Africa's response to childhood infection

The AfSPID BULLETIN

Volume 3 (1) Newsletter of the African Society for Paediatric Infectious Diseases January 2015

CONTENTS

EDITOR'S COMMENTARY

Dear Colleagues

Welcome to the third edition of our newsletter.

AfPIDS has been in existence for 2 years. In this edition we publish the society's constitution, an important milestone in the development of the society. The EXCO should be congratulated for finalising this document. The constitution defines the society's structure and functions. To sustain AfSPID, the EXCO should now produce a strategy for growing its membership. In this edition we also publish guidelines for prospective authors. This should hopefully streamline the submission of articles and contributions from our members, and standardise the formatting of manuscripts.

The Ebola outbreak has had a major impact on our continent. It has had tragic consequences for many but has also drawn attention to deficiencies in infection control practice within our health systems. In this edition we feature two somewhat complementary articles on the outbreak. Firstly, Adegoke Falade describes in detail the epidemic in West Africa and comments on the impact of the Ebola on children in the region. Thereafter, Regina Oladokun provides a perspective on the outcome of Ebola in Nigeria. We also focus on two arboviral infections. In an excellent overview Stephen Korsman discusses Chikungunya infection in children. Then Mary Matilu writes about Dengue infection in Kenya. She recently convened & chaired a symposium on arboviruses at the International Congress of Tropical Paediatrics which took place from 24 to 27 August 2014 in Nairobi. She reflects on some of the developments presented during the arbovirus symposium.

The South African Paediatric Association conference took place in Cape Town from 11 to 14 September 2014. More than 600 delegates participated. This conference was preceded by several pre-conference workshops covering a wide spectrum of paediatric disciplines. The South African Paediatric Infectious Diseases Society (SASPID) hosted a pre-conference day-long workshop on 10 September 2014 entitled "Current issues in paediatric ID" Most of the talks from this workshop may be downloaded from the FIDSSA website at: http://www.fidssa.co.za/A_IDSSA_presentations.asp In this newsletter Nicolette du Plessis summarises her presentation on antibiotic stewardship. The Southern African HIV Clinicians Society held their 2nd biennial conference in Cape Town in September 2014, attended by more than 1200 delegates. Lisa Frigati summarises paediatric symposia and talks presented at this conference.

Ombeva Malande comments the American Academy of Pediatrics 2014 guidelines on bronchiolitis and what it means for Africa. The importance of establishing the aetiology of persistent parasitic diarrhoea is discussed by Lourens Robberts. He provides a succint description of the therapeutic options for a wide spectrum of diarrhoea-causing parasites. The 11th Vaccinology Scientific Conference took place in October 2014 in Ballito, Durban, South Africa. This annual conference for invited delegates focusses on vaccine developments in relation to South Africa and Southern Africa. In 2014, South Africa introduced the HPV vaccine into the public sector. Two talks from this conference that addressed aspects of HPV vaccination are summarised. Regina Oladokun describes the proceedings of the 9th International RSV conference, which took place at the Spier conference centre in Stellenbosch, Cape Town. This highly specialised conference attracted more than 350 delegates from all over the world. Finally we draw attention to a few recent publications.

I hope that you find the spectrum of topics interesting. All authors are commended for excellent contributions.

Kind regards, Brian Eley

CONSTITUTION OF THE AFRICAN SOCIETY FOR PAEDIATRIC INFECTIOUS DISEASES

ARTICLE 1: NAME

The society shall be called "*The African Society for Paediatric Infectious Diseases",* and herein after referred to as the *Society*.

ARTICLE 2: OBJECTIVES

The objectives of the *Society* shall be:

i. To advance the understanding of and exchange of information on paediatric infectious diseases, related medical microbiology, immunology, vaccinology and virology.
ii. To foster greater collaboration between the clinical and laboratory-based disciplines for the above objective.
iii. To promote the development and exchange of knowledge, information and ideas to support the prevention and control of hospital- and community-acquired paediatric infections.
iv. To advise on training and maintenance of standards within the disciplines.
v. To forge links with societies representing similar interests throughout the world.

ARTICLE 3: LIABILITIES

The *Society* is a corporate body and is vested with all the powers and obligations required for achieving its objectives.

i. No member of the *Society* shall by virtue of his/her membership have any claim to the assets of the Society.
ii. No member of the *Society* or of the EXCO of the *Society* shall be personally liable for fulfilling any financial obligation for debt incurred by the *Society*.

ARTICLE 4: MEMBERSHIP

Members of the *Society* shall consist of Honorary, Ordinary and Associate members.

i. Honorary members. Any member of the *Society*, seconded by two other ordinary members of the *Society*, may nominate a person or persons for election as honorary members on the grounds of special contribution to paediatric infectious diseases or the *Society*. The EXCO shall consider such nominations. Honorary membership is retained for life, and honorary members will have the rights and privileges of members, but they shall not be required to pay any membership fees.
ii. Ordinary membership will be granted to paediatricians, medical practitioners, medical scientists, medical technologists, pharmacists and nurses who have made a contribution to or are involved in any way with the discipline of paediatric infectious diseases.
iii. Associate membership is offered to other interested parties such as members of pharmaceutical industry involved with aspects of infectious diseases and students (both postgraduate and undergraduate) who do not fully meet the criteria listed in ii
iv. Membership may cease due to withdrawal, exclusion or cancellation of membership.
v. Members may leave the Society at any time and should inform the secretariat in writing.
vi. Members can be excluded from the Society for good cause. Upon the Executive Committee's application, the General Assembly shall decide upon the exclusion by simple majority. The exclusion of a member shall become effective upon the passing of the respective resolution.
vii. Membership of the Society may be cancelled if a member is in arrears for three consecutive years with the membership fee and has failed to settle the outstanding amount within three months of receiving a written reminder from the Executive Committee.

ARTICLE 5: OFFICERS AND TRANSACTION OF BUSINESS

An executive committee elected from ordinary members of the *Society* will conduct the business of the *Society*

ARTICLE 6: EXECUTIVE COMMITTEE (EXCO)

i. The responsibilities of the Committee include:
    a. Carrying out the policies of the Society
    b. Determining the location of the next general meeting
    c. Considering applications for membership from individuals, organizations or countries
ii. Membership of EXCO: The EXCO will have representation from each of the following regions: North Africa, East Africa (including Mauritius), West Africa, Central Africa, and Southern Africa
    a. The president
    b. Two vice-presidents
    c. The secretary
    d. The treasurer
    e. Regional Representatives – 2 from each region – (These may include the other office bearers
    f. Two additional members, one of whom shall be the immediate past-president. The EXCO shall have the power to co-opt members should it be necessary.
iii. The president or nominated representative shall also represent the *Society* at any meeting.
iv. The EXCO members shall be elected for a four (4) year term and may be eligible for re-election.
v. Nominations for members of the EXCO shall be made on nomination forms and shall reach the secretary two weeks before the general meeting. Each nomination shall bear the signature of at least two ordinary members as proposer and shall have been accepted in writing by the nominee. Alternatively, nominations and elections may take place at the general meeting of AfSPID coinciding with the end of term of the existing EXCO.
vi. Election of officers shall be by majority vote of the ordinary members of the *Society* present at the meeting when elections are scheduled.
vii. Duties and responsibilities of office-holders
    a. The president shall chair the General Assembly and EXCO meetings. In the case of his/her absence, the president may assign this function to the one of the vice-presidents. The president or designee from the EXCO can represent the Society. The vice presidents will support the president and one will officiate by consensus between the two Vice-Presidents in the absence of the President.
    b. The secretary is responsible for all administrative matters relating to the Society.
    c. The treasurer is responsible for Society's financial affairs and shall submit an annual financial statement

to the EXCO for approval and then to the General Assembly.

viii. If any member of the EXCO shall resign, refuse to accept office or become incapable of acting through illness or any other reason, he/she shall *ipso facto* cease to be a member of the EXCO.

ix. The EXCO may continue to act notwithstanding that its number is reduced by death, retirement or otherwise below its full number. Provided that if at any time its number is reduced below four, its continuing members shall only act for purposes of filling up vacancies.

x. If any member of the EXCO shall and without satisfactory reason absent himself or herself from three consecutive meetings thereof, the EXCO may declare his/her office vacant and he/ she shall thereupon cease to be a member of the EXCO.

xi. In the event of the death or resignation of an EXCO member, the current EXCO shall appoint a successor for the remainder of the term of office.

xii. If there should be a deadlock on any decision at a business or committee meeting, the president will have a deliberative as well as a costing vote (2 votes).

xiii. The president may call special meetings of the membership. The time and place will be determined by a majority vote of the EXCO. Written or printed notice, stating the purpose, place and hour of any special meeting shall be sent to each member not less than 28 days before the date of such meeting. The same applies to business meetings of the *Society*

xiv. A *quorum* is 5

xv. No EXCO member shall receive remuneration for services to the *Society*

ARTICLE 7: CONGRESS

i. AfSPID sessions linked to international meetings: AfPIDS-sponsored sessions will be linked to international meetings as decided by the EXCO. At these meetings, there will also be an EXCO meeting. The president will organize AfPIDS sessions, with approval of the EXCO. At such a meeting, there will be an EXCO meeting plus a general meeting. General assembly of the Society shall be held at least every two years at a venue decided by consensus, depending on availability of sufficient funds. In principal, AfSPID meetings will be linked to regional or international meetings as decided by the EXCO.

ii. When sufficiently resourced, AfPIDS will organize its own independent meetings and will include the following:
    a. The programme of the general assembly shall include:
    b. Scientific, instructional sessions and exhibits
    c. The business meeting of the Society
    d. The EXCO meeting of the Society

    For independent meetings, the following arrangements will apply:

    a. Local organizing committee (LOC): The arrangements for the congress will be made by a LOC that will be represented by the *Society*
    b. The *Society* will nominate two suitable candidates
    c. The LOC will elect a chairperson and shall have the power to co-opt any other members of the Society should it be necessary
    d. Most of the appointed members of the LOC should preferably reside in the same geographical area where the general assembly is scheduled to take place
    e. The nominated members in conjunction with other LOC members shall be responsible for decisions regarding the "theme of the congress", academic programme including plenary topics and parallel sessions of paediatric infectious diseases, acceptance of applicable papers and social program
    f. The EXCO of the Society, in conjunction with LOC, shall be responsible for decisions regarding the acceptance of the planning budget
    g. The event manager to arrange a congress launch cocktail party for pharmaceutical sponsors at least one year in advance
    h. The LOC and event coordinator shall be accountable and a short report, full financial statement and audited accounts shall be submitted for approval to the council within six months of the conclusion of the meeting

ARTICLE 8: SUBSCRIPTION, DUES AND FUNDS

The EXCO of Society will collect annual subscriptions on behalf of the Society.

i. The subscription fee for membership of the Society shall be determined by a majority vote of members at the Society's business meetings.

ii. The EXCO shall control the funds of the Society and to this end shall maintain such bank account or accounts in the name of the Society as it sees fit.

iii. Subscription fees shall be paid before the 1st July of each year for that calendar year membership

iv. The secretariat and treasurer will send out accounts to all members of the *Society* and will collect the dues on behalf of the *Society*

v. Honorary members shall be exempt from dues

vi. Membership subscription funds to the *Society* shall be deposited in the joint bank account in a recognized financial institution.

vii. The President and an additional designated member must sign any cheques. The EXCO will determine signing powers for financial transactions with each change in leadership

viii. Grants and Endowments: The Society EXCO is authorized to accept in the name of the *Society*, any grants or endowments which are designated for administration and use by the *Society*, provided that the purpose of such grants and endowments is, in the judgment of the EXCO, consistent with the objectives and purposes of the *Society*

ix. The subscriptions, grants and endowments shall be allocated to the *Society* and expended, subject to the control of the EXCO of the *Society*

x. The EXCO is empowered to invest the capital of the *Society* as they consider advisable but otherwise have no financial control over the funds of the *Society*
xi. The treasurer shall present an audited financial report on the financial status of the *Society* at the EXCO and business meetings of the Society. The EXCO shall arrange for the production of annual accounts, which will be inspected by an Independent auditor to be appointed by the EXCO and ratified by the General Assembly.
xii. Depending on the generation of profit at the Society's congress, the *Society* will decide on its allocation

ARTICLE 9: NEWSLETTER

The *Society* will publish and distribute a newsletter one to four times per annum

i. This will be distributed to all members of the *Society*
ii. The editorial board will be represent the *Society* and the *Society* will nominate two members to the editorial board in liaison with the editor-in-chief
iii. A subcommittee of the editorial board will be appointed to assist inexperienced members of the *Society*, in preparing relevant papers that are of the required standard for submission and approval

ARTICLE 10: AMENDMENTS TO CONSTITUTION

Any amendments to the constitution of the *Society* will be dealt with as follows:

i. Amendments shall first be submitted in writing to the secretary for consideration by the EXCO
ii. Thereafter the proposed changes together with recommendations of the EXCO shall be circulated to all members of the *Society* at least one (1) month before the business meeting of the *Society*
iii. A two-thirds majority vote of those present at the business meeting of the *Society* will be required for adoption of the proposed amendments

