Microbiology Nuts & Bolts: Session 5: Fever in a returned traveler

- 30-40% of patients admitted to hospital will receive an antibiotic
- It is critical to pick out those with life-threatening conditions in order to manage them appropriately and correctly in order to give them the best chance of survival
- It is also important to know how to diagnose and manage common infections so that complications do not occur and patients get better as quickly as possible
- Knowing about antibiotics ensures the correct ones are used for the correct indications, prevents prescribing errors and keeps patients safe
- Everyone working in a healthcare setting has a responsibility to protect patients from harm including cross infection from other patients

- It is often the young and previously fit and well who present with fever after they have been travelling
- The majority of these patients actually don't have something exotic, they have the same normal infections that people who haven't travelled will get e.g. UTI, influenza, pneumonia etc
- 20-70% of travellers to developing countries develop a fever
  - 1-5% seek medical attention
  - 0.1% need treatment
  - Only 0.001% (1 in 100,000) die from their infection

- The most important part of the assessment of a patient with fever after travelling is the history, and in particular the details of where they have been e.g. it is not enough to just say someone has been to Thailand, you want to know exactly where in Thailand they have been as the types of infection risk can vary within a country

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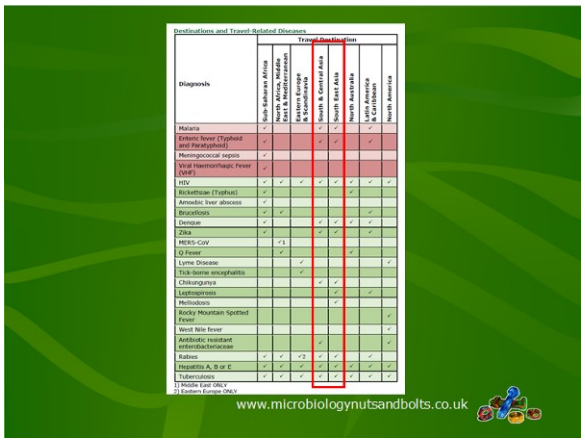
- It doesn't take much effort, but the travel history for Paul gives enough information to start to produce a differential diagnosis of the types of tropical infections he may have been exposed to
- Another important aspect of the history is whether he was vaccinated and did he take malaria prophylaxis

- Formulating a differential diagnosis appears to be going out of fashion but it is essential if diagnoses are not to be missed
- A systems approach (e.g. respiratory, cardiac, Gastrointestinal, genitourinary, neurological, skin, bone, joint, etc) can be fitted to a template of life-threatening, common, uncommon in order to complete the differential but considering the life-threatening first ensures these are dealt with as early as possible
- It is not a static process but can change throughout a patients management as new information becomes available and their clinical condition changes



- The table helps to start the process of developing a differential diagnosis
- It is difficult, if not impossible, for most doctors to remember the kinds of infections that occur in different regions of the world, so a simple "*aide memoire*" can really help

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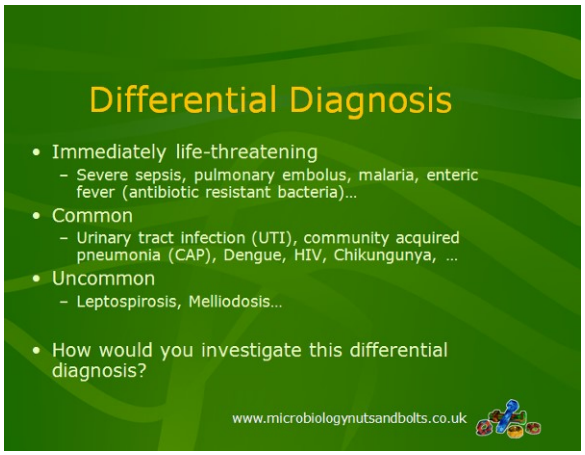
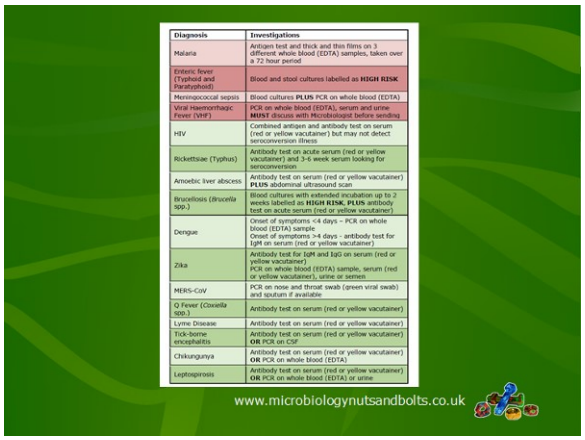


