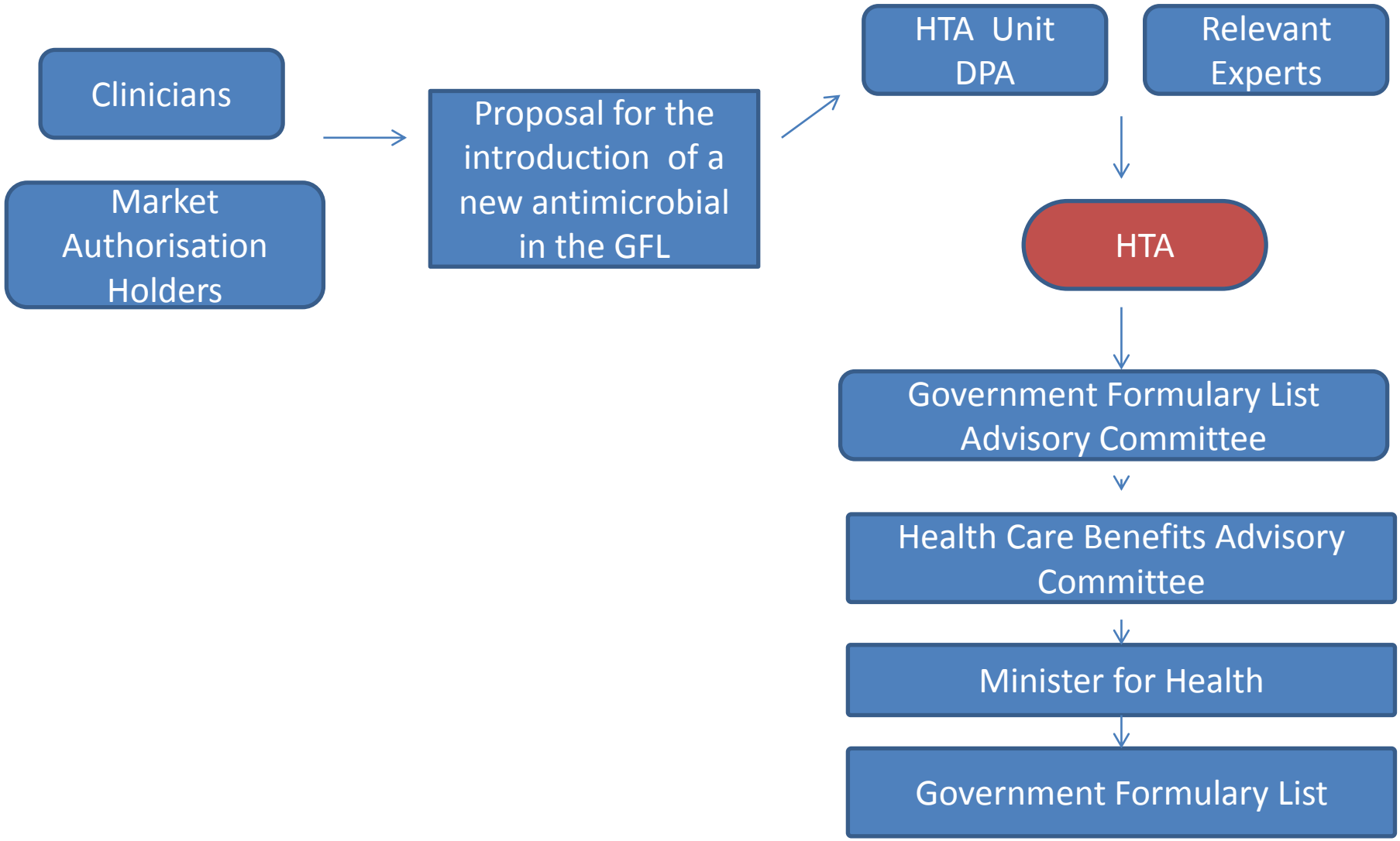
An overview of the Health Technology Assessment and Decision Making Process, with discussion of Key Uncertainties