ARTICLE 11: DATABASE

The Society secretariat is responsible for maintaining a separate database of members of the *Society*

i. The Society database is not for distribution unless for *bona fide Society* purposes
ii. Any request for details that are received such as suitable advertisements, position and vacancies should be vetted by the council of the *Society*
iii. For pharmaceutical requests if accepted by EXCO, a quote should be provided with a charge to the *Society*

ARTICLE 12: LEGAL PERSONALITY

The *Society*, a legal entity that exists independent of its members, has perpetual legal succession regardless of the variation of membership and is a non-profit making organization

i. The *Society* can act as a defendant or plaintive in any competent court
ii. The *Society* can obtain, retain or expropriate its own assets, can deal with them and can undertake its own obligations
iii. These assets and liabilities are independent of each individual member's assets and liabilities

ARTICLE 13: DISSOLUTION

In the event of the *Society* being dissolved the remaining assets shall be paid to a non-profit organization devoted to medical research to be designated by the EXCO of the Society at the time of dissolution

EBOLA VIRUS DISEASE EPIDEMIC IN WEST AFRICA: THE UNPRECEDENTED SPREAD AND IMPACT ON CHILDREN

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The current Ebola virus disease (EVD) epidemic in West Africa is caused by a novel variant of Zaire Ebolavirus species (EBOV, Zaire) named EBOV/Mak after the Makona River close to the border between Liberia, Guinea, and Sierra Leone.[1] The Zaire Ebolavirus species is the most lethal of the known EVD-causing viruses. This and four other species : Bundibugyo virus (BDBV), Sudan virus (SUDV), Taï Forest virus (TAFV) and the fifth virus, Reston virus (RESTV), which is pathogenic only in non-human primates, as well as the two species of Marburg virus belong to the family *Filoviridae*.[2-4]

In 1976, the first EVD epidemics occurred simultaneously in remote areas of Zaire, now called Democratic Republic of the Congo (DRC), and South Sudan (southern part of the old Sudan). The Zaire epidemic caused by EBOV Zaire, was more fatal than the Sudan epidemic caused by Sudan virus.[5] The EBOV Zaire was named after the Ebola River, close to Yambuku village where the first case was detected.[5] From 1977 through 2013, the World Health Organization (WHO) reported a total of 1,716 cases of EVD in 24 sporadic outbreaks in sub-Saharan Africa (Figure 1).[6,7]

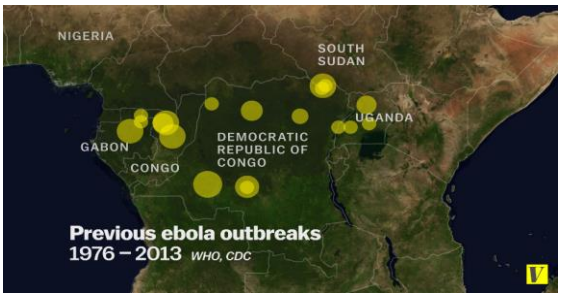

Figure 1: Previous Ebola virus disease epidemics from 1976 through December 2013

The zero patient of the current EVD epidemic in West Africa is believed to be a 2-year-old boy, who died on 28 December, 2013 in the village of Meliandou, near the town of Guéckédou Prefecture, a forest region of Guinea close to the borders of Sierra Leone and Liberia.[8] Because EVD epidemic had never been reported in West Africa, the early cases were misdiagnosed as malaria which has similar symptoms of high fever, headaches and muscle pains, thereby delaying quarantine measures. The disease

spread for months before it was recognized as Ebola in February 2014, spreading into Liberia in March, and Sierra Leone in May 2014 (Figure 2).[8] The first cases of EVD got to Nigeria on 20 July, Senegal on 29 August, and Mali on 23 October, 2014 and further cases were reported in Mali in November, 2014.[9,10]

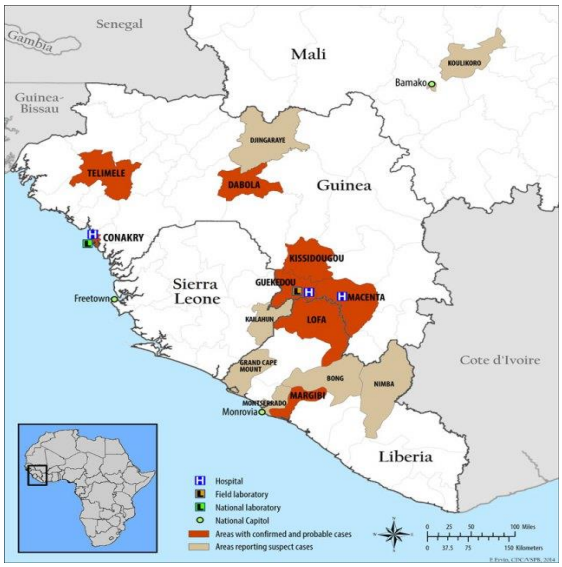

Figure 2: Spread of the ebola virus disease from Guéckédou, Guinea to the capital Conakry as well as nearby Liberia and Sierra Leone (Source: Wikipedia)

The current epidemic has exploded beyond rural Meliandou to reach cities in six West African countries (Figure 3), with exportations or transport of patients to France, Germany, Norway, Spain, the UK, and the United States of America leading to secondary infections of medical workers in only Spain and the US, but have not spread further.[11] It is the largest, most complex and most severe in history, affecting 19,643 West Africans, i.e., 11 times as common as all the previous epidemics over the last 37 years put together and killing 7,644 (Table 1), even though WHO indicated that these numbers may be vastly underestimated.

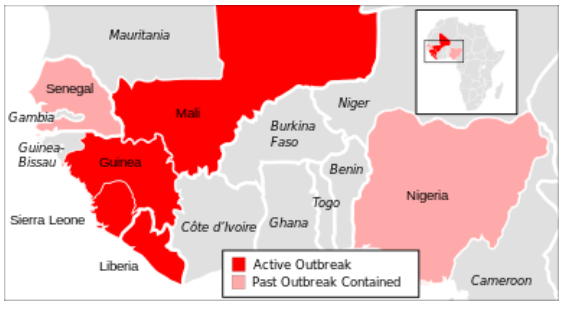

Figure 3: Ebola virus diseases epidemic in six countries in West Africa.

This communication describes the unprecedented EVD epidemic caused by a new variant of EBOV Zaire [12], including its impacts on the paediatric age group in whom there is a dearth of information. The pathogenesis will not be discussed as it is beyond the scope of this work.

Virology

Ebolavirus is a filamentous, single-stranded, negative-sense RNA virus (Figure 4). All the known human pathogenic filoviruses are endemic only in sub-Saharan Africa.

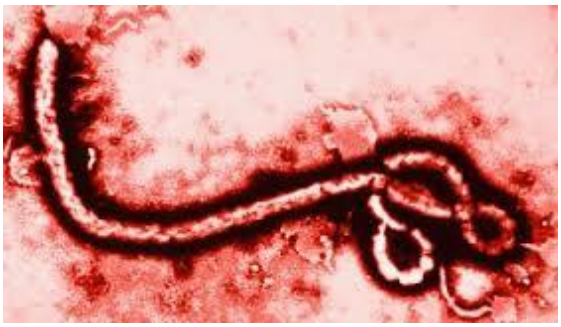

Figure 4: Transmission electron micrograph of the *Zaire ebolavirus* (genus *Ebolavirus*, family *Filoviridae*, order *Mononegavirales*).

Transmission

Three species of fruit bats – *Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata* - are the most likely natural reservoir of Ebola virus.[13] A human infection occurs through inadvertent direct exposure to an infected bat faeces or saliva following entry into caves, mines, and forests. However, investigation of the zoonotic origins of the current epidemic suggests the index case may have been infected by playing in a hollow tree housing a colony of insectivorous free-tailed bats, *Mops condylurus*.[14] Additional sources of infection to humans are from gorillas, chimpanzees, and duiker antelopes that may become infected from bat contact and serve as intermediate hosts that transmit Ebola virus to humans through contact with their blood and bodily fluids, usually associated with hunting and butchering. Subsequently, human-to-human transmission of Ebola virus occurs primarily through unprotected direct contact of skin (through breaks or small abrasions) or mucous membranes with blood or body fluids (e.g., faeces, saliva, urine, and vomitus) of a person who is ill with EVD, or the corpse of a deceased patient who had EVD. Infection through fomites - contact with objects, including door knobs contaminated with the blood or body fluids of an infected person – cannot be excluded. Ebola is not spread through the air, by water, or in general by food, the exception is bush meat. Aerosol respiratory spread of virus does not occur.

There is no risk of transmission from infected asymptomatic people during the incubation period. The virus is present on a patient's skin after symptoms develop. The virus can survive for a few hours on dry surfaces like doorknobs and can survive for several days in puddles or other collections of body fluid.

Spread of EVD in West Africa

Guinea: On 26 December 2013, a 2-year-old boy (the first West Africa's case of EVD) in the remote forested village of Meliandou fell ill with fever, black stools, and vomiting. He died two days later. The source of infection was unknown. Following the death of the index case, the disease continued to smoulder undetected for more than three months, causing several chains of deadly transmissions (Figure 5). Four common factors that favoured the spread of EVD in the most affected countries (Guinea, Sierra Leone and Liberia) are: severely damaged health infrastructures during years of civil unrest, rampant poverty, pervasive salaried unemployment driving quest to find work, thereby contributing to unhindered population movements across extremely porous borders. Cases began to appear at a hospital in Guéckédou, a city in the

same hot zone which, is located where the borders of Guinea, Liberia and Sierra Leone converge (Figure 2), and a correct diagnosis was only made in mid-March when an experienced and intuitive Médecins Sans Frontières /Doctors Without Borders (MSF) disease detective in Geneva suspected Ebola virus haemorrhagic fever which, was later confirmed at the Institut Pasteur Laboratory in Paris.

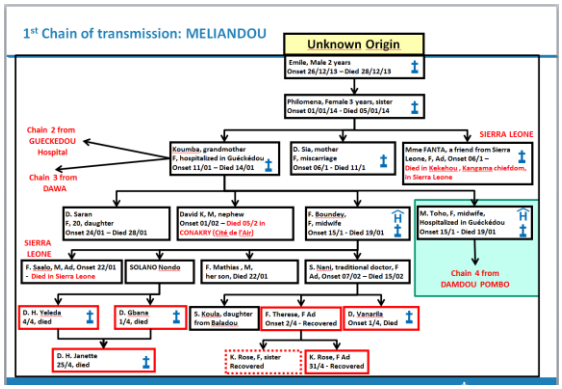

Figure 5: Transmission of Ebola virus disease from the zero patient, 2-year-old male toddler to the first 14 cases in Guinea and beyond into Sierra Leone (Source: WHO)

Despite all the efforts by the WHO Global Outbreak Alert and Response Network (GOARN) umbrella, to control the epidemic, the virus spread relentlessly to Conakry on 27 March, 2014 and even beyond to other areas of the country. To worsen the already grim situation, violence ensued from a terrified population that did not understand what hit it. Health workers in several parts of the country were viciously attacked by angry mobs, their vehicles vandalised and equipment publicly burnt forcing some medical teams to flee for their lives

Sierra Leone: The first confirmed case of EVD in Sierra Leone was a young woman admitted to a Government General Hospital, Kenema following a miscarriage on 24 May, 2014. She survived and her source of infection was tracked to attendance of the funeral of a well-known female traditional healer in Kenema, who became infected with the Ebola virus and died, while taking care of Guineans with EVD. As many as 365 mourners from other nearby towns, that participated in the traditional funeral and burial ceremony got infected and died of EVD. By mid-June, Kenema was in an explosive outbreak, and the government hospital could no longer cope. The hospital nurses were infected, and 12 of them died depleting response capacity of hitherto thin number of medical staff. Kenema Government General Hospital which has a well-equipped Lassa fever (another viral haemorrhagic fever) isolation ward, employed the Lassa Fever Programme contact-tracing staff and skills to contain the outbreak to no avail. As in Guinea, the virus marched into the capital city, Freetown, where it took advantage of overcrowded living conditions and fluid population movements to multiply very rapidly.

Sadly, on 29 July, the head of the country's Lassa Fever Programme, 39-year-old Dr. Sheik Umar Khan died of Ebola virus disease. A breakthrough in the scientific understanding of Sierra Leone's outbreak came on 28 August, 2014 from a published work by Gire *et al* that traced the start of the outbreak to the healer's funeral and its further spread.[12] The study also demonstrated a pattern of adaptive mutation in the virus necessitating a call for an urgent scaling up of control measures to prevent the virus adapting to establish permanent residence in the affected areas.

Liberia: Throughout the country, very few treatment beds were available for the management of Ebola patients whose numbers were increasing exponentially. Similar to the situation in Sierra Leone, some of Liberia's experienced doctors working at the ill-equipped John F Kennedy Medical Center in Monrovia, became infected with Ebola virus disease and died. Thereafter, the Island Clinic, fully funded by WHO, and further supported by UNICEF, the World Food Programme, and USAID, provided dedicated Ebola treatment unit of 120 beds, with 30 beds in a triage area, a design feature that improves safety for patients and staff. It augmented Monrovia's existing and woefully inadequate 240-bed treatment capacity. Thereafter, the United States Government, through its Centers for Disease Control and Prevention (CDC), set up a new laboratory. This additional capacity facilitated availability of diagnostic results within four hours of suspected cases to guide their admission to the Clinic or transfer to another health facility.