- The differential diagnosis for Paul includes a mixture of normal home grown infections as well as the more exotic diagnoses



- In combination with a list of the type of infections that occur in different parts of the world, it is useful to have a list of the tests done for each condition
- The table of causes by region and the list of tests for those conditions are available in the book and on the website, Microbiology Nuts & Bolts.

- The tests represent a pretty standard initial screen for fever in a returned traveller.
- Whilst the list may appear long, it actually doesn't require a large number of samples:
  - 1x EDTA – for FBC and Malaria screen
  - 2x Clotted or lithium heparin – 1 for biochemistry, 1 for serology
  - Urine
  - Sputum
  - Blood cultures
- It is always worth sending a serum sample even if you don't know at the time what tests to request, ask for the sample to be saved (which can be done in most serology labs for up to 18 months) and give good clinical information (the lab will do the tests you should have asked for even if you didn't know what they were)

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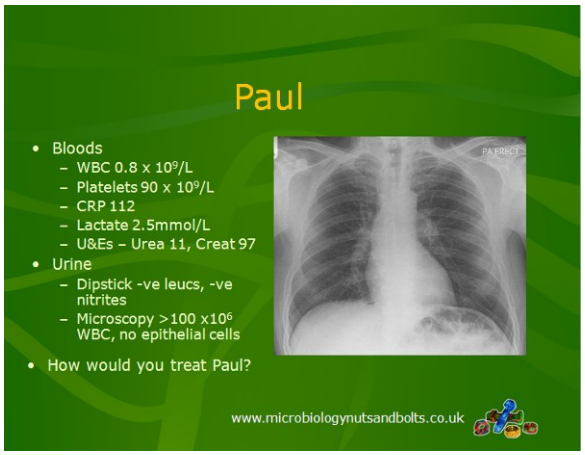
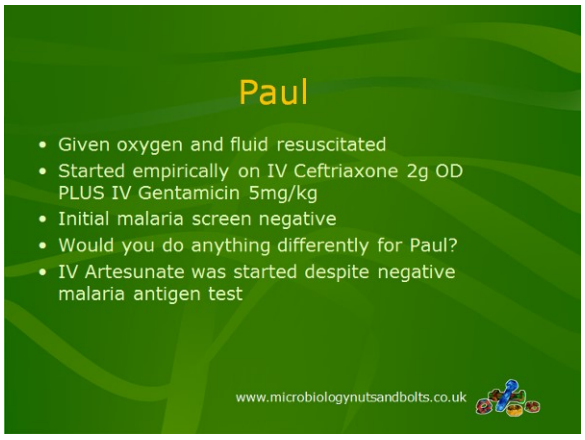
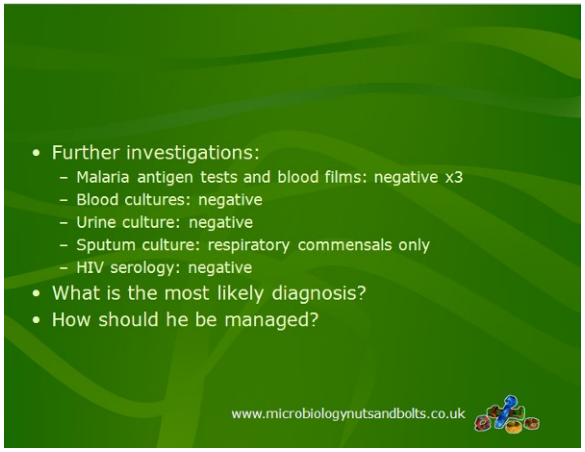