(Special Focus on Antibiotic Resistance)

Miriam Azzopardi
Consultant, Public Health
Office of the Chief Medical Officer

MINISTRY FOR ENERGY AND HEALTH
PALAZZO CASTELLANIA, MERCHANTS STREET, VALLETTA, MALTA

Decision making for medicines reimbursement in Malta with particular reference to decision making for the reimbursement of new antimicrobials



Health Technology Assessment

- Health Technology Assessment (HTA) is way of assessing the ways science & technology are used in healthcare and disease prevention. It covers medical, social, economic, and ethical issues.

- It provides policy-makers with objective information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective.

- HTA should be transparent, unbiased, robust and systematic - firmly rooted in research and the scientific method.

- Diagnostic and treatment methods, medical equipment, pharmaceuticals, rehabilitation & prevention methods, but also organisational and support systems used to deliver healthcare are examples of Health Technologies.

Antimicrobial Resistance – A Growing Public Health Threat

- We are facing a serious global problem of antimicrobial resistance that affects virtually all of the pathogens we have previously considered to be readily treatable.

- Many important drug options for the treatment of common infections are becoming increasingly limited and expensive and, in some cases, non-existent.

- Antimicrobial resistance can affect patient outcomes by enhancing virulence, causing a delay in the administration of appropriate therapy, limiting available therapy and requiring the use of antimicrobial therapies that are more toxic.

- During 2011, **25 000 patients were dying annually** as a result of infections caused by resistant bacteria in the EU. The costs incurred by drug resistant infections amount to an estimated **€1.5 billion** annually, due to increases in healthcare expenditure costs and productivity losses.

- As resistance to antibiotics is increasing at a faster pace than it can be controlled, the future will resemble the pre-antibiotic era.

Antimicrobial Resistance – A Growing Public Health Threat

- In 2012, WHO reported a gradual increase in resistance to HIV drugs, albeit not reaching critical levels. Since then, further increases in resistance to first-line treatment drugs were reported, which might require using more expensive drugs in the near future.

- In 2013, there were about 480 000 new cases of multidrug-resistant tuberculosis (MDR-TB). Extensively drug-resistant tuberculosis (XDR-TB) has been identified in 100 countries. MDR-TB requires treatment courses that are much longer and less effective than those for non-resistant TB.

- There are high proportions of antibiotic resistance in bacteria that cause common infections (e.g. urinary tract infections, pneumonia, bloodstream infections) in all regions of the world. A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or multidrug-resistant Gram-negative bacteria.

- Treatment failures due to resistance to treatments of last resort for gonorrhoea (third-generation cephalosporins) have been reported from 10 countries. Gonorrhoea may soon become untreatable as no vaccines or new drugs are in development.

Antimicrobial Resistance – A Growing Public Health Threat

- Resistance to one of the most widely used antibacterial drugs for the oral treatment of urinary tract infections caused by *E. coli* – fluoroquinolones – is very widespread.

- **Antimicrobial resistance jeopardizes health care gains to society -** The achievements of modern medicine are put at risk by antimicrobial resistance. Without effective antimicrobials for prevention and treatment of infections, the success of organ transplantation, cancer chemotherapy and major surgery would be compromised.

- It impacts the healthcare system through increased costs and prolonged hospital stays, contributing to bed shortages.

Antimicrobial Resistance – A Growing Public Health Threat

- In the European Union alone, a subset of drug-resistant bacteria is responsible annually for some 25 000 deaths, with extra health care costs and lost productivity due to antimicrobial resistance amounting to at least €1500 million.