The US scaled up support to Liberia through building of 17 new treatment facilities, as well as training of around 500 health care personnel each week. Apart from supporting more treatment capacity, such training created badly needed jobs in Liberia.

The United Nations Mission for Ebola Emergency Response (UNMEER) was founded to relieve WHO from some burdensome and time-consuming tasks, such as transporting essential supplies and medical personnel. The WHO then focused on data collection and reporting, assessment and management of risks, streamlining laboratory requirements, increasing the number and safety of facilities providing state-of-the-art supportive care, and getting more of its hand-picked doctors and other medical personnel deployed under the WHO GOARN umbrella. In addition, the maternal and child health programme made moribund by the EVD epidemic was resuscitated.

Nigeria: Nigeria successfully combated EVD epidemic with cases confirmed in Lagos (one of the most populous cities in Africa) and in Port Harcourt, about 618 km away from Lagos. The Ministry of Health responded urgently, appropriately and effectively. Contact tracing by highly-trained local health workers, aided by staff from WHO and the United States CDC, reached nearly 100% of all exposed persons. Unlike the case in the three hardest-hit countries, Nigeria's Ministry of Health created the facilities to isolate exposed persons during the requisite 21-day monitoring period. The government also built two new Ebola-specific treatment centres, one in Lagos and a second in Port Harcourt. In addition, WHO supported the government's response with several clinicians and with an epidemiological investigative team that worked closely with Nigerian health officials.

In all, Nigeria confined the outbreak to only 15 confirmed cases in Lagos and four in Port Harcourt. Altogether, seven deaths (excluding the index case) were reported. But, sadly, five of these deaths occurred among doctors and nurses tending the ill.

The fact that the worst-case scenario never happened in Nigeria supports two important lessons. First, conventional control tools – like early detection, contact tracing, isolation and monitoring of those exposed, adequate supplies of personal protective equipment for medical and nursing staff, and strict

procedures for infection prevention and control – are indeed highly effective when a country's first imported case was detected early enough and managed as recommended by WHO. Second, if Nigeria can control an outbreak caused by such a deadly and highly contagious virus, right from the start, any country in the world can do the same.

Senegal: These lessons were borne out when Senegal confirmed its first and only case in a Guinean national who entered Senegal by road on 29 August, 2014. To support the government, WHO immediately responded in emergency mode, with a risk assessment, airlifting of adequate quantities of medical supplies, and the deployment, within a day, of three of its most senior epidemiologists. Contact tracing was excellent. Numerous suspected cases were identified, tested, and then discharged as all test results were negative. Dakar further benefitted from the presence of the Institut Pasteur Laboratory with world-class diagnostic capacity. The first case received excellent supportive care, completely recovered, and was released from the hospital.

Country	Total cases	Total Deaths	CFR (%)	Last update (2014)
Guinea	2,597	1,607	61.9	21/12
Liberia	7,862	3,384	43	20/12
Sierra Leone[ǂ]	9,155	2,639	43	23/12
Nigeria	20	8	40	20/10*
Senegal	1	0	0	17/10*
Mali	8	6	75.0	16 Dec
Subtotal	19,643	7,644	38.9	
USA	3 (8)	1 (2)	25	21/12*
Spain	1 (3)	0 (2)	0	02/12*
Total	**19,647**	**7,645**	**38.9**	

Table 1: Ebola virus diseases in West Africa including medically evacuated cases to the United States of America and Spain.

Footnotes: ǂ Sierra Leone accounts for the most cases (9,155) as against 7,862 for Liberia. But Sierra Leone's fatality of 2,639 is far less than 3,384 recorded in Liberia, raising doubts on the credibility of the data reported by Freetown; *Date when the national outbreak ended; The numbers in parentheses represent total number including medically evacuated cases.

Mali: There were two unrelated waves of Ebola infection outbreak in Mali. The first case of EVD was confirmed on 23 October, 2014 in a 2-year-old female toddler in the town of Kayes, Mali. This girl arrived Mali with a family group from Guinea, who had attended a burial ritual of her father that contracted Ebola virus in a private clinic he worked for, and later died. A number of family members also died of Ebola.[15]

On the 12 November, Mali reported deaths from Ebola in the second wave of ebola outbreak. The index case was an Imam who fell ill on 17 October in Guinea and was transferred to the Pasteur Clinic in Bamako, capital of Mali for treatment. He was treated for kidney failure and died on 27 October, 2014. A nurse and a doctor who had treated the Imam subsequently fell ill with Ebola and died. The next three fatal cases were related to the Imam: a man who had visited the Imam while he was in hospital, his wife, and his son. On 22 November, the final case related to the Imam was reported: a friend of the Pasteur Clinic nurse who had died from the Ebola virus. On 12 December, 2014 the last case on treatment recovered and was discharged.

EVD in Children

Clinical Features

The mean incubation period in the current outbreak is estimated at 11.4 days, typical range, 2-21 days.[16] The symptoms and signs of EVD in children are similar to those in adults. Early symptoms are nonspecific and flu-like; and include fever (axillary or skin temperature, 37.5^{o}C; or core, 38.0^{o}C), chills, myalgia, and malaise. This is followed several days later by gastrointestinal symptoms: severe watery diarrhoea, nausea, vomiting and abdominal pain. Other symptoms are chest pain, shortness of breath, headache or confusion, conjunctival injection, hiccups and seizures. Bleeding is not universally present but can manifest later as petechiae, ecchymosis/ bruising, or oozing. Frank hemorrhage is less common. Some develop diffuse erythematous maculopapular rash that can desquamate.

Epidemiology

Children and adolescents comprise less than a fifth of cases in all reported outbreaks. For instance, in the 1995 outbreak in Zaire, only 9% of the 315 EVD cases were younger than 18 years despite more than half of the population being younger than 18 years.[16] In the current outbreak in Guinea, less than a fifth of the cases (18% of 823) were children.[17] As at September 2014, 13.8% of cases from four affected countries (Guinea, Sierra Leone, Liberia and Nigeria) were younger than 15 years.[18] There are fewer paediatric cases of EVD than adults because children are not typically primary caregivers of sick individuals and are less likely to participate in funeral rituals that involve touching and washing of the deceased person's body, which are high risk activities for transmission of EVD.[18]

In the current outbreak, the case fatality rate was 73.4% in children younger than 15 years, compared with 66.1% for those aged 15 to 44years, and 80.4% for those older than 44 years.[18] It has been suggested that this was due to more prolonged contact with ill caregivers. In this West African outbreak, young uninfected children were often admitted to EVD treatment unit isolation wards with their ill parents because of the reluctance of other adults to care for them due to fear of being infected.[19]

Diagnosis of Ebola Virus Infection

Ebola virus infection is considered in a person who develops a fever within 21 days of travel to an area with ongoing epidemic such as Sierra Leone, Liberia, and Guinea, as well as Mali in this 2014 outbreak.

Laboratory diagnostic tests include: testing of blood by reverse transcriptase-polymerase chain reaction (RT-PCR) assay, enzyme-linked immunosorbent assay (ELISA) for viral antigens or immunoglobulin (Ig) M, and cell culture, with the latter being attempted only under biosafety level-4 conditions. Viral RNA generally is detectable by RT-PCR assay within 3 to 10 days after the onset of symptoms.

Management

A patient suspected of having Ebola virus infection should be quarantined immediately and public health officials notified. The mainstay of clinical management is focused on supportive care of complications, e.g., hypovolaemia and electrolyte abnormalities.[20] The challenge is getting paediatric patients to drink a lot of oral rehydration salt solutions. If this is not successful, nasogastric tube and intravenous route is employed. This requires direct contact with the patient and increases the risk of transmission to the healthcare worker.[20] More important, venous access in children is much more daunting than in adults.

Other treatments include use of vasopressors, blood products, total parenteral nutrition, antimalarial and antibiotic medications covering for intestinal microbiota when co-infections are suspected or confirmed

(www.cdc.gov/vhf/ebola/treatment/index.html). Nonsteroidal anti-inflammatory drugs, aspirin, and intramuscular injections should be avoided because of the risk of bleeding.

Control Measures

Contact Tracing: People with potential Ebola virus exposure are categorised into high risk, some risk, low risk, and no identifiable risk; and are monitored according to the recommendations on the CDC Web site (www.cdc.gov/vhf/ebola/exposure/monitoring-and-movement-of-persons-with-exposure.html). People being actively monitored should measure their temperature twice daily, monitor themselves for symptoms, report as directed to the public health authority, and immediately notify the public health authority if they develop fever or other symptoms.

Vaccine: At least two Ebola virus vaccine candidates are presently in Phase I trials in humans.[20]

Breastfeeding: Infants whose mothers are infected with Ebola virus already are at high risk of acquiring Ebola virus infection through close contact with the mother and are at high risk of death overall. Therefore, when safe replacements to breastfeeding and infant care exist, mothers with probable or confirmed Ebola virus infection should not have close contact with their infants (including breastfeeding). In developing countries where bottle-fed infants are at increased risk of death from diarrhoeal diseases, breastfeeding must be carefully weighed against the risk of Ebola virus infection. Breastfeeding is resumed after a mother's recovery, when her milk has been demonstrated to be Ebola virus-free by laboratory testing.

Hygiene: Careful hygiene which includes washing of hands with soap and water or a 9:1 water to bleach solution, using an alcohol-based hand sanitizer, avoiding contact with blood and body fluids, should be practised.

Environmental Control: There must be no exposure to fresh blood, bodily fluids, or meat of wild animals, especially non-human primates but also bats, porcupines, duikers (a type of antelope), and other mammals, in areas with endemic EVD (2015 Red Book, in press).

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EBOLA VIRUS DISEASE & THE NIGERIAN CONTAINMENT SUCCESS STORY

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A total of 20,206 confirmed, probable, and suspected cases of Ebola virus disease (EVD) have been reported in five affected countries (Guinea, Liberia, Mali, Sierra Leone, and the United Kingdom) and four previously affected countries (Nigeria, Senegal, he United States of America and Spain) up to the end of 28 December 2014. There have been 7,905 reported deaths[1].

Patient zero of the current Ebola outbreak

The EVD outbreak appears to have originated near the town of Guéckédou, which is in the forest region of Guinea and close to the borders of Sierra Leone and Liberia. A 2-year-old boy was identified as 'patient zero' in the current Ebola outbreak. The boy died in December, 2013 after a mysterious illness that caused fever, black stools and vomiting. About a week after his death, the sibling got sick and died, shortly followed by their pregnant mother and grandmother. Thereafter, through human-to-human spread, and regional and international travel, the outbreak extended to 9 countries.

Transmission

The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission. Infection results from direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other bodily fluids of infected people, and indirect contact with environments contaminated with such fluids. Fruit bats of the *Pteropodidae* family are considered to be the natural host of the Ebola virus.[2]

Health-care workers are particularly at risk of infection with the virus while treating patients with suspected or confirmed EVD, especially when infection control precautions are not strictly practiced. A total of 678 health-care workers (HCWs) are known to have been infected with EVD, 382 of who have died[1].

Manifestations and outcome

In order to gain insight and understand the clinical illness in the current outbreak better, Schieffelin *et al.* carried out a review of available epidemiologic, clinical, and laboratory records of patients in whom EVD was diagnosed between May 25 and June 18, 2014. Of 106 patients in whom EVD was diagnosed, 87 had a known outcome, and 44 had detailed clinical information available. The incubation period was estimated to be 6 to 12 days, and the case fatality rate was 74%. Fever was the most common symptom at presentation, occurring in 89% of patients, followed by headache (80%), weakness (66 %), dizziness (60%) diarrhoea (51%), abdominal pain (40%) and vomiting (34%). Bleeding was an infrequent finding, having occurred in only 1 patient.

Clinical and laboratory factors at presentation that were associated with a fatal outcome included fever, weakness, dizziness, diarrhoea, and elevated levels of blood urea nitrogen, aspartate aminotransferase, and creatinine. Furthermore, patients under the age of 21 years had a lower case fatality rate than those over the age of 45 years (57% vs. 94%, P = 0.03). Thirty three percent of patients with viral load of <100,000 copies/ml at diagnosis ultimately died, compared with 94% mortality in those whose had ≥10 million copies/ml.[3]

Management

There are no licensed vaccines or drugs are available for the treatment of EVD though several therapies are being evaluated. Profuse vomiting and diarrhoea can cause dehydration. Supportive care with adequate intravenous fluids and nutrition, and maintaining blood pressure is crucial. Death is usually due to shock and organ failure.

Containment: The spectacular success of Nigeria

Good outbreak control relies on applying a package of interventions, namely case management, surveillance and contact tracing, a good laboratory service, safe burials and social mobilization.

According to WHO recommendations, the end of an Ebola virus disease outbreak in a country can be declared once 42 days (twice the maximum incubation period of 21 days) have passed and no new cases have been detected. This 42-day period starts from the last day that any person in the country had contact with a confirmed or probable Ebola case[4].

Nigeria - the most populous country in Africa, with 160 million people - had 20 cases, including eight deaths (40% case fatality rate), lower than elsewhere across the affected regions. Nigeria's containment of Ebola was deemed a "spectacular success story". On October 20, 2014, Nigeria reached the 42-day mark after the last case tested negative, and was declared “Ebola-free”.