- It is essential to know the normal values of all tests within your hospital
- Full blood count (FBC)
  - The total white blood cell count can go up or down in infection
  - The differential white blood cell count can help to point to the type of organism but nothing is 100% (neutrophils = bacteria/fungi, lymphocytes = viruses, eosinophils = parasites)
  - Platelets are an acute phase reactant and go up in infection (they can go down in severe infections when disseminated intravascular coagulation DIC develops)
- CRP (C reactive protein)
  - Produced in liver in response to inflammation, often goes up in bacterial infection
  - >200 usually significant, otherwise need to know what the trend is i.e. increasing, decreasing
  - Beware, patients in liver failure do not produce much CRP – use other markers of liver synthetic function to guide you e.g. INR, Albumin
- Urea & Electrolytes (U&Es)
  - Antibiotics can only be prescribed safely if the patients kidney function is known
- Urine point of care includes a dipstick test
  - Leucocytes indicate the presence of white blood cells and hence inflammation in the urinary tract
  - Bacterial nitrites are breakdown products from the action of bacteria on Urea and indicate the presence of bacteria
  - Urine samples are prone to contamination so it is important to advise patients how to take a proper MSU
    - Part the labia or retract the foreskin, void the first part of the urine stream and discard, then catch the middle part of the stream.
    - The first part of the urine is prone to bacterial contamination from the urethra giving false positive results
- Chest X-ray is required by the British Thoracic Society in order to diagnose pneumonia in hospital

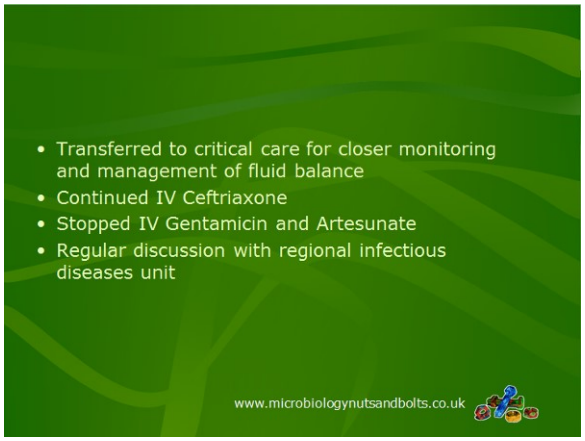


- Sometimes it is possible to wait before starting antibiotics in patients, and if they are cardiovascularly stable this is the right thing to do most of the time. Once antibiotics have been started it is very difficult to grow bacteria, and this compromises the ability to make a definite diagnosis
- Paul's observations though show that he is not stable and treatment needs to be started straight away
- Because the exact diagnosis is unknown, empirical treatment should be aimed at the most serious infections:
  - Ceftriaxone PLUS Gentamicin – sepsis including typhoid and paratyphoid
  - Quinine – severe malaria
- It is always prudent to discuss sick patients who have recently returned from abroad with the local Infectious Diseases Physicians, as this is there area of expertise

- Paul is very unwell, he is starting to go in to organ failure
- Senior support is required, as is Critical Care advice
- He should be discussed again with the local Infectious Diseases service, who will want an update on all of his latest results

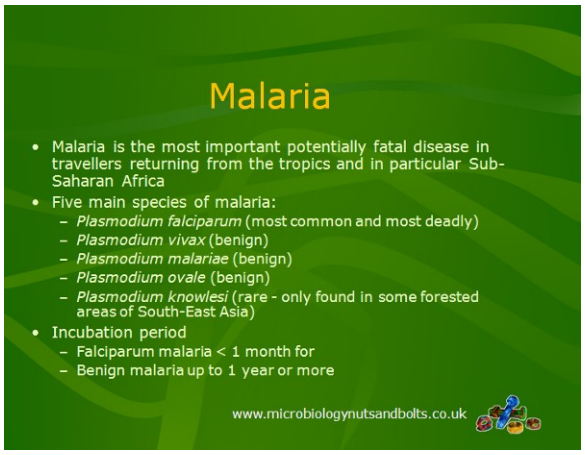


- Of the original differential diagnosis, the only one that causes all of Paul's symptoms (including the rash) which has not yet been excluded is Dengue
- It is important to be aware of the signs of the serious and potentially life-threatening versions of these types of infections: in this case if Paul has Dengue then the narrow pulse pressure suggests Dengue Shock Syndrome which has a mortality of up to 40%!
- If you don't know the warning signs then discuss the patient with an Infectious Diseases Physician and specifically enquire about what you should be looking out for then document it clearly in the patient's notes and let the rest of the team know.



