-coated nanospheres. Furthermore pharmacodynamic results (hypocalcaemia) showed significant reduction in calcium level up to 24 h post administration compared to eel calcitonin solution. The improved absorption was attributed to the combined effect of mucoadhesion and opening of epithelial tight junction by chitosan. This concept of augmenting the desirable properties of microparticulate DDS by coating them with mucoadhesive polymers have been extended to liposomes [16]. Many other mucoadhesive polymers have been evaluated in drug delivery by the pulmonary, nasal or oral routes. These include cellulose derivatives like HPC, HPMC (hydroxypropylmethyl cellulose), CMC (carboxymethyl cellulose), polyacrylic acids, hyaluronic acids, gelatin, albumin, chitosan, dextran, PVA (polyvinyl alcohol) as well as derivatives of these polymers [17].
A. Pulmonary delivery for local lung disorders

1. Introduction

The past 30 years of biotechnology discoveries unleashed a wave of therapeutic proteins, also known as biomolecules, macromolecules, biotherapeutics, and biologicals. Most are administered via injection or intravenous methods to avoid degradation in the gastrointestinal tract. Patients, however, fear and avoid injections and IV treatments, which are painful, inconvenient, and expensive. Pulmonary delivery offers a patient-friendly, non-invasive alternative to injections and can also be a more efficient and effective way to deliver a drug and achieve patient compliance.

Pulmonary delivery utilizes the natural permeability of the lung to transfer molecules to the bloodstream. The systemic delivery of biomolecules via the lungs is an under-exploited route today. About 85 protein and peptide therapeutics are currently marketed, and about 350 more are undergoing clinical evaluation. In 2002, drug companies sold $33 billion in protein therapeutics, and sales of $71 billion are projected by 2008 (Market for Bioengineered Protein, 2004). This same report predicts that the market for protein drugs will grow at an annual rate of 12.2% from 2003 to 2008, faster than the industry’s overall annual growth rate of 8%. Sales of drugs using pulmonary delivery systems also are predicted to grow from $8 billion in 2001 to $15 billion by 2006 (Minter 2003). Although today, most of these drugs include those that treat local lung disease such as asthma and chronic obstructive pulmonary disease (COPD). With the approval of Pfizer's Exubera® (human insulin [rDNA origin]) Inhalation Powder, the promise of pulmonary delivery has finally been delivered and this advance opens up a myriad of possible candidates for pulmonary delivery. Many of these biologics are already under development and being tested in clinical trials. Some likely biomolecules that could benefit from pulmonary delivery are listed in Table 1.

Pulmonary drug delivery refers to treatments inhaled through the mouth rather than the nose. Some nasal formulations reach the lung, but it has been shown to be an ineffective delivery route, as most formulations are absorbed through the nasal membranes and as a result have low bioavailability unless they are enhanced. The nasal mucosa cannot transport doses of large biomolecules, and enhancers to increase bioavailability can cause irritation with repeated use. Nasal formulations may represent forerunners of more efficient inhaled drugs, and some nasal drugs will be described when appropriate.
Trends and Opportunities

Asthma and COPD

Humans have inhaled a wide range of substances since ancient times. Until recently, pulmonary delivery of drugs focused on medications to treat asthma and other lung diseases. Aerosol systems that deliver bronchodilators to relax airways and corticosteroids to control inflammation in asthma and COPD are widely used today and carry a proven track record. Today’s inhaled drug delivery market is dominated by this class of treatments. More than 300 million people worldwide suffer from asthma, and annual sales of asthma products in the U.S. and Europe in 2003 reached $11.8 billion, up from $9.7 billion in 2002. The current market for COPD therapies is estimated at $4 billion yearly, with a predicted growth to $10 billion by 2010 (Asthma and COPD Market Outlook, 2004).