Nigeria's outbreak began in Lagos with a single infected Liberian diplomat who flew in on a commercial flight on July 20, bringing the terrifying disease to Africa's most populous city. He was treated for malaria initially when he denied any exposure to Ebola but when he did not respond to treatment, Ebola was suspected and he subsequently tested positive. He died five days after he arrived. Unfortunately, several people who cared for him contracted the disease.

The success in the containment of the disease in Nigeria had been credited to strong tracking and isolation of people exposed to the virus, and aggressive rehydration of infected patients to counter the effects of vomiting, diarrhoea and other symptoms. The eight deaths included two doctors and a nurse.

There was swift coordination among state and federal health officials, the WHO and the U.S. Centers for Disease Control and Prevention. Isolation wards were constructed and Ebola treatment centres designated. Health workers tracked down nearly 100 percent of those who had contact with the infected, paying 18,500 visits to 894 people. Entry and exit screening was also established at ports. Apart from the contact tracing, the Nigeria ensured a highly organized, methodical, and informed response to the outbreak. Strong public awareness campaigns, teamed with early engagement of traditional, religious and community leaders, also played a key role in successful containment of the outbreak.

In the worst affected countries, while the case incidence appears to be reducing in some communities, transmission remains high in others. This goes to demonstrate that the epidemic is far from over and as long as there is one case of Ebola in any country, it remains a threat to the country, region and the world. The expedited trials of two antivirals (favipiravir and brincidofovir) as well as convalescent plasma are welcome developments in the concerted effort to control the disease. One must not forget thousands of children orphaned by Ebola who have unmet social needs.

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PAEDIATRIC CHIKUNGUNYA

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Chikungunya is a severely debilitating disease caused by Chikungunya virus, an *Alphavirus* transmitted mostly by *Aedes* mosquitoes, traditionally *A. aegypti*. It was first discovered in Tanganyika (modern-day Tanzania), and has historically caused isolated infections and outbreaks in Africa, South Asia, and South-east Asia.

Virology

Chikungunya virus is an arbovirus (arthropod-borne virus), and a member of the genus *Alphavirus*, in the family *Togaviridae*. It has a single-stranded positive sense RNA genome, and has a lipid envelope. Glycoproteins E1 and E2 are responsible for cell entry, as well as haemagglutination (E1), and neutralising antibodies are formed against E2. There are three main genotypes – West African, Central/East African, and Asian (which is derived from the Central/East African genotype.)

Epidemiology

There are two main epidemiological forms – the African sylvatic cycle and the Asian urban cycle. In Africa, the virus is spread by *A. aegypti* and *A. africanus*, and non-human primates are the natural reservoir maintaining the virus in the wild. Humans become infected due to contact with mosquito populations in rural areas. In Asia, however, the virus is spread from human to human via *A. aegypti*, and this urban cycle applies to most subsequent regions to which the virus has spread.

Recent epidemiology

Recent outbreaks in Reunion and surrounding islands, Kenya, India/Bangalore, Thailand, and Cambodia occurred within the area between Africa and South-east Asia known for the presence of the virus. However, the 2005-6 outbreak in Reunion most likely had *Aedes albopictus* as the vector for transmission of the virus, and it was subsequently shown that a point mutation in the viral E1 glycoprotein allowed for enhanced replication and spread by *A. albopictus*.[1] A further 2007 outbreak in Italy was the first outbreak in Europe, and the first outbreak definitively caused by transmission from *A. albopictus*, which had first been identified in Italy in 1990 and has since been observed to have spread further into Europe than previously. The Italian outbreak began with imported Chikungunya from Kerala, India, which subsequently entered the local *A. albopictus* population.[2] Although Chikungunya infection due to blood transfusion has not been documented, the concern had a significant impact on the availability of blood and blood products during the outbreak.

Subsequent outbreaks in France in 2010 and 2014 also likely had *A. albopictus* as a vector. Both *A. aegypti* and *A. albopictus* appear to have adapted to colder weather, and have thus expanded their natural range further north. Furthermore, *A. albopictus* (but not *A. aegypti*) is able to survive winter by undergoing diapause as eggs, allowing survival in colder parts of Europe and North America.

In December 2013, an outbreak began in the Caribbean, which has resulted in local transmission in all Caribbean countries, northern and eastern South America, and North America from Florida and Mexico southwards. As of December 2014, there have been over 1 million suspected cases in the region.[3] Further spread into the Pacific islands has also occurred.

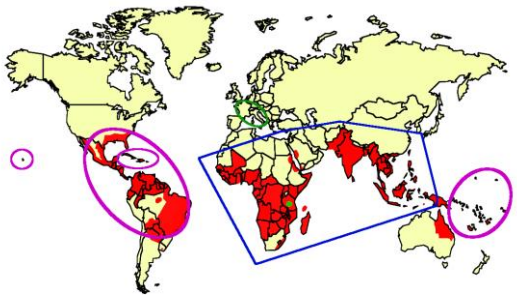

Figure 1. This map shows the historical range of *Aedes aegypti*, which is traditionally the main vector for the Chikungunya virus. Key: Red – regions with *Aedes aegypti*; solid green circle – original discovery of Chikungunya virus in Tanzania; blue polygon – the region historically affected by Chikungunya virus; purple ovals – new regions in which current Chikungunya outbreaks are taking place; green oval – local transmission of Chikungunya in Europe. Map adapted from original by Gary G. Clark, US Department of Agriculture, on Wikimedia Commons at https://commons.wikimedia.org/wiki/File:Dengue06.png.

Clinical features

Approximately 85% of infected persons develop symptoms. After a 2-7 day (up to 12 days) incubation period, it presents in adults with an acute onset of fever, headache, and arthralgia, usually of small joints in the hands and feet. A rash may be present in 70-80% of cases, and significant haemorrhagic symptoms are rare and usually limited to gum bleeding. Thrombocytopenia is common – haemorrhagic symptoms are believed to be as a result of platelet clumping due to viral attachment to platelets. Gastrointestinal symptoms are rare in adults. Mortality is usually low (0.01%), and treatment is only symptomatic. Neurological complications (meningoencephalitis, neuropathy, convulsions, Guillain-Barre syndrome, sensorineural deafness, optic neuritis) are rare in adults, and more common in children, especially neonates. Animal studies suggest that fibroblast tropism accounts for muscle and joint disease; neurotropism does not appear to be as significant as with the typically neurotropic Alphaviruses (Eastern, Western, and Venezuelan Equine Encephalitis viruses). In one district in Uganda, 47% of adults were noted to have antibodies to Chikungunya virus.[4] It is not clear whether there was a high asymptomatic infection rate in this population, or if clinical infection, when it occurred, was underdiagnosed.

Clinical features – paediatric

In contrast, children may present with pharyngitis, nausea, vomiting and abdominal pain, and a mild haemorrhagic fever-like presentation is more common than in adults, whereas rash and arthritis may be rarer. Hospitalisation is more commonly required in children, due to the higher complication rate, and the greater complexity of providing symptomatic relief to young children.

In study of outpatients with Chikungunya in Thailand, children presented differently from adults, with most (71%) of children having pharyngitis. Vomiting was the most common presenting complaint (35%), and rash and arthritis/arthralgia were absent in all patients, and Chikungunya was responsible for 8% of suspected haemorrhagic fever cases, which were mild in presentation.[5,6] However, in a case series of 30 paediatric patients in Reunion with neurological complications, rash (67%) and arthralgia/pain (90%) were common, along with gastrointestinal symptoms (63%).[7]

Mother-to-child transmission of Chikungunya virus was first reported during the 2005-6 outbreak in Reunion.[8] All cases involved peri-partum transmission, and the transmission rate was believed to be about 50%. Mortality was higher than previously reported in older children and adults (3%, n=1/38), and significant morbidity was noted, with high complication rates. 40% of infants had complicated infection – neurological (neuropathy, meningoencephalitis, hypotonia, convulsions), cardiac (conduction disorders, myocardial hypertrophy, pericarditis, coronary artery dilatation), and hepatic manifestations were noted in addition to the haematological sequelae (thrombocytopenia, DIC). Interestingly, the complicated and uncomplicated cases presented with a syndrome more closely resembling adult Chikungunya (rash, fever, evidence of pain) than that described in older Thai children.

It is thought that children may also be more prone to Chikungunya infection. One explanation for this is that, in the afternoon, children are more likely than adults to take a nap, and during this time they are more prone to mosquito bites.

Vaccine development

Currently there is no vaccine available to prevent Chikungunya virus infection. Vaccine development halted in the early 2000s due to lack of funding and a concern over marketing. The vaccine had been a live attenuated vaccine, and had entered phase II clinical trials, but has not been pursued further due to concerns over safety and the low number of mutations required to back-mutate to wild-type virus. Subsequently a virus-like particle (VLP) vaccine has been developed and has shown promising results in a phase I trial.[9] Several other candidates are being developed but have yet to enter human trials.

Conclusion

Chikungunya is probably an under-diagnosed condition on the African continent, with paediatric Chikungunya, with possible atypical presentation, likely to be less easily identified. At present, Chikungunya shares most preventative measures – mainly vector control and bite prevention – with malaria, which in Africa is responsible for far greater mortality and morbidity. When confronted with unusual symptoms, especially pharyngitis, abdominal pain, or mild haemorrhagic symptoms, clinicians should consider the possibility of an atypical presentation of Chikungunya on the differential, and should consider enquiring about a history of rash and arthritis in the community.

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DENGUE FEVER IN KENYA

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During the 10th International Congress of Tropical Paediatrics (ICTP) held in Nairobi in August 2014, one of the priority conditions highlighted was arboviral illnesses including Dengue, Chikungunya, Yellow fever and West Nile viruses. Why? Arboviruses cause widespread morbidity and mortality in sub-Saharan Africa but their true incidence remains largely unquantified.

The global burden of dengue is large with an estimated 50 million infections occurring per year worldwide, but it is a neglected tropical disease more so in Africa. Dengue infections in Africa remain largely unquantified, but recent outbreaks suggest that substantial parts of the continent may be at risk for increasing dengue transmission. All 4 DENV serotypes have been documented to circulate in Africa. Outbreaks have been reported in Tanzania, Zanzibar, the Comoros, Benin, and Cape Verde and substantial numbers of cases reported in Angola, Kenya, and Somalia. Until recently, severe dengue had been reported infrequently in Africa.[1]

The apparent emergence of dengue fever in Africa is thought to be due to increased awareness of the disease, availability of better diagnostic tests, and improved access to specialized laboratories. However, the non-specific nature of dengue makes diagnosis difficult as it mimics the many febrile illnesses in Africa including malaria, bacterial and other viral infections. There is a low index of suspicion among clinicians where the disease is not recognized as endemic hence dengue is not considered in the differential diagnosis of these common conditions.

Dengue fever is an acute viral infection caused by 4 serotypes of the dengue virus of the flaviviridae family. Infection with one serotype produces lifelong immunity but only temporary and partial immunity against the other serotypes. In Africa, dengue is transmitted by the *Aedes Egypti* and *Aedes albopictus* mosquitos. Currently, there is no cure or effective vaccine for dengue infection.[2,3]

Clinical Presentation

Classic dengue disease is characterized by fever, headache, retro-orbital pain, bone and muscle pains, nausea and vomiting and often a rash. There are two important complications, dengue hemorrhagic fever and dengue shock syndrome. Severe dengue is a potentially life threatening illness. It presents with fatigue, abdominal pain, vomiting, hepatomegaly, hemorrhagic symptoms e.g epistaxis, heamaturia. Dengue shock syndrome presents with restlessness, cold clammy skin, rapid weak pulse, and narrowing of pulse pressured/or hypotension.

The Kenyan situation

In most parts of Kenya, many clinicians are unfamiliar with arbovirus infections and dengue and other arboviruses are not considered as differential diagnoses in acute febrile illness. Many unknown febrile illnesses are treated empirically with antimalarials and or antibiotics. However recently, an outbreak of dengue fever has been reported in Northern kenya and cases have also been reported in Eastern and Coastal parts of the country. Matilu et al identified that 16.6% of 1,462 serum samples surveyed in coastal Kenya (2012-2013) had evidence of recent exposure to Dengue virus. Surveillance studies have also identified dengue fever exposure in children in Western Kenya (Matilu *et al.* – unpublished) and in adults, North Eastern and Coastal provinces (Inoue *et al*., Sang *et al*. - unpublished).

In order to advance the understanding of the epidemiology of, and for effective strategies for control or prevention of dengue in Africa, the following issues need to be addressed: Dengue diagnostic tools must be made more widely available in the health care setting in Africa; representative data need to be collected across Africa to uncover the true incidence of dengue and more clearly define its transmission in the region; established networks should collaborate to produce needed types of data. Fourth, policy needs to be informed by improved information to take necessary steps for dengue vector control and provision of health services. Clinicians and the community need to be educated on the recognition of dengue infection.

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Acknowledgements

Dr Shingo Inoue, Dr Rosemary Sang & Professor Matilu Mwau provided unpublished data on the current situation on Dengue in Kenya which they presented at the 10th ICTP.

ANTIBIOTIC STEWARDSHIP: PRINCIPLES AND PRACTICE IN PAEDIATRICS

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As paediatricians, especially working in the field of infectious diseases, we all prescribe antibiotics. We must continue to prescribe these highly valuable life-saving therapeutic agents; we just need to do it in conscience.