- Malaria has been ruled out, and there is little need to continue with empirical Gentamicin given that the blood cultures and urine are negative
- Typhoid and Paratyphoid have not been ruled, and given the nature of his rash it is possible that Paul has meningococcal sepsis which is now added to the differential diagnosis, and hence the Ceftriaxone is continued

- Paul is confirmed as having Dengue
- There is no specific treatment for Dengue, supportive care is required
- Paul's physiological parameters are consistent with Dengue Shock Syndrome



- There are up to about 1500 cases of Malaria diagnosed every year in the UK
- It is recommended that all patients with Malaria diagnosed in the UK are admitted to hospital for 24 hours as they can deteriorate rapidly
- Once they are stable they can usually be managed as an outpatient with oral medication

- Malaria is a disease of the tropics because this is where the Anopheles mosquito is found
- It is only the female mosquito that bites, the male is vegetarian!
- Biting tends to occur at dusk when the mosquito is most active
- Travellers to malaria areas should be advised about bite avoidance using insect repellents, wearing long trousers and shirts with long sleeves, sleeping under a mosquito net and taking malaria prophylaxis

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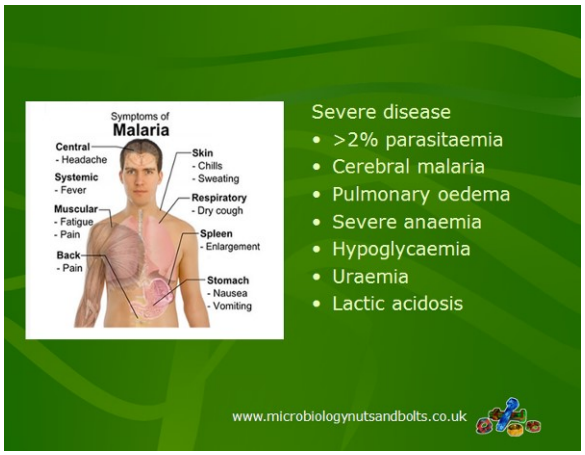
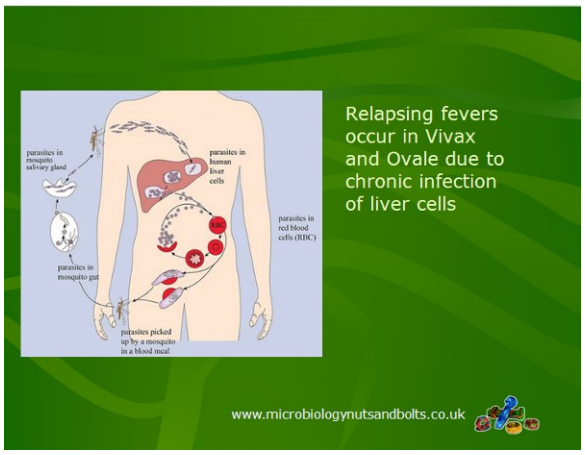
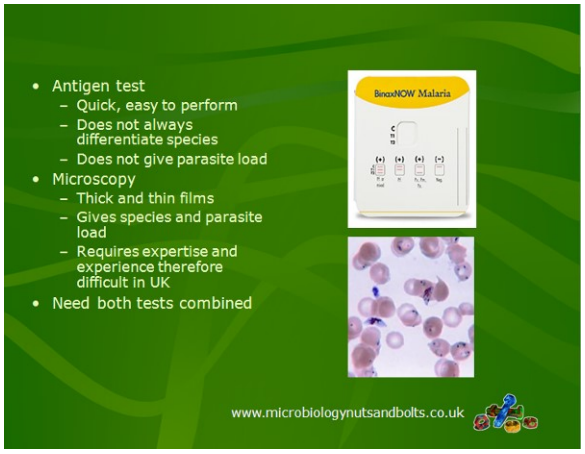