The three main drug classes (bronchodilators, corticosteroids, and anti-cholinergics) contain agents with similar efficacy and side effects. Products from GlaxoSmithKline (GSK) and AstraZeneca lead the market in sales. Slight advantages over competitors are explored and marketed using new delivery devices or combination formulations to deliver a more effective payload of medicine. For example, Vogelmeier et al. (2005) demonstrated that AstraZeneca’s combination product Symbicort (containing the corticosteroid budesonide and long-acting bronchodilator formoterol) reduces the risk of severe asthma attacks by 24 %, compared to GSK’s Seretide (fluticasone/salmeterol), in a one-year, head-to-head trial of 2,143 patients. Symbicort is also approved for COPD, and its worldwide sales in 2004 totaled $797 million. Patients find it more convenient to use one inhaler, and combination products simplify treatment. Sales of combination treatments showed an impressive growth of 47 % in 2003, according to the Asthma and COPD Market Outlook (2004).

As a first-in-class asthma therapy, Genentech/Novartis introduced the monoclonal antibody Xolair (omalizumab) in 2003 to treat asthma. Xolair blocks IgE, preventing a cascade of asthmatic symptoms. Although Xolair offers a novel approach, it requires

<table>
<thead>
<tr>
<th>Growth hormone</th>
<th>Nesiritide</th>
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<tr>
<td>Calcitonin</td>
<td>Alpha-1 proteinase inhibitor</td>
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<tr>
<td>Parathyroid hormone</td>
<td>Colony-stimulating factor</td>
</tr>
<tr>
<td>Interferons</td>
<td>Somatostatin</td>
</tr>
<tr>
<td>Interleukins and antagonists</td>
<td>Luteinizing hormone releasing hormone</td>
</tr>
<tr>
<td>Erythropoietins</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Nerve growth factors</td>
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<tr>
<td>Monoclonal antibodies</td>
<td>Adenosine deaminase</td>
</tr>
<tr>
<td>Heparins</td>
<td>Gene vectors</td>
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<tr>
<td>Coagulation Factors</td>
<td>Chorionic gonadotropin</td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td>Granulocyte colony stimulating factor</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Human deoxyribonuclease I</td>
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Table 1: Possible macromolecules for pulmonary delivery.
subcutaneous injections every 2 to 4 weeks, and so is not widely used. The yet unexplored pulmonary delivery of monoclonal antibodies could allow for wider use and appeal of antibody treatments. COPD, a chronic disease linked to smoking, comprises chronic bronchitis and emphysema and causes one million deaths annually. Short-acting bronchodilators form the traditional therapy for COPD, but the newer anti-cholinergic agent tiotropium proves more convenient and effective, according to Cooper and Tashkin (2005). Boehringer Ingelheim launched the dry powder inhaler Spiriva (tiotropium) in 2001 as a first-line therapy for COPD management. Novartis developed Foradil (formoterol fumarate powder) for asthma and COPD, which acts within 5 min and lasts 12 h. Foradil is approved in several European countries. In addition, Novartis teamed with SkyePharma (London, U.K.) to develop a dry powder form of the drug marketed as the Foradil Certihaler.

An inhaled drug known as VR496, which is made by Vectura (Wiltshire, U.K.), and currently under development, breaks down mucus in the lungs and may help COPD and cystic fibrosis (CF) patients. The active ingredient is an undisclosed, off-patent drug never developed as an anti-mucolytic agent. It appears that the future of asthma/COPD therapy lies in combination products or novel single agents with convenient dosing.

3. Other lung disorders

3.1. Anti-infectives

Considering the rapid, local action of asthma and COPD drugs, inhaled medicines and vaccines seem a practical consideration for nearly every lung disease. Inhaled anti-infectives already provide local control of respiratory infections, such as pneumonia and cystic fibrosis (CF). The first inhaled protein ever approved, Genentech’s Pulmozyme (dornase alfa), was marketed in 1993 to treat CF. This aerosol treatment reduces the incidence of respiratory infections requiring intravenous antibiotics and improves overall lung function. U.S. sales of Pulmozyme have grown from $22 million in 1994 to $44 million in 2004.