Gould called it the “the perfect storm” whilst Owens talks about “an epic struggle for survival”.[1,2] They are describing the alarming international emergence of drug-resistant pathogens, both nosocomial- and community-acquired in nature. From the start of the antibiotic era in 1930s and 1940s, clinicians recognized that resistance against our arsenal of antimicrobial agents were increasingly documented. New entities such as pan-drug–resistant and extremely drug-resistant pathogens started to emerge. With only 2 antimicrobial agents that have novel mechanisms of action (linezolid and daptomycin) released during the last 2 decades, our resource of effective antimicrobial agents is critically low. Efforts to control the emergence of further drug-resistant pathogens need collaboration between multiple industries such as the health care sector and the agricultural community.

Although there is a paucity of publications about paediatrics prescribing practices in low-income and lower-middle-income settings, there is data that suggest that over-prescription of antibiotics for common childhood diseases such as coryzal symptoms and simple diarrhoea occur.[3]

The implementation of strategies to ensure the best use of the antimicrobials that are currently available and to prevent the development of bacterial resistance has become a priority for all health workers. Antibiotic stewardship (AS) is one such initiative. The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) published guidelines in 2007 for developing institutional AS programs. They defined the primary goal of AS programs: “to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance”.[4] Antibiotic Stewardship practices should also be adopted outside of hospital settings, because a large proportion of antibiotic prescribing occurs in outpatient clinics.

The overuse of antibiotics is driving the selection of antibiotic resistance. Given the right circumstances, the resistant bacteria that are selected out can either colonize a patient (be present, potentially transmissible, but not cause clinical disease i.e. infection) or cause infection. It follows that the more antibiotics that are used, the greater the likelihood of selecting out antibiotic resistance, and the broader the spectrum of antibiotic that is used, the greater the number of different types of resistant bacteria will be selected out. The fact that it is estimated that half of all antibiotics prescribed in human health are unnecessary e.g. for viral upper respiratory tract infections, demands our renewed efforts to make antibiotic prescribing appropriate. When it is indicated, an antibiotic must be the right choice at the right dose, dosing interval and route, and for the right duration, and when it is not indicated, that antibiotic must not be prescribed.[5]

Antibiotic stewardship principles

The 2 core strategies that form the foundation for an antibiotic stewardship program are (1) prospective audit with intervention and feedback and (2) formulary restriction and preauthorization.[4] An example of important core and supplemental strategies are summarised and available from the Centers for Disease Control and Prevention (CDC) website. The Get Smart for Healthcare campaign focus on improving prescribing practices in inpatient healthcare facilities and have resources that can be downloaded.[6]

The caring physician needs to be aware of the following basic principles of appropriate antibiotic prescription practices:

1. Timely antibiotic therapy management

In critical situations, such as in septic shock, antibiotic therapy is required urgently. Patients with risk factors for serious bacterial infections, such as febrile neutropenic patients, patients with indwelling catheters or immune-compromised individuals should receive the appropriate antimicrobial agents timeously. Antibiotic stewardship programs should have protocols and interventions in place to reduce time to antibiotic administration in the high risk patient group. Local clinics should have access to life-saving antimicrobials, such as intramuscular ceftriaxone, when patients present with a suspected life-threatening infections such as meningitis.[7]

Conversely, the overuse of antibiotics in both in- and outpatient settings is well described and is a major driver of antibiotic resistance. Studies have indicated overuse in paediatrics is common in children with respiratory diseases such as asthma, pharyngitis, and viral bronchiolitis. National and international management guidelines should be advocated to curb this trend.

2. Appropriate selection of antibiotics

Antibiotics are usually prescribed as either empiric or definitive therapy. For an appropriate empiric regimen, it is important to know the local pathogen-specific resistance rates, pathogen-specific epidemiology, and patient profiles. Specific resistance pattern of pathogens in the paediatric population is also an important consideration when guiding clinicians in selecting effective antibiotics. Strategies that are used by AS programs include selective susceptibility reporting, antibiotic consultation ward rounds in hospitals, restricted use of certain antimicrobials, antibiotic cycling programs, and antibiotic guidelines specific to each unit.

3. Appropriate administration and de-escalation of antibiotic therapy

Prospective surveillance and feedback of antibiotic use within a unit or hospital has been an effective tool to ensure appropriate antimicrobial usage. Therapeutic drug-level monitoring has been a valuable tool in identifying and correcting drug dosing and prescription. The design of protocols and standardized prescription orders to ensure that antibiotics are administered correctly in situation such as surgical interventions is important tools to reduce antimicrobial resistance. De-escalation of therapy should be prioritized, and can be achieved by reducing the number of antibiotics, selecting narrow- over broad-spectrum antibiotics, or converting parenteral to oral therapy.

4. Use of expertise and resources at point of care

Multidisciplinary teams are needed to help provide guidance to medical professionals in both the state and private hospital facilities. Teams consisting of infectious diseases specialists, pharmacists, microbiologists, infection prevention and control nurses can only be successful with support from hospital administration to provide appropriate authority and financial resources.

5. Continuous and transparent monitoring of antibiotic use

Finally, continuous and transparent monitoring of antimicrobial use to evaluate how and why certain antimicrobials are being used is an essential component of an AS program. Monitoring of the prescribing practices of medical professionals will enable prospective assessments of the effectiveness as well as the need for improvement of current AS programs, which in turn can lead to modifications in existing antimicrobial protocols. Developing standardized prescription charts is one example of an effective monitoring tool.

Conclusion

Antibiotic stewardship principles should be adapted by all institutions in order to govern and guide medical professionals in this very important daily task of preventing emergence of further resistant organisms whilst providing expert and appropriate antimicrobial treatment as indicated. All paediatricians should be committed to the practice and promotion of appropriate, timely, and efficacious antibiotic prescription in neonates and children.

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HIGHLIGHTS FROM THE 2nd SA HIV CLINICIANS SOCIETY CONFERENCE

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The 2nd Biennial Southern African HIV Clinicians Society Conference took place in Cape Town from 24 to 27 September 2014. The theme of this year's conference was 'Excelling in clinical care'. There was a strong paediatric track that focused on (1) HIV-infected adolescents, (2) neurocognitive issues, and (3) prevention of HIV in the 'high risk' infant and starting early ART in the HIV-infected neonate. This update will focus on these three key areas.

We were fortunate to have Dr Sabrina Bakeera- Kitaka from Makerere University in Uganda share her expertise on adolescents with HIV in a plenary lecture as well as during the clinical cases presentations. She along with Dr Candice Fick and Dr Lee Fairlie (both from University of Witwatersrand, RHI) highlighted the scale of the problem. In 2012 there were 2.1 million adolescents (10-19 years of age) living with HIV, 82% in sub-Saharan Africa and 58% of these were female. According to the WHO there were also 15 000 new infections in adolescents in 2012 and HIV

was the second leading cause of death in adolescents in that same year.[1]

Adolescents have increased risks of mental health problems such as anxiety, post-traumatic stress disorder, depression and suicide. In South Africa 18.5% of adolescents had considered suicide.[2] Other issues highlighted were alcohol and substance abuse. The comprehensive 'Friday Adolescent Clinic' at Mulago Hospital which offers a multitude of services including career counseling, life skills training, mental health assessments as well as medical examinations and sexual health services including contraception and HPV immunization provided us with insight on an ideal adolescent clinic.

Dr Mo Archary from the University of Kwa-Zulu Natal in South Africa presented the WHO adolescent guidelines and highlighted the differences between these and South African adolescent guidelines. WHO classify adolescents from 10 to 19 years and recommend starting antiretroviral therapy at a CD4 count below 500 cells/mm^3, or WHO Stage 3 or 4. Interestingly, the distinction between paediatric and adult staging is 15 years with adolescents falling in between. For adolescents above 35kg, WHO recommend TDF + 3TC (or FTC) + EFV. AZT and Abacavir are recommended if TDF cannot be used.

Dr Fick introduced a handbook 'Working with adolescents living with HIV: A Handbook for healthcare providers' developed through a collaboration between University of the Witwatersrand and the Southern African HIV Clinicians Society. The Handbook and accompanying Toolkit allows a holistic approach to the care of adolescents focus on issues of mental illness, neurocognitive disorders and disclosure.

Disclosure of HIV status to adolescents is essential to improve adherence and encourage participation (Mellins et al 2002, Menon et al 2007, Vreeman et al 2013) and retention in care, without increased risk of harm or increase in mental disorders after disclosure (Butler 2009).

Neurocognitive disorders in HIV-infected adolescents and children and the lack of specific neurocognitive screening tools for children were addressed. There is a spectrum of neurocognitive disorders in children which can result in decreased concentration, attention, memory and difficulties in learning and higher level functioning such as planning, decision making, judgement and organization. Dr Jaqueline Hoare (University of Cape Town) a paediatric psychiatrist with a special interest in HIV presented the role of neuroimaging in defining neurocognitive disorders. A systemic review of neuroimaging studies in vertically infected HIV-infected children and adolescents found that the most frequently reported brain abnormalities were ventricular enlargement, cortical and subcortical atrophy, basal ganglia involvement, frontal white and frontal grey matter abnormalities, calcifications and damage to the corpus callosum.[3] Other research by Dr Hoare and colleagues suggest that novel imaging techniques such as Diffusion Tensor Imaging (DTI) can elucidate underlying pathology in HIV-infected children. A study involving 'slow progressors' who were relatively asymptomatic and not needing ART showed that they scored significantly worse than their HIV- uninfected age -matched counterparts, correlating with their DTI results. Data from these DTI results suggests that demyelination may be the cause of this.[4] Another study following vertically infected HIV infected children found that increased radial diffusivity (RD), a measure of myelin loss, was associated with among other variables, lower haemoglobin and albumin, suggesting that there may be an association between treatable clinical variables such as malnutrition and anaemia and neurocognitive outcome (study ongoing).

In a symposium on HIV and the Neonate Professor Eley (and Dr James Nuttall) highlighted the urgency in starting children on ART in the first few weeks of life due to increased morbidity and mortality. A recent study showed that 62% of 403 infants who initiated cART at median 8.4 weeks of age had advanced HIV disease (CD4 <25% or <1500 cells/mm33or WHO Stage 3 or 4 and in the absence of ART, HIV-related mortality peaks at 2-3 months of age in South Africa.[5,6] Problems of the most appropriate regimen and doses were discussed. Kaletra® is contraindicated in the first two weeks of life and before a completed gestational age of 42 weeks due to reports of cardiovascular, renal and CNS toxicity. There is no data on the use of Abacavir in infants below 3 months. A suggested dose of Nevirapine of 6mg/kg to be used in full term infants was proposed. The ongoing P1106, P1110, P1097 and P1115 IMPAACT studies will hopefully advance our knowledge in this important area.

In another symposium focusing on 'PMTCT- getting to Zero -2015' Professor Louise Kuhn highlighted the possible benefits and disadvantages of the B+ approach and also the problem of NNRTI mutations among newly diagnosed PMTCT –exposed HIV infected infants.

The best poster award was awarded to Dr. Clair Edson and colleagues from Tygerberg Children's Hospital (Stellenbosch University) for 'Early outcomes of children on third line antiretroviral medications in a public health setting'. They described a small cohort of children successfully managed on third line ART using combinations of ritonavir boosted Darunavir, Raltegravir and Etravirine with other NRTIs. All children were virologically suppressed with minimal side effects.

In summary, the conference was well attended thanks to local and other African experts as well as international speakers, offered a practical, clinical update in HIV infection particularly relevant to practitioners on the continent.

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NEW AAP 2014 GUIDELINES ON BRONCHIOLITIS: IMPLICATIONS FOR PAEDIATRIC PRACTICE IN AFRICA

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Bronchiolitis, a viral lower respiratory tract infection, is one of the most common lower respiratory infections in infancy. It is characterized by acute inflammation, edema and necrosis of epithelial cells lining small airways, increased mucus production, and bronchospasm. The usual symptoms and signs of bronchiolitis typically include rhinitis, tachypnea, wheezing, cough, crackles, and use of accessory muscles, with or without nasal flaring[1].

The commonest cause is the respiratory syncytial virus (RSV), with ninety percent of children infected with RSV in the first 2 years of life[2], while up to 40% of them will have lower respiratory infection[3-5]. Usually, infection with RSV does not confer long-term immunity, and reinfections are common; often occurring throughout life[1]. Some of the other viruses that can cause bronchiolitis include human metapneumovirus, influenza, adenovirus, and parainfluenza virus[2].