- Malaria is a potentially fatal infection
- Severe Malaria requires hospital admission, IV medication and usually critical care support
- Every doctor who might look after a patient with malaria should be familiar with the signs of severe infection



- Some species of Plasmodia can cause relapsing fevers, and present months to years after the original infection
- They remain in the hepatocytes from where they are released intermittently and cause fever
- They can be difficult to diagnose because often there is no recent travel history to give a clue to the diagnosis



- The diagnosis of Malaria is made by testing EDTA blood samples on 3 consecutive days by antigen and thick and thin films
- It is important that patients stop there malaria prophylaxis whilst they are being investigated as this can interfere with making the diagnosis and the patient will not come to harm if the prophylaxis is restarted once the diagnosis has been excluded (don't forget to restart it!)
- The antigen diagnoses malaria and the films give the species and assess the severity, you need both

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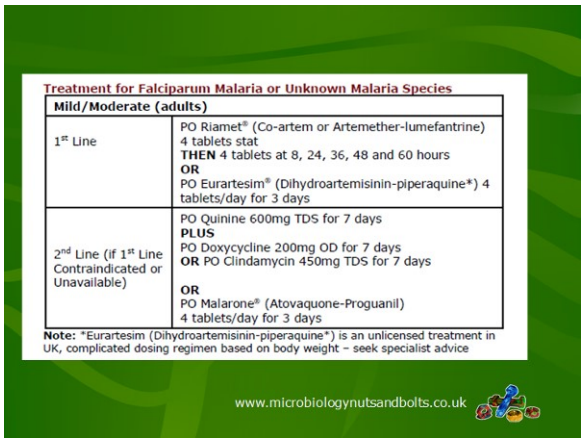
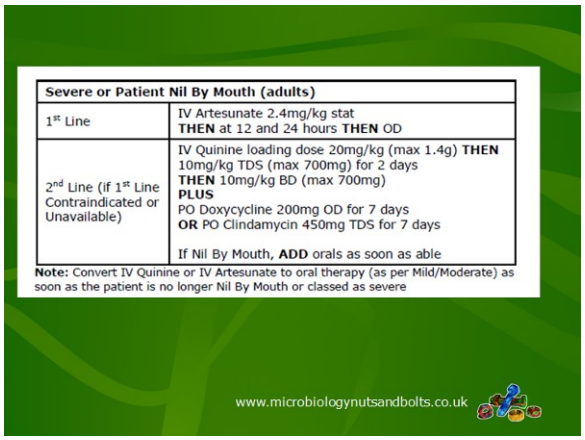
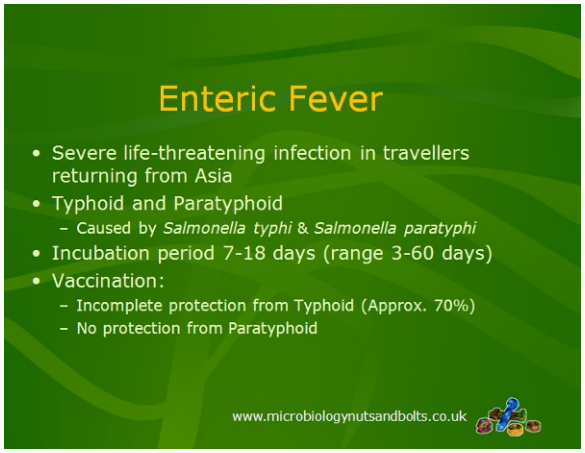


- Malaria treatment is based upon severity, but the British Infection Society recommend that all patients irrespective of how they are treated should be admitted to hospital for the first 24 hours because they can deteriorate rapidly
- Artemether is the treatment of choice
- Both Quinine and Artemether are derived from plants that grow in malaria areas – isn't nature clever?!