- The constant evolution of AMR together with little new antimicrobial development raises the spectre of currently treatable infections becoming untreatable, and a return to the limited treatment options of the pre-antibiotic era. A report by the European Centre for Disease Control and European Medicines Agency found that as of March 2008, there were only 15 potential investigational antimicrobials with new mechanisms of action and only 5 had progressed to phase III or higher level trials

Antimicrobial resistance is a complex and multifaceted public health issue – The elements of uncertainty

- When will resistance appear? How fast will it grow? Who will be susceptible to it?
- Categorisation of infections has become blurred (e.g.: community acquired, hospital acquired)
- Also, international travel and trade may result in drug-resistant pathogens that emerge in distant corners of the world being introduced into EU Member States.
- The precise clinical impact of antimicrobial resistance is poorly defined. This is reflected in the lack of correlation between laboratory susceptibility testing and clinical outcome. For example, although penicillin resistant *Streptococcus pneumoniae is frequently reported, cases of treatment failure due* to penicillin resistant *S. pneumoniae are rare when treated with adequate doses of penicillin,* suggesting that the laboratory phenomenon does not necessarily translate into a clinical effect.

Antimicrobial resistance is a complex and multifaceted public health issue – The elements of uncertainty

- Recent research using genome sequencing approaches suggests that the vast majority of *C. difficile infections in one study arose due to inappropriate antimicrobial use rather than* person to person transmission. This disproved, to some extent, the longstanding belief that poor hygiene and transmission are responsible for the majority of infections. These findings raise a centrally important question in AMR research because many of the existing hospital interventions are based around hand hygiene, cohorting, barrier nursing, etc. While these approaches have led to some success in the reduction of MRSA infections for example, further research in this area is needed.

- Antibiotic resistant microbial infections can be of a polymicrobial nature. Polymicrobial infections involve several infectious agents and may also be referred to as complex, complicated, mixed, dual, secondary, synergistic, concurrent or co-infections. It is now felt that such microbial communities contribute to the development of resistance. These mixed microbial communities are able to share resistance determinants between the same or different species. At present there are no specific strategies to prevent transmission of antimicrobial resistance determinants in polymicrobial infections.

Antimicrobial resistance is a complex and multifaceted public health issue – The elements of uncertainty

- We are entering a period where standard frontline antibiotics used in clinical practice will become obsolete in treating life-threatening infections.

- Coupling this to the lack of investment from both the pharmaceutical industry and academic research funders in the development of novel antimicrobial strategies, it is clear that we are about to reach crisis point. The reasons for this situation have been well documented, and include a lack of perceived return on investment for pharmaceutical companies and difficulties in identifying suitable broad-spectrum antimicrobials.

Filling the Gaps- Addressing uncertainty

- The incidence, prevalence, range across pathogens and geographical patterns related to antimicrobial resistance are all information that is needed to be made accessible in a timely manner in order to guide the treatment of patients; to inform local, national and regional actions; and to monitor the effectiveness of interventions.

- International standards on harmonization of national antimicrobial resistance surveillance and monitoring programmes were adopted by OIE s members in 2012, but there are no internationally agreed standards for collection of data and reporting on antibacterial resistance in human health, and no harmonizing standards across medical, veterinary and agricultural sectors. There is also no global forum for the rapid sharing of information on antimicrobial resistance.

What Public Health Can Do

- Special efforts are needed to translate research findings into medically useful products for human and agricultural /veterinary use, such as novel antimicrobial therapeutics, diagnostic tests, vaccines and other tools for preventing AR emergence and spread.

- In consultation with academia and the private sector, identify and conduct human clinical studies addressing AR issues of public health significance that are unlikely to be studied in the private sector, such as:

• Novel therapies;

• Existing antimicrobials administered in treatment regimens and combinations that may not be included in approved indications and dosing schedules; and

• Other products and practices relevant to the control and treatment of antimicrobial-resistant pathogens including devices, diagnostics, anti-microbial soaps, disinfectants, etc.