The 2006 American Academy of Pediatrics (AAP) clinical practice guideline[2] that provided evidence-based recommendations on the diagnosis and management of bronchiolitis in infants less than 2 years of age emphasized using only diagnostic and management modalities that have been shown to affect clinical outcomes. The AAP based these recommendations on the conclusion that "bronchiolitis is a clinical diagnosis that does not require diagnostic testing".[2] "Many of the commonly used management modalities have not been shown to be effective in improving the clinical course of the illness. This includes the routine use of bronchodilators, corticosteroids, ribavirin, antibiotics, chest radiography, chest physiotherapy, and complementary and alternative therapies," the recommendation added[2]. The 2006 guideline[2] summarized thus:

- That clinicians should diagnose bronchiolitis and assess disease severity on the basis of history and physical examination. Clinicians should not routinely order laboratory and radiologic studies for diagnosis (recommendation).
- That clinicians should assess risk factors for severe disease such as age less than 12 weeks, a history of prematurity, underlying cardiopulmonary disease, or immunodeficiency when making decisions about evaluation and management of children with bronchiolitis (recommendation).
- That bronchodilators should not be used routinely in the management of bronchiolitis (recommendation).
- That a carefully monitored trial of α-adrenergic or β-adrenergic medication is an option. Inhaled bronchodilators should be continued only if there is a documented positive clinical response to the trial using an objective means of evaluation (option).
- That corticosteroid medications should not be used routinely in the management of bronchiolitis (recommendation).
- That ribavirin should not be used routinely in children with bronchiolitis (recommendation).
- That antibacterial medications should only be used in children with bronchiolitis who have specific indications of the coexistence of a bacterial infection. When present, bacterial infection should be treated in the same manner as in the absence of bronchiolitis (recommendation).
- That clinicians should assess hydration and ability to take fluids orally (strong recommendation).
- That chest physiotherapy should not be used routinely in the management of bronchiolitis (recommendation).
- That supplemental oxygen is indicated if the oxyhaemoglobin saturation (Spo_2) falls persistently below 90% in previously healthy infants. If the Spo_2 does persistently fall below 90%, adequate supplemental oxygen should be used to maintain an Spo_2 at or above 90%. Oxygen may be discontinued if Spo_2 is at or above 90% and the infant is feeding well and has minimal respiratory distress (option).
- That as the child's clinical course improves, continuous measurement of Spo_2 is not routinely needed (option).
- That infants with a known history of hemodynamically significant heart or lung disease and premature infants require close monitoring as oxygen is being weaned (strong recommendation).
- That clinicians may administer palivizumab prophylaxis for selected infants and children with chronic lung disease or a history of prematurity (less than 35 weeks' gestation) or with congenital heart disease (recommendation).
- That when given, prophylaxis with palivizumab should be given in 5 monthly doses, usually beginning in November or December, at a dose of 15 mg/kg per dose administered intramuscularly (recommendation).
- That hand decontamination is the most important step in preventing nosocomial spread of RSV. Hands should be decontaminated before and after direct contact with patients, after contact with inanimate objects in the direct vicinity of the patient, and after removing gloves (strong recommendation).
- That alcohol-based rubs are preferred for hand decontamination. An alternative is hand-washing with antimicrobial soap (recommendation).
- That clinicians should educate personnel and family members on hand sanitation (recommendation).
- That infants should not be exposed to passive smoking (strong recommendation).
- That breastfeeding is recommended to decrease a child's risk of having lower respiratory tract disease (recommendation).
- And finally that clinicians should inquire about use of complementary and alternative medicine (option).

On December 2, 2013, a retrospective, observational cohort study published online in Pediatrics [6] found that the use of chest radiography, steroids, and bronchodilators for infants and toddlers with bronchiolitis decreased significantly after the American Academy of Pediatrics (AAP) published evidence-based clinical practice guidelines in 2006. Antibiotic use also trended downward, but the magnitude of the change did not achieve statistical significance. "For hospitalized patients with bronchiolitis aged 1 to 24 months, we show a temporal association between publication of the 2006 AAP bronchiolitis

guidelines and a decrease in resource use, including both diagnostic tests (CBC [complete blood cell] count and CXR [chest radiography]) and therapies (corticosteroids and bronchodilators)," wrote the authors, who added that "although we cannot demonstrate a causal relationship, this reduction of diagnostic testing and treatment resources for bronchiolitis after guideline publication is striking and may be reducing costs associated with this common respiratory illness".[6] The authors however acknowledged the limitations of the study, which included the fact that administrative and billing database used by the researchers did not include detailed clinical information, and that the team relied on diagnosis and procedure codes to select patients. In addition, the database did not include community hospitals, which treat more than 70% of infants and toddlers with bronchiolitis.

The 2006 recommendations have recently been replaced by a new set of updated guidelines issued by the American Academy of Pediatrics (AAP) and published online on 27 October 2014 in Pediatrics.[1] While observing that bronchiolitis is the most common cause of hospitalization among infants younger than 1 year, the new guideline emphasizes that only supportive care, including oxygen and hydration, is strongly recommended for young children with bronchiolitis. The major changes included the following:

- That management of bronchiolitis in children aged 1 to 23 months no longer requires testing for specific viruses because multiple viruses may cause bronchiolitis.
- That routine radiographic or laboratory studies are also unnecessary, and clinicians should diagnose bronchiolitis and assess its severity on the basis of history and physical examination.
- That the AAP also no longer recommends a trial dose of a bronchodilator, such as albuterol or salbutamol, because evidence to date shows that bronchodilators are ineffective in changing the course of bronchiolitis (evidence quality: B, strong recommendation).
- That, in accordance with a policy statement published in July 2014 by the AAP[7], the new guideline updates recommend that though otherwise-healthy infants with gestational age of 29 weeks or more should not receive palivizumab; during the first year of life, infants with hemodynamically significant heart disease or chronic lung disease of prematurity should receive palivizumab (maximum of 5 monthly doses, 15 mg/kg per dose, during the respiratory syncytial virus season) [1, 7].
- That when making decisions about the assessment and management of children with bronchiolitis, clinicians should evaluate risk factors for severe disease, such as age less than 12 weeks, prematurity, underlying cardiopulmonary disease, or immunodeficiency.
- Finally, that clinicians should not give epinephrine to infants and children diagnosed with bronchiolitis, nor should they receive chest physiotherapy.

From an African stand point, these new AAP recommendations on management of Bronchiolitis[1] should not be read and implemented in isolation, but rather should be read and implemented together with the new 2014 WHO guidelines and recommendations for the management of pneumonia in children.[3]

There have been concerns that this guideline could easily be called a negative or a non-interventional guideline. The challenge is that while as much as possible guidelines ought to be evidence based, most of the available bronchiolitis related evidence can be described as negative. This guideline discourages diagnostic imaging or labs, and recommends that a history and physical should focus first on distinguishing viral bronchiolitis from other disorders. In most African paediatric practice settings, bronchiolitis is and remains a purely clinical diagnosis. Most children with what would be considered as bronchiolitis as per these AAP guidelines, are managed in Africa for pneumonia or severe pneumonia. Indeed the WHO in its guidelines released in late 2014[3] now categorises these children as either having pneumonia or severe pneumonia.

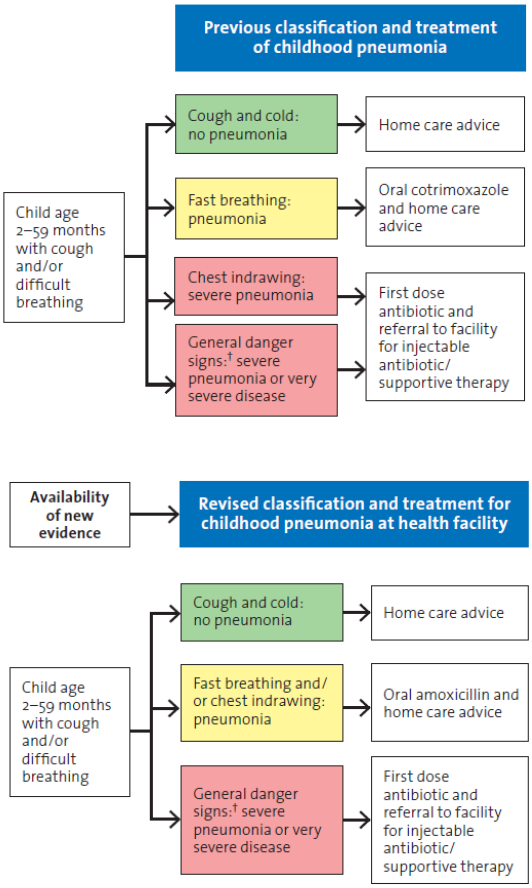

Figure 1: Comparison of the previous and 2014 revised WHO classification and treatment of childhood pneumonia[3] † = Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition

Opinion is divided on whether an algorithm from the AAP for management of bronchiolitis would have been helpful. Most African settings are greatly resource constrained, with patients hardly able to afford most of the expensive diagnostic investigations and virologic/radiologic studies that clearly appear to add little benefit to management decisions and outcomes in children with bronchiolitis. The lack of studies and trials makes development of an algorithm difficult. Younger children are more likely to suffer from severe disease, but that doesn't mean that all young patients will have severe bronchiolitis. While children born prematurely tend to have more severe bronchiolitis, there are many premature infants who have relatively non-severe bronchiolitis. Generally, babies have low tone, and the ability to cough is an important skill in weathering bronchiolitis. This enhances concerns that this guideline does not offer any good way of distinguishing disease severity, however patients who appear to require intensive care therapy may be handled differently. The

other challenge however is that there really aren't any specific therapies in the intensive care setting that have been proven to be particularly effective either. The revised 2014 WHO recommendations for pneumonia management are summarized in Table 1.

Recommendation 1 Children with fast breathing pneumonia with no chest indrawing or general danger sign should be treated with oral amoxycillin: at least 40mg/kg/dose twice daily (80mg/kg/day) for five days. In areas with low HIV prevalence, give amoxycillin for three days.
Recommendation 2 Children aged 2-59 months with chest indrawing pneumonia should be treated with oral amoxycillin: at least 40mg/kg/dose twice daily (80mg/kg/day) for five days.
Recommendation 3 Children aged 2-59 months with severe pneumonia should be treated with parenteral ampicillin (or penicillin) and gentamicin as first-line treatment.
Recommendation 4 Ampicillin (or penicillin when ampicillin is not available) plus gentamicin or ceftriaxone are recommended as a first-line antibiotic regimen for HIV-infected and –exposed infants and for children under 5 years of age with chest indrawing pneumonia or severe pneumonia. For HIV-infected and –exposed infants and for children with chest indrawing pneumonia of severe pneumonia, who do not respond to treatment with ampicillin or penicillin plus gentimicin, ceftriaxone alone is recommended for use as second-line treatment.
Recommendation 5 Empiric cotrimoxazole treatment for suspected *Pneumocystis jirovecii* pneumonia (previously *Pneumocystis carinii*) pneumonia (PCP) is recommended as an additional treatment for HIV-infected and –exposed infants aged 2 months up to 1 year with chest indrawing or severe pneumonia. Empiric cotrimoxazole treatment for *Pneumocystis jirovecii* pneumonia (PCP) is not recommended or HIV-infected and –exposed children over 1 year of age with chest indrawing or severe pneumonia.

Table 1: The revised 2014 WHO recommendations for managing pneumonia[3]

The current recommendation that albuterol, epinephrine, corticosteroid, antibiotics, and chest physiotherapy should not be used goes against a common practice to treat a child with bronchiolitis with albuterol and assess response, especially use of bronchodilators as relates to first-time-wheezing infants and those with atopy or a family history of asthma. In the African setting, adherence to the new WHO guidelines suggests that most of these children would satisfy the criteria for either pneumonia or severe pneumonia, and would thus each receive a course of antibiotic treatment. As discussed in the AAP guideline[1], while the Tucson Children's Respiratory Study[8] found that as high as 30% of children may wheeze before the age of 3 years, and about 5-10% of children go on to have asthma, it is still hard to predict which of those children are asthmatic the first time they wheeze, and recurrent wheezing does not accurately predict who will respond to albuterol.

With the risk of significant tachycardia, irritability, and other of the side effects from albuterol, the guideline committee appears to have concluded that the harm of exposing the larger cohort of infants to a trial of bronchodilators far outweighed the potential benefit when applied across the entire population. Another recommendation that may be challenging for some clinicians is that the use of continuous pulse oximetry in particular is discouraged now in this new guideline. Pulse oximetry has proved reliable in management of pneumonia and bronchiolitis children in Africa. Two recent studies on use of hypertonic saline in infants in the ED setting came to different conclusions[9, 10]. However, the AAP guideline endorsed its use in instances in which length of stay may be greater than 3 days, since short-term use of hypertonic saline doesn't have much clinical impact. A Cochrane review[11] published in 2013 showed a 1-day decrease in length of stay. While hypertonic saline may be useful in bronchiolitis, it appears that it may need to be administered in a sustained fashion over a relatively prolonged period.

In general, these new AAP guidelines may not change much in the management of bronchiolitis or pneumonia in children in Africa, and most would receive antibiotics if managed according to the new WHO 2014 revised recommendations for management of pneumonia in children.

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THE IMPORTANCE OF AETIOLOGICAL DIAGNOSIS OF PERSISTENT PARASITIC DIARRHOEA

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A 15-year-old male was brought to a local hospital with complaints of persistent intermittent diarrhoea over the past several months. Stools were non-bloody and watery with 10-12 episodes/day. The patient was severely dehydrated and cachexic with significant weight loss (12% in the last 3 months). Reports of routine biochemical investigations were within the normal limits. An HIV rapid test was Reactive and subsequently confirmed Positive by the hospital microbiology laboratory. One stool sample collected on the day of presentation was submitted to the laboratory and yielded no enteric bacterial pathogens and no parasites were seen on direct smear with iodine.