- Severe malaria should be treated with IV Artesunate
- Keep in contact with Infectious Diseases teams for patients with severe malaria



- Enteric fever is a serious infection of the gastrointestinal tract that leads to sepsis and systemic infection, for which the mortality in untreated cases is up to 40%
- It is caused by *Salmonella typhi* and *Salmonella paratyphi*
- The first line treatment of enteric fever in hospital is IV Ceftriaxone, out of hospital PO Azithromycin is the most reliable
- Ciprofloxacin resistance is too high to recommended it's use first line (60% in Typhoid, 85% in Paratyphoid)

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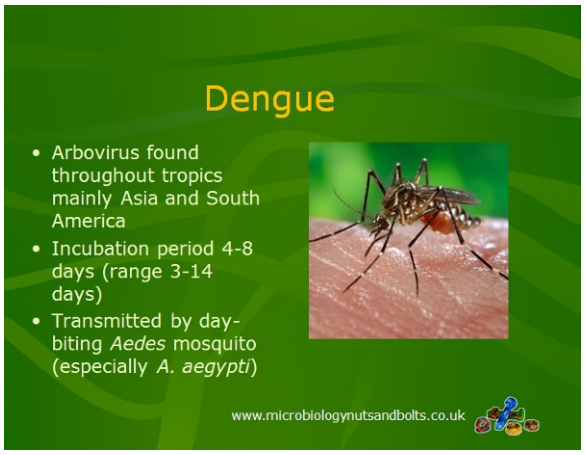
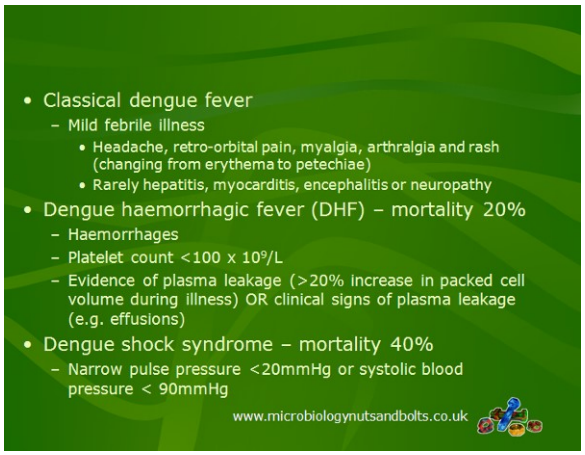
- Enteric fever can often be mistake for meningitis given the headache that often occurs, but in practical terms this does not stop you treating the patient appropriately because both infections are treated empirically with IV Ceftriaxone
- Pure cultures of *Salmonella typhi* and Sal*monella paratyphi* are potentially hazardous for laboratory staff to handle therefore all samples from patients where this is a possible diagnosis should be labelled "High Risk"

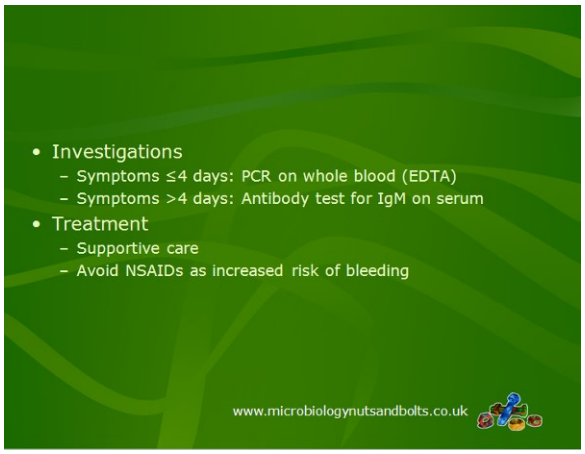
- Enteric fever is treated empirically with IV Ceftriaxone
- Patients with enteric fever will improve clinically on Ceftriaxone although their temperatures often do not settle for 4-5 days
- Mild infections can be treated orally with PO Azithromycin as the normal first line treatment