What Public Health Can Do

Encourage basic and clinical research in support of novel approaches to preventing or treating infections with resistant organisms that occur in humans and animals by partnering with academia and the private sector. Novel approaches may include:

- Bacteriophage therapy;
- Active (vaccine) and passive (antibody, hyperimmune globulin) immunization
- Host-derived antimicrobial agents;
- Nonantibiotic antimicrobials and nonchemical approaches with broad or nonspecific anti-infective activities (e.g., defending and nonspecific immunostimulants, such as defensins, ribozymes, etc.); and
- Microbial ecology (probiotics, direct fed microbials, etc.).

Problems the Pharmaceutical Industry is Facing

- Needed products include not only new classes of antimicrobials able to kill otherwise resistant organisms, but also vaccines and anti-infective devices with the potential to prevent infections as well as improved diagnostic tools to aid in appropriate use of therapeutics.

- With respect to antimicrobial drugs, each new agent represents a major investment by a pharmaceutical company, which must shepherd the product through pre-clinical studies and clinical testing, followed by large and expensive clinical trials.

- Pharmaceutical companies may be reluctant to invest extensive resources in the development of drugs, such as those antimicrobials targeted to resistant organisms, since:
- They are often given for short time periods to small numbers of patients.
- Appropriate use policies may limit sales and profits.
- On the other hand, when a drug is used widely, allowing recovery of costs and profitability, resistance may develop more rapidly and shorten the useful life of the drug.

Problems the Pharmaceutical Industry is Facing

- Result: WHO Expert consultative Group on Research and Development has defined this as a “Market Failure and a particular cause of concern”

- Possible solution: The cost of investment in research and development may need to be de-linked from price and the volume of sales to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines and other results from research and development in all countries.

A Health Technology Assessment

Various models of HTAs can be used but in all two major elements are considered:

- Clinical effectiveness – how do the health outcomes of the technology compare with available treatment alternatives?

- Cost-effectiveness - are these improvements in health outcomes commensurate with the additional costs of the technology?

Impact of an Anti Microbial resistant Infection

OUTCOME	ASPECTS CONSIDERED
Mortality	In hospital, attributable to infection; in hospital and after discharge, all cause.
Morbidity	Length of hospitalisation, need for ITU stay, need for surgery or other procedures, activity level of discharge, loss of function (loss of work)
Economic	Hospital costs and charges, resource utilisation, total health care costs, outpatients costs, effect on waiting lists
Hospital	Inpatient morbidity/mortality, costs
Third party payer	Inpatient and outpatient health care costs
Patient	Decreased functional status, loss of work
Societal	Total Health care costs , loss of available antimicrobial classes.

Are we failing somewhere? Antimicrobial resistance - ? A case of its own

- Has antibiotic resistance has fallen victim to evidence based policy making?

- Policy making prioritises health problems by economic burden and cost effectiveness of interventions. Health economists have been unable to show that antibiotic resistance costs enough to be a health priority. Estimates of the actual economic impact may not be accurate because the research used to produce these estimates is limited.

- Economic estimates are based on the incremental costs and focus on a specific infectious disease or set of diseases: estimates are based on the cost of extra treatment of a resistant infection compared with susceptible infection, such as costs of additional investigations, more expensive drugs, side effects from extra treatments, longer hospital stay, and greater mortality. Some may also include costs associated with surveillance and activities associated with trying to control resistance. Most studies are based in hospitals and include the costs related to additional hospital stay and treatment but not early mortality.

Are we failing somewhere?
Antimicrobial resistance - ? A case of its own

- None of the studies considered the bigger picture—a world in which there are no effective antibiotics for situations where they are currently used routinely, such as in hip replacement or cancer patients.

- A concern is that today's limited estimates will be used to project future costs.

- Will the current worst case scenario place antibiotics high enough up on the health agenda to ensure adequate action?

- Economic impact assessments are needed on the health and broader socioeconomic burden of antimicrobial resistance, and should compare the cost of doing nothing against the cost and benefit of action!

THANK YOU