The attending physician may have some options available provided in national Standard Treatment Guidelines (STGs) and Essential Drugs Lists (EDLs) – care plans created by many leading African countries to ensure equitable access to standardized treatment for its citizens. For South African hospitalized children with persistent diarrhoea drug treatment with metronidazole for 7 days is indicated for *Giardia lamblia* infestation. The guideline indicates that no effective treatment is available for *Cryptosporidium* spp. No treatment guidelines or drug indications are provided for persistent diarrhoea caused by other parasites[1].

Persistent diarrhoea refers to diarrhoeal episodes of presumed infectious aetiology that begin acutely, but have an unusually long duration. The term does not include chronic or recurrent diarrhoeal disorders such as tropical sprue, gluten-sensitive enteropathy, other hereditary diarrhoeal disorders or blind-loop syndrome. Persistent diarrhoea does not represent a statistically determined subgroup of acute episodes, and its definition is arbitrary. In most studies it is operationally defined as an episode that lasts at least 14 days. Using this definition, studies in several developing countries have shown that 3-20% of acute diarrhoeal episodes in children less than 5 years of age become persistent[2].

Giardia lamblia and *Dientamoeba fragilis*, commonly referred to as intestinal flagellates typically respond well to the nitroimidazole group of drugs including metronidazole and the once a day tinidazole alternative, although resistance to metronidazole has been reported. The activity of the benzimidazoles (albendazole and mebendazole) and paromomycin is lower than that of nitroimidazoles[3]. Of the intestinal amoebae, *Entamoeba histolytica* is of greatest concern. Although the nitroimidazoles are effective tissue amoebicides targeting trophozoites, a luminal amoebicide effective against *E. histolytica* cysts are also required in the form of paromomycin, iodoquinol or diloxanide furoate[4]. *Cryptosporidium* is a well-known cause of persistent diarrhoea in children and adults, particularly those immunocompromised by HIV and malnutrition[5]. In the Western Cape province of South Africa Nel *at al.* identified a four times greater *Cryptosporidium* mortality in HIV-infected children than that of HIV-uninfected children with all deaths occurring in severely immune-compromised children[6]. The licensing of nitazoxanide in the United States in 2002 under the trade name Alina® was a landmark event. Nitazoxanide was the first new anti-Giardia drug released in more than 20 years. More significantly, it was the first ever drug licensed for treatment of cryptosporidiosis. Paromomycin has been disappointing in clinical trials against cryptosporidiosis and therefore antiretroviral therapy to improve $CD4^+$ cell count have been the only possibility of surviving cryptosporidiosis for many in resource limited settings without access to newer drugs[7]. The Ministry of Health in Zambia has made nitazoxanide available on the STG for children with chronic diarrhoea, recognizing the significance of targeted therapy aimed at this opportunistic pathogen[8]. Other African countries should consider similar programs which will have the benefit of necessitating improved laboratory diagnostic services to identify the drug targeted parasite.

Although the flagellates, amoebae, and *Cryptosporidium* are well known parasitic causes of persistent diarrhoea they are by no means the only groups of parasites that should be considered in children with diarrhoea. The coccidia of humans include *Isospora belli*, *Cyclospora cayetanensis*, *Sarcocystis hominis* and *S. suihominis*. These infestations are increasingly recognized as causing persistent diarrhoea in children and adults in Africa[9-12]. The coccidia respond to prolonged therapeutic doses of trimethoprim-sulphamethoxazole, typically not listed for treatment of chronic diarrhoea in STG's. Furthermore, the contribution of microsporidia, a group of small parasitic organisms comprising *Enterocytozoan*, *Encephalitozoan* and other genera, are increasingly recognized as significant causes of persistent diarrhoea in immunocompromised adults and children, including renal transplant recipients[10,13,14]. Microsporidia respond favourably to the benzimidazole drugs including albendazole and mebendazole, given for 21 days, much longer than the typical 3 to 5 days therapy effective against intestinal worm infestations[15].

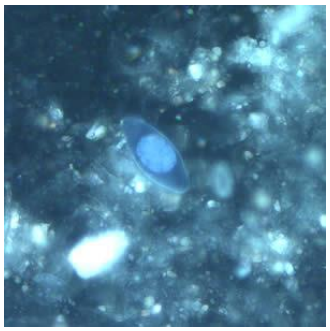
Many pathology laboratories in Africa, and elsewhere in the world, are embarking on laboratory capacity strengthening efforts in collaboration with international partners to improve diagnostic capabilities, including the differential diagnosis of opportunistic infections. The direct wet- and iodine smears traditionally used for intestinal parasitic diagnosis fall short on the ability to reliably detect and differentiate many emerging aetiologies. Improved detection of the coccidia can be achieved using the characteristic autofluoresence of *Isospora* and *Cyclospora* oocysts and the sporocysts of *Sarcocystis* by fluorescence microscopy (excitation at 450 – 490 nm which is the same used for tuberculosis microscopy). If a fluorescent microscope is not available, the laboratory may choose one of the acid-fast stains such as the modified Kinyoun's or modified Ziehl-Neelsen's acid-fast stains which will also improve detection of *Cryptosporidium* spp. Sensitivity can be improved with relatively simple stool concentration techniques such as the formalin-ethyl acetate sedimentation technique[16]. To identify microsporidia laboratories may choose to implement a special stain such as the Ryan's modified acid-fast trichrome stain[17,18] or opt to maximize utilization of a fluorescent microscope by using a fluorochrome stain such as Uvitex 2B or Calcofluor White stain[19]. In addition to traditional microscopic methods, rapid diagnostic methods based on antigen detection may become more popular in the future when reagents become more affordable.

Syndromic management of persistent diarrhoea has undoubtedly saved millions of lives, however, the limited activity of drugs recommended by STGs and EDLs combined with the emergence of previously unrecognized aetiologies are necessitating the improvement of pathology services to support the management of diarrhoea, malnutrition and ultimately bringing the Millennium Development Goals within reach. Malnutrition

is a major contributor to mortality and is increasingly recognized as a cause of potentially lifelong functional disability. Yet, a rate-limiting step in achieving normal nutrition may be impaired absorptive function due to multiple repeated enteric infections. This is especially problematic in children whose diets are marginal. In malnourished individuals, the infections are even more devastating[20].

It is most important to ascertain the etiologic agents of diarrhoea in children in developing countries, as this is the predominant group that dies from diarrhoea and is subject to the vicious cycle of diarrhoea and malnutrition. Aetiological diagnosis of chronic intestinal parasitosis is necessary as the clinical presentation, haematological markers and biochemical parameters are not predictive of the presence of pathogens, or the site of infection. In addition, identification of the cause of disease prevents unnecessary and costly invasive endoscopy and biopsy procedures[21]. Recognition of the aetiological causes contributing to the burden of diarrhoea morbidity and mortality will permit a more informed allocation of resources for the development of treatments and vaccines and should be a research priority[22].

From the case presented, two subsequent stool specimens were subjected to concentration and fluorescent microscopy. *Isospora belli* oocysts, measuring 32 µm X 14 µm was identified. The patient was treated with trimethoprim-sulfamethoxazole (160/800mg) *q.i.d* for 12 days resulting in a decrease of diarrhoea and a decrease of abdominal pain within 3 days after treatment. After day 12 of treatment three stool specimens were cleared of oocysts. Many parasites appear in stool on a cyclical basis and a series of two or three specimens is considered a minimum for an adequate examination. Specimens should be collected every other day or every day, but not within the same day.



The Ministry of Health of Zambia has set an example by including nitazoxanide in the STG for the treatment of *Cryptosporidium*-associated persistent diarrhoea in children. With improved pathology services for aetiological diagnosis and targeted therapy successful control of persistent diarrhoea is possible and within reach.

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INTRODUCTION OF HPV VACCINE IN SOUTH AFRICA

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The following article is based on two talks presented at the at 11th annual Vaccinology Scientific Conference, which took place on 20 & 21 October 2014 at the Fairmont Zimbali Resort, Ballito, South Africa.[1,2]

Global epidemiology

Human Papilloma Virus (HPV) is the cause of cervical carcinoma. It is also linked to cancers of the anus, vulva, vagina and penis, and causes benign muco-cutaneous lesions such as genital warts, skin warts and laryngeal papillomatosis. Recent estimates indicate that HPV causes 5% of all malignancies and 100% of cervical carcinomas. Cervical carcinoma is the second leading cause of cancer among women and the leading cause of cancer among African women. In 2012, an estimated 528,000 new cases of cervical carcinoma occurred and approximately 266,000 women died of cervical carcinoma throughout the world. More than 85% of cases and deaths occurred in low- and middle-income countries.[3]

Important HIV types

Human Papilloma Virus is a non-enveloped double-stranded DNA virus belonging to the family Papillomaviridae. More than 190 types of HPV have been identified, based on the genetic sequence of the outer capsid protein L1. Twelve of these types are considered "high risk" because of their oncogenic potential i.e. types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Types 16 and 18 are responsible for approximately 70% of all cervical carcinoma. Other types are responsible for benign muco-cutaneous lesions. Types 6 & 11 are responsible for >90% of anogenital warts. Types 6 & 11 also cause the rare condition, recurrent respiratory papillomatosis.[3,4]

Up to 80% of women will acquire HPV infection during their lifetime, commonly within 2-5 years of onset of sexual activity. "High risk" types cause approximately 50% of all these HPV infections. Most of these infections are asymptomatic and clear within 2 years of acquisition. Only a small proportion of infections caused by "high risk" types progresses to cervical carcinoma.[1,4]

HPV vaccines

HIV vaccines are sub-unit vaccines composed of the L1 protein of specific HPV types. The L1 protein molecules self-assemble forming virus-like particles, i.e. empty protein shells without viral DNA. Two commercially manufactured vaccines have been licensed in South Africa, (1) a bivalent vaccine directed against types 16 and 18, registered for use in females aged 10 to 25 years of age for the prevention of cervical cancer and precancers, and (2) a quadrivalent vaccine directed against types 6, 11, 16 & 18, registered for use in females aged 9 to 26 years for the prevention of cervical cancer and precancers, and for males aged 9 to 26 years for the prevention of genital warts. Both vaccines are licensed for use in 3-dose schedules. Both vaccines are well tolerated and safe, and both have an efficacy in excess of 90% for preventing persistent infection, pre-cancerous and cancerous leasions caused by types 16 & 18. In addition, the quadrivalent vaccine confers almost 100% protection against anogenital warts associated with typs 6 & 11.

WHO position

The World Health Organization first published a position paper on HPV vaccination 2009 in which it advocated routine HPV vaccination provided that (1) prevention of cervical carcinoma and other HPV-related disease is a health priority, (2) vaccine introduction is programmatically feasible, (3) sustainable funding can be secured, and (4) the cost-effectiveness of vaccination has been considered in the country or region.[5]

In April 2014, the WHO's Strategic Advisory Group of Experts (SAGE) on immunization was requested to consider optimal HPV vaccination schedules in girls. Based on a review of the existing evidence, SAGE concluded that a 2-dose prime-boost schedule given with a minimum interval of 6 months was non-inferior to a 3-dose schedule. It reiterated the importance of targeting HPV vaccination for girls aged 9 – 13 years prior to initiation of sexual activity, and futhermore recommended (1) a 2-dose schedule with an interval of at least 6 months between doses for girls <15 years of age (even for girls aged ≥15 years at the time of their second dose), (2) if for any reason the interval between the 1st and 2nd doses is shorter than 5 months, a 3rd dose should be administered at least 6 months after the first dose, and (3) a 3-dose schedule (0, 1-2 & 6 months) is recommended for girls >15 years of age and for immunocompromised subjects including those known to be HIV-infected. These recommendations apply to both bivalent and quadrivalent vaccines.[6]

A revised WHO position statement published in October 2014 incorporates these SAGE recommendations. While focussing on the prevention of cervical carcinoma, the new position statement also considers the broader spectrum of cancers and benign diseases that are preventable by HPV vaccination.[4]

Cervical cancer screening

HPV vaccination should not be regarded as an alternative to cervical cancer or "pap" smear screening. Approximately 30% of cervical carcinomas are caused by non-16 & -18 HPV types. Therefore, routine cervical cancer screening should continue to be offered.[1]

HPV vaccination in South Africa[2]

In South Africa, approximately 5750 women develop cervical carcinoma and more than 3000 die from cervical carcinoma each year. The Minister of Health during his 2013 budget speech announced that South Africa would introduce the HPV vaccine in 2014.

The HPV vaccination programme uses the bivalent vaccine (types 16 & 18) and targets all girls in grade 4 who are more than 9 years of age. The programme focusses on girls attending public schools including special schools. Girls attending private schools are currently excluded from the programme. In 2013, the target group was estimated to be approximately 500,000 girls in 17,000 schools based on data provided by the Department of Basic Education (DBE). A 2-dose schedule was adopted.

A National HPV Working Group was convened to co-ordinate the HPV vaccination programme. Provincial, district and facility plans were devised to ensure that all schools within the drainage area of health facilities designated to administer the HPV vaccinewould be covered. The 1st round of the annual HPV vaccination campaign (dose 1) was completed between 10 March and 11 April 2014, and dose 2 was completed between 29 September and 31 October 2014. Prior to the 1st round of the campaign, provinces, districts and sub-districts were visited to ensure readiness. Furthermore, extensive social mobilization and communication with all stakeholders preceded the 1st campaign. Health professionals also received HPV vaccination training. The results of the 1st round of the campaign are summarised in Table 1.