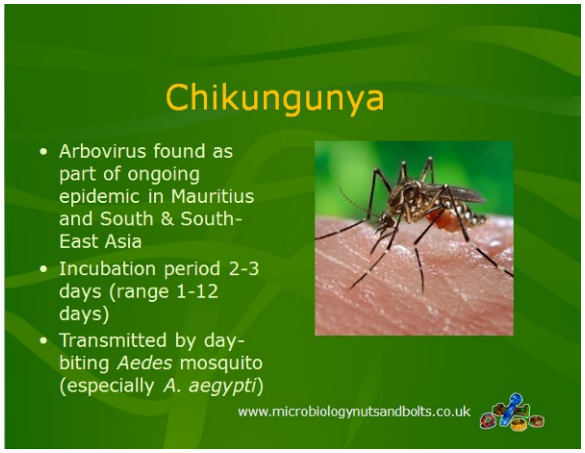
- Dengue is a viral infection transmitted by the Aedes mosquito which bites during the day (this is different to the Anopheles mosquito that transmits malaria when biting at dusk)
- Travellers to Dengue areas should be advised to cover up with long trousers and long sleeved shirts as well as use insect repellents during the day time, however they often don't as these areas tend to have hot climates and travellers find long clothes uncomfortable… you can only advised, you can't force them to comply!



- Dengue is often thought of as a mild self-limiting febrile illness but it is important to remember that Dengue can kill
- There are 4 main sub-types of Dengue, and the more you have had the more severe your Dengue becomes – it is actually the immune response that becomes more severe and damages the body
- It is worth telling patients who have had Dengue once about the risks of getting Dengue again in the future… next time they might actually cover up in the day time as advised
- Patients with severe Dengue need Critical Care support and should ideally be cared for by Infectious Diseases Physicians



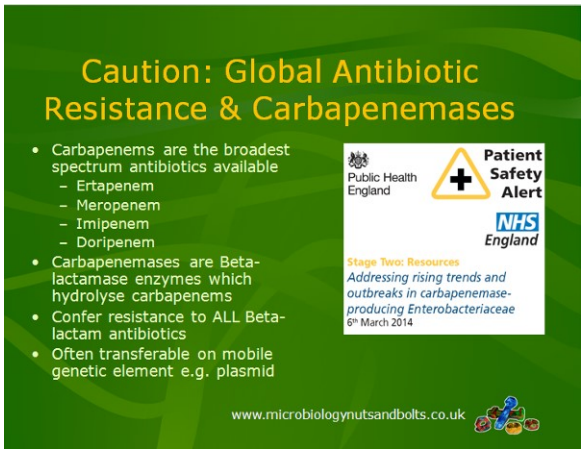
- Dengue is diagnosed with a combination of molecular and serology tests
- The mainstay of Dengue treatment is good supportive care



- Like Dengue, Chikungunya is a viral infection transmitted by the Aedes mosquito which bites during the day (this is different to the Anopheles mosquito that transmits malaria when biting at dusk)
- Travellers to Chikungunya areas should be advised to cover up with long trousers and long sleeved shirts as well as use insect repellents during the day time, however they often don't as these areas tend to have hot climates and travellers find long clothes uncomfortable… you can only advised, you can't force them to comply!

- Chikungunya does not appear to cause severe infections in the same way as Dengue, however long term joint problems are common

- Chikungunya is diagnosed with a combination of molecular and serology tests
- The mainstay of Chikungunya treatment is good supportive care



- Antibiotic resistance is becoming a major world health problem, and people who travel can acquire resistant bacteria that may not cause symptoms and signs at the time but which become part of their normal flora
- 85%of infections are caused by a person's own bacterial flora getting in to a site where they should not be e.g. bowel flora getting in to the urinary tract to cause a UTI
- If a patients bacterial flora is resistant to antibiotics then most of the infections that patient gets will be due to resistant bacteria
- The latest cause for concern around the world are Gram-negative bacteria such as *E. coli* and *Klebsiella* sp. that produce carbapenemases