Nektar Therapeutics (San Carlos, CA, U.S.A.) and Chiron, a Novartis company (Emeryville, CA, U.S.A.) are collaborating on a next-generation, dry powder tobramycin to treat lung infections in cystic fibrosis patients. This product which is currently in Phase III trials is called Tobramycin inhalation powder or TIP. Chiron introduced TOBI in 1998 as the first inhaled antibiotic given by nebulizer to CF patients. Nektar’s dry powder formulation represents a next generation therapy that allows patients to receive higher doses for improved efficacy without the lengthy administration time of TOBI. A 12-person trial showed that 3.5 times more inhaled TOBI reaches the lung using a dry powder formulation than with a nebulized liquid solution, report Newhouse et al. (2003). As Chiron’s second highest selling drug, TOBI’s sales reached over $220 million in 2004. Nektar is also collaborating with Bayer HealthCare AG to develop an inhaled, dry powder formulation of ciprofloxacin to treat CF and other chronic lung infections.
Inhaled gentamicin is an established treatment for chronic *Pseudomonas aeruginosa* (PA) infections in CF. Heinzl (2002) demonstrated that daily inhalations of gentamicin delays the acquisition of chronic PA infections and decreases disease progression in children with CF.

Relenza (zanamivir), made by GSK, was the first inhaled anti-viral medication approved by the FDA in 1999. The dry powder is inhaled twice daily for five days to reduce the duration and severity of flu symptoms. Relenza inhibits neuraminidases, which are essential for the release of influenza virus from infected cells. By concentrating on the surface of the respiratory tract, Relenza prevents the influenza virus from replicating (Hayden *et al.* 1997) directly at the site where it promotes infections.

Pentamidine, an inhaled treatment for pneumocystis carinii pneumonia (PCP), sells generically or under the brand names Nebupent or Pentam. Intravenous pentamidine causes serious side effects of anemia, low blood sugar, arrhythmias, and kidney problems. In contrast, inhaled pentamidine produces milder side effects like chills, headache, and cough.

Nektar is also evaluating an inhaled antifungal product to prevent pulmonary aspergillosis in immunosuppressed patients. ABIP (amphotericin B inhalation powder) is designed to target the site of infection directly with a novel formulation of amphotericin B, a broad spectrum, “gold-standard” antifungal drug. Pulmonary delivery directly at the site of infection could potentially eliminate systemic, dose-limiting toxicities found with current formulations of amphotericin B that are delivered intravenously. Aspergillosis has a high mortality rate of over 50%, and in some immunosuppressed patient groups the mortality rate may be as high as 100% (Lin *et al.* 2001).

### 3.1. Pulmonary arterial hypertension

In 2004, the FDA approved Ventavis (iloprost), an inhaled treatment for pulmonary arterial hypertension, made by CoTherix (South San Francisco, CA, U.S.A.). In pulmonary arterial hypertension, severe restriction of blood vessels results in early death. Iloprost naturally dilates blood vessels.

### 3.2. Cancer chemotherapy

Lung cancer is the leading cause of cancer deaths globally, and inhaled chemotherapy seems a logical approach to treat lung tumors. Despite new chemotherapeutic agents for lung cancer, the 5-year survival rate of 15% has not changed in 50 years, according to Placke *et al.* (2002). Pulmonary delivery increases the cytotoxic dose of drugs that can reach tumors to improve responses, while minimizing systemic toxicity.

A multi-center Phase I clinical trial is evaluating Resmycin™ (doxorubicin HCl inhalation solution) in lung cancer patients (Otterson *et al.* 2005). Made by Zivena, Inc., a subsidiary of BatellePharma (Columbus, OH, U.S.A.), Resmycin delivers more doxorubicin to lung tumors than can be achieved intravenously. In earlier studies in dogs, Resmycin following surgical removal of primary lung tumors extended survival time to 199 days, compared to 63 days for dogs receiving surgery alone (Placke *et al.* 2002). As many as 400,000 lung cancer patients could benefit from inhaled chemotherapy, which could capture a large share of the $3 to $5 billion inhaled oncolytics market.
A team led by Koshkina (2004) gave aerosolized paclitaxel solution to mice with lung tumors. The treatment significantly reduced lung tumors and prolonged survival. Aerosol delivery of the anti-cancer agents difluoromethylornithine and 5-fluorouracil reduced lung tumors in mice 50% and 60%, respectively, according to Wattenberg et al. (2004). Interleukin-2 (IL-2) stimulates immune function in cancer patients, but injections cause fever, malaise, and local swelling. In a Phase I study of patients with lung metastases who inhaled IL-2, Skubitz and Anderson (2000) report no significant toxicity; efficacy was not evaluated.