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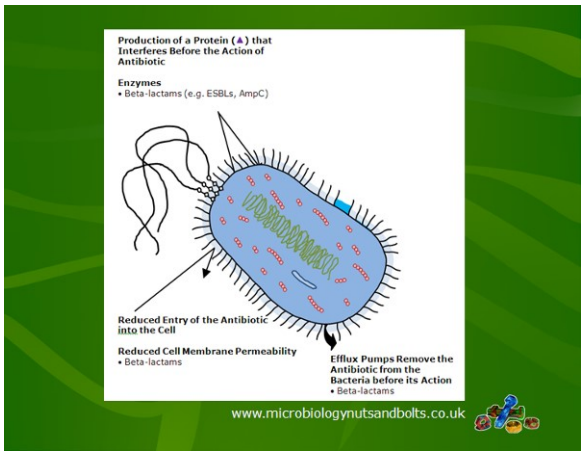
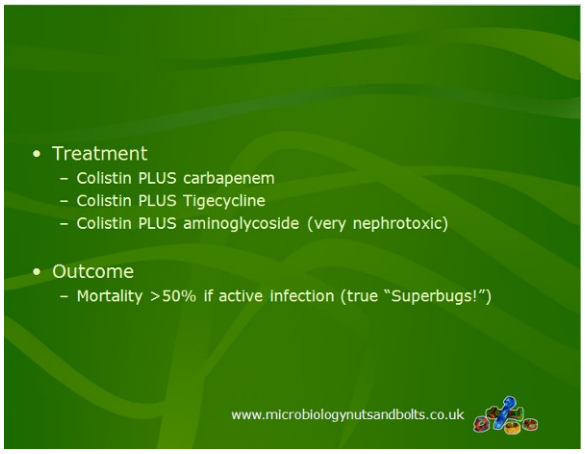


- Bacterial resistance to the carbapenem antibiotics is usually due to either the production of an enzyme e.g. carbapenemase, or the combination of an enzyme e.g. AmpC, ESBL with the loss of a prion in the bacterial cell membrane (the combination lets less antibiotic in to the bacteria, and some of what does get in is then broken down by the enzyme)

- There are recent guidelines from the DoH which are supposed to help us manage carbapenemase producing bacteria, but they are quite cumbersome and difficult to implement



- The recommended treatments for the carbapenemase producing bacteria involve the combination of Colistin with another antibiotic
- If the bacteria is not too resistant to Meropenem (a carbapenem) then this can be combined with Colistin
- Tigecycline can be used for systemic infections and pneumonia caused by carbapenemase producing bacteria but not UTIs because Tigecycline is not active in the urinary tract
- The combination of Colistin with Amikacin (an aminoglycoside) is very effective at killing Gram-negative bacteria, unfortunately it is also very good at killing the patients kidneys and so is often only used as a last resort

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- Prior to 2015 it was believed unlikely that transferable Colistin resistance could occur in Gram-negative bacteria
- In 2015 the Chinese found plasmid mediated Colistin resistance in 25% of meat at the point of sale (pork and poultry)
- Up until this time China did not use Colistin in humans but were the World's highest consumers of Colistin because they used it extensively in animal husbandry

- Colistin resistant bacteria where found in the UK

- A patient in the USA died from an infection with a multiple antibiotic resistant Gram-negative bacterial infection which had been acquired in India that was not sensitive to any available antibiotics

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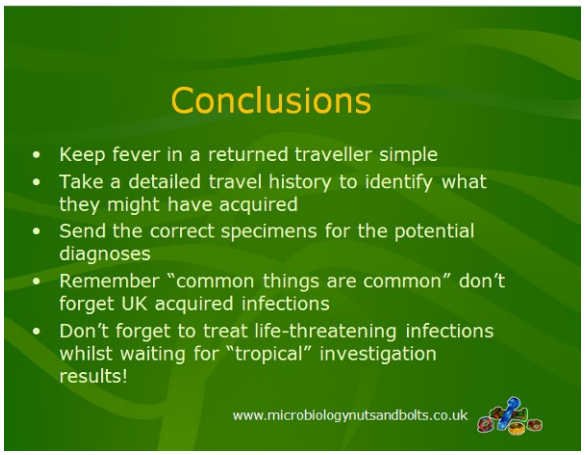

- Doctors often get confused about managing fever in a returned traveller but as long as a systematic approach is used then it need not be too difficult
- The most important part of managing these patients is to take a detailed travel history; it may not mean much to you but an Infectious Diseases Physician will want to know and it will probably mean more to them
- Patients who have returned from exotic locations can still get the home grown infections everyone else gets so don't forget to manage for those as well
- If in doubt and the patient is unwell, cover for the serious and life-threatening infections whilst waiting for results of investigations to come back