People who inhale carcinogens in cigarette smoke account for half of lung cancer deaths in the U.S. Mulshine and Hirsch (2003) propose that inhaled chemopreventive drugs may block early epithelial damage in smokers. They showed in rodents that aerosolized retinoids significantly reduce lung tumor nodules caused by tobacco carcinogens, whereas oral retinoids do not bring protection.

### 3.4. Vaccines

Nearly 100 vaccines are approved in the U.S. (Fig. 1). About half of these prevent respiratory infections, yet all are currently injected. Inhaled vaccines are an untapped market opportunity. Not only would they address needle fears, especially in children, but they could also generate more potent local immune responses than when they are injected into muscles.

As a proof-of-concept, an inhaled measles vaccine given by nebulizer (created by vaccine pioneer Albert Sabin) brings superior immunogenicity at lower doses than an injected counterpart, as demonstrated by trials in Mexico (Bennett et al. 2002). The Measles Aerosol Project of the World Health Organization is coordinating the development of better delivery devices and a dry powder formulation. Measles infects 30 to 40 million children in underdeveloped nations.

As far back as the 1960s, influenza experts tested aerosol flu vaccines. Waldman et al. (1969) found that volunteers receiving aerosolized flu vaccine had 79% fewer cases of influenza. This is compared to injected volunteers who only had 27% fewer illnesses against controls receiving no vaccine. The aerosol vaccine also shortened the duration of infections and caused as few side effects as a placebo. Nonetheless, in-

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![Fig. 1: Licensed vaccines in the U.S. (2000). Source: Jordan Report (2000).](image)

- 94 Licensed vaccines
  - 27 pathogens targeted
  - 53% of pathogens are respiratory
  - Current routes of vaccine delivery
    - 87 by injection
    - 7 oral (adenovirus, 2; polio, 4, typhoid, 1)
    - None delivered by inhalation

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haled influenza vaccines are still not available. The approval of the nasal influenza vaccine FluMist (MedImmune; Gaithersburg, MD, U.S.A.) raises the hope of pulmonary flu vaccines for flu and other unmet needs listed in Fig. 2.

B. Pulmonary delivery for systemic administration of medicines

1. New indications

The success of inhaled asthma/COPD drugs led to attempts to deliver other therapies via the lung, particularly biomolecules. Developers of pulmonary delivery first focused on inhaled insulin, described in section 4. Other efforts include pulmonary treatments for pain, osteoporosis, infections, and gene delivery.

Indeed, the rapid relief asthmatics experience from inhaled drugs could be extended to patients experiencing pain, anxiety attacks, hypertensive crisis, insomnia, arrhythmias, Parkinson’s “lock up”, and several others conditions (Table 2). These conditions are treated with oral small molecule drugs. A few are slowly making the conversion to inhaled formulations, but no inhaled small molecules are yet approved.

1.1. Pain

In 2003, 168 million people were prescribed pain medications and sales of these drugs reached $19.6 million (CNS Market Outlook, 2004). Most pain drugs are oral, but alternative routes are available, such as pain patches, sublingual fast-melting tablets, and inhaled pain medication. The general anesthetic fentanyl is being explored for

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<table>
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<tr>
<th>Bacterial Infections</th>
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<tbody>
<tr>
<td>Chlamydia pneumonia</td>
<td>10% of all pneumonias</td>
</tr>
<tr>
<td>Group A Streptococci</td>
<td>25 million cases per year in U.S.</td>
</tr>
<tr>
<td>Group B Streptococci</td>
<td>Leading cause of death in newborns</td>
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<tr>
<td>Nontypeable Haemophilus influenza</td>
<td>Most common ear infection, 25 million office visits per year</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>A major cause of lower respiratory infections in adults (COPD), 3rd most common ear infection</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
<td>15 million cases per year</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Common in CF and HIV patients</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2 billion infections worldwide</td>
</tr>
</tbody>
</table>

Fig. 2: Respiratory bacterial infections – no vaccines yet. Source: Jordan Report (2000).