In conclusion, while HIV vaccination has been successfully launched in South Africa, several challenges remain including difficulty reaching the target population, the cost of vaccination, whether or not girls attending private sector schools would be integrated into this programme, and the integration of HPV vaccination into the country's national immunization programme.[2]

School Coverage	
The projected, total number of schools based on DBE data	17,629
Number of schools visited during the 1st round of the campaign	15,771
Percentage of schools visited	89.5% (target = 80%)
Coverage of targeted population	
Projected number of girls i.e. the number of girls in grade 3 in 2013	476,722
Number of girls in grade 4 identified by the HPV teams prior to vaccination	463,051 (95% of projected girls)
Number of eligible girls in grade 4 i.e. >9 years of age	408,273 (12% of girls <9 years)
Number of girls who received the 1st dose of HPV vaccine	353,564 (87% of eligible girls; target = 80%)

Table 1: Summary of the 1st round of the HPV vaccination campaign, conducted in March & April 2014

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HIGHLIGHTS FROM THE 9TH INTERNATIONAL RSV CONFERENCE

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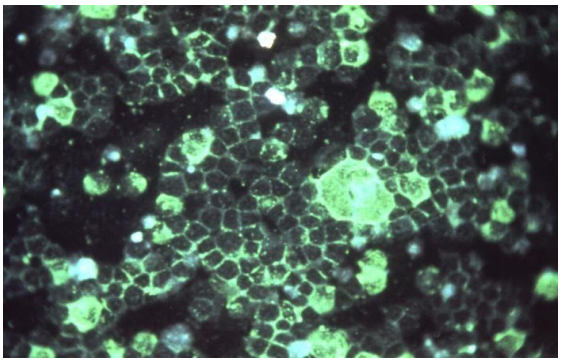
The 9th International respiratory syncytial virus (RSV) symposium held at Spier Hotel and Conference Centre in Stellenboch, between 9th and 13th of November, 2014 with the sub-theme RSV – A global health challenge, to bring to attention to the burden of the disease in both industrialized and developing countries. The conference was hosted by the South African Society for Paediatric Infectious diseases (SASPID). Topics such as epidemiology, clinical aspects, diagnostics, molecular biology, immunology and vaccines were addressed. RSV is also major cause of pneumonia in young children, the elderly and immunocompromised. Globally, RSV is the most common cause of acute lower respiratory tract infections (ALRI) – broncholitis and pneumonia, in children and a major cause of admission to hospital as a result of severe acute respiratory infection- pneumonia and bronchiolitis. Globally, it is estimated that RSV causes more than 30 million new ALRI annually, resulting in more than 3.4 million hospital admissions, and as many as 199,000 deaths annually in children younger than 5 years of age. One-third of RSV-related deaths occur in the first year of life, with 96 percent of these deaths occurring in low-resource countries.[1]



Among children, the well documented predisposing factors include prematurity, congenital heart disease and bronchopulmonary dysplasia.[2]

Among HIV-infected children, prolonged hospitalization and increased number of mortalities are associated with RSV infection. It has also been noted that HIV-infected children shed virus asymptomatically for many months.[3]

Source of RSV infection

With regards to epidermiology of RSV, Patrick Munywoki from KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya, presented data on the source of RSV infection in households. In a household study of 493 individuals in 47 households, 17000 nasopharyngeal swabs were collected during 2010 and analysed using multiplex PCR, targeting RSV among other respiratory viruses. RSV was detected in 37 households (84%) and 173 participants (38%) and 28 study infants (64%). The infants acquired infection from within (15 infants; 54%) or outside (9 infants; 32%) the household. In 4 households the source of infant infection was inconclusive. Older children were index case patients for 11 (73%) of the within-household infant infections and 10 of these 11 children were attending school. The importance of older children in introducing RSV into households with young infants was highlighted from these findings. Children in daily contact with many other children, particularly in schools, are important in bringing RSV infections into the households. Vaccine targeting older siblings may help break the chains of transmission. Universal vaccination of older infants and children will also offer indirect protection.[4]

Clinical aspects of RSV in children

The session on the clinical aspects of RSV infections in children started with a keynote lecture by Louis Bont titled "clinical aspects of RSV brochiolitis, any gaps in knowledge left".

He identified gaps in the epidemiology of RSV infection, including gender, age, mortality, bacterial coinfection, relationship with asthma, viral interference, risk for Sudden Infant Death Syndrome, elderly, prediction severe infection, normal children and seasonality. Some of these gaps are discussed below.

Gender

The first gap identified was bias in gender as a risk factor for RSV infection. There are differences in the reports about gender bias among researchers. The overall incident rates increased in boys.[5] Male gender has been identified as a risk factor for severe disease. For many

pathogens susceptibility is higher in males, which can be partially explained by the observation of stronger Th1 immune responses in females.[6] Yet, data from a 5-year, prospective, population-based surveillance for young children hospitalized who had RSV acute respiratory illness showed that the overall seasonal rates of RSV hospitalization were not significantly affected by gender.[7]

Age

The age distribution of patients with RSV ALRI at the time of RSV admission was another gap identified. There are conflicting reports on the age distribution of RSV ALRI. Immune immaturity in neonates may be associated with imbalanced RSV-specific immune responses that favour disease enhancement particularly in premature infants born before 28 weeks of gestation, before transfer of maternal antibody occurs.[5] It is well documented that RSV ALRI is most commonly observed during the first 3 to 6 months of life.[8] From Kilifi, Kenya, a hospital RSV surveillance study also showed that 37% of RSV disease was in children aged less than 3 months, and 58% in those less than 6 months of age.[4]

In contrast, a population based study from Indonesia reported that the highest incidence was found at the age of 6 to 24 months. The incidence of RSV ALRI in children less than 6 months was low and none was recorded in infants less than 3 months of age.[9] The full explanation for the lack of RSV in children less than 3 months of age is not clear.[10] One possible explanation could be protection by maternal antibodies.[11] However, protection provided by maternal antibodies is only partial.[12]

RSV and asthma

A gap was also identified in the relationship between asthma and RSV infection. The causal relationship between the two conditions is not yet conclusive. Abnormal preexisting lung function may increased risk of asthma in RSV hospitalised bronchioloitis. The role of premorbid lung function in the severity of RSV disease has been suggested in preterm and high risk infants. Furthermore, impaired neonatal lung function was found to precede a severe course of RSV infection in term infants, accounting for the majority of hospitalizations for RSV bronchiolitis in a recent study. This study also provided evidence that decreased lung function at birth predisposes to post-RSV wheeze.[13]

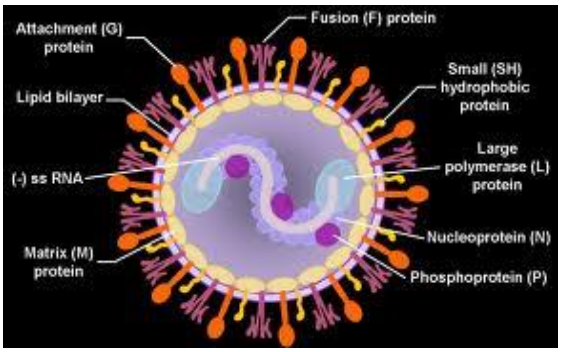
Tina Hartert presented evidence for the role of RSV in the development of asthma. RSV broncholitis contributes significantly to the burden of asthma as up to 40 % of all children experience wheezing after an RSV infection.[14] RSV infection was implicated as an important mechanism of recurrent wheeze during the first year of life in healthy preterm infants in a randomized controlled trial that showed a significant reduction in wheezing days after treatment with palivizumab.[15] RSV ALRI has also been shown to be an independent risk factor for the subsequent development of wheezing.[16]

There is also ecological evidence documenting an increased broncholitis rate in parallel with an increase in asthma prevalence in the same populations of children[17] Host determinants are also important as immune response genes in the host are genes associated with both severe RSV infection and asthma.[18] Biological mechanisms may also be involved as infection results in clinical, immunologic and pathologic changes in animal models that are similar to asthma phenotype.[19]

Pathophysiology & vaccine development

There are two major RSV genetic subtypes, A and B. These subtypes co-circulate, and the predominance of one over the other varies by year and geographic location.[20] The two major glycoproteins on the surface of the respiratory syncytial virus (RSV) virion, the attachment glycoprotein (G) and the fusion glycoprotein (F), control the initial phases of infection. G targets the ciliated cells of the airways, and F causes the virion membrane to fuse with the target cell membrane. The F protein is the major target for antiviral drug development, and both G and F glycoproteins are the antigens targeted by neutralizing antibodies induced by infection.

RSV has an important effect in the architecture of the lung. The pathologic process in RSV is characterized by acute inflammation, oedema, and necrosis of epithelial cells lining small airways, increased mucus production and bronchospasm.



Natural infection with RSV does not provide complete protection against future infection. RSV through poorly understood mechanisms evades local adaptive immunity and can cause repeated infections. The first infection is generally most severe, while re-infections usually associate with a milder disease.

It is over 50 years since the discovery of the virus and no safe and effective vaccine is currently available. No vaccine exists today to prevent RSV infection due to an incomplete understanding of the body's immune response to the virus, which has challenged and delayed RSV vaccine development efforts. The lack of success to date highlights the biological difficulties in developing an RSV vaccine. However, the efficacy of immune prophylaxis suggests a safe and effective vaccine is achievable. The epidemiologic and pathophysiologic characteristics of RSV suggest that there is potential for designing different vaccine types for different target populations - young infants, young children, pregnant women and the elderly.[21]

Vaccine development for RSV faces several unique challenges which include the young age of infection, the multiple mechanisms RSV uses to evade innate immunity, lack of durable protective immunity induced by natural infection, vaccine-enhanced disease and animal models do not faithfully replicate the pathogenesis of human RSV.[22] Apart from the immaturity of the immune system of infants, presence of maternal RSV-specific antibodies are associated with suboptimal vaccine responses.

The first vaccine against RSV was developed in the 1960s but was associated with a devastating outcome. Vaccine-enhanced disease was first observed in clinical studies of the formalin-inactivated RSV vaccine (F1-RSV). Younger FI-RSV recipients experienced more severe RSV disease requiring hospitalization when naturally infected with RSV after having been vaccinated. Vaccination also caused two deaths.[23] The full explanation for the vaccine adverse related events is not fully understood. Possible mechanisms of RSV enhanced disease include stimulation of innate immunity, antibody presentation and cellular immunity.[24,25,26]

An ideal RSV infant vaccine candidate must therefore, be safe and suitable for administration early in life to infants since they bear the greatest burden of the disease. The vaccine needs to provide protection in the presence of maternal antibody, not interfere with the safety or efficacy of other vaccines routinely administered to infants (and vice versa), and elicit protection with minimal reactogenicity.[27, 28]

Current vaccine approaches

An infant vaccine
Peter Colin presented current vaccine approaches with regards to RSV vaccines. There are several vaccine candidates under various stages of development targeting RSV. The replicating vaccines are the live attenuated RSV, live vectors and nucleic acid while the non-replicating vaccines include the inactivated vaccine, subunits and peptides.

The advantages of live RSV vaccines are that they are not associated with enhanced disease, intranasal administration is needle-free and these vaccines induce broad stimulation of the immune system. However there is a concern that compensatory mutations in the live-attenuated vaccines may cause reversion to pathogenic phenotypes and lead to increased frequencies of adverse reactions *in vivo*.[28]

Reverse genetics offers the opportunity of developing live-attenuated RSV vaccine candidates with improved features. RSV ΔM2-2 (deletion of RNA regulatory protein), RSV cps2 (partially stabilized) and RSV ΔNS2Δ1313 are live attenuated native RSV candidate vaccines undergoing clinical trials in sero-negative infants and are showing some promise. Human parainfluenza virus (hP1V) types 1, 2 and 3 have been used as vectors for RSV-F (RSV-G) protein. The advantage is the provision of bivalent hPIV and RSV vaccine protecting children from both infections. When compared to the live-attenuated RSV vaccines, the vector based vaccines are more stable in response to environmental temperature changes, an important consideration, especially for developing countries.

Maternal immunization & rationale for maternal immunization
Immunization of pregnant women may provide passive protection for infants until their airways are larger and till active immunization can be more effective.

Administering certain vaccines to pregnant women can help improve the mother-to-child transmission of antibodies, which can provide critical protection during the early stage of a newborn's life when direct vaccination is not an effective option. Some infectious diseases cannot be addressed with current infant immunization strategies. Maternal immunization has been shown to be effective for diseases such as tetanus, influenza and pertussis.

As the immaturity of the infant immune system and interference from maternal antibodies may be problematic, there is potential through maternal immunization for protection of 2 individuals with one strategy. The risk of vaccine enhancement is also reduced.

RSV vaccine candidates appropriate for maternal immunization use the non-replicating; protein based approach inducing neutralizing antibodies to RSV fusion protein. RSV F glycoprotein is the primary target for subunit vaccines. Furthermore, most neutralizing antibodies are directed against RSV F and there is little antigenic variation in RSV F (unlike RSV G).

Passive immunoprophylaxis - monoclonal antibody

RSV antibodies delivered prophylactically to children reduced the incidence of severe RSV disease. Palivizumab is a humanized monoclonal antibody against the RSV F glycoprotein. It binds to highly conserved region on the extracellular domain of the pre-fusion and post-fusion F, referred to as antigenic site II. It is given as monthly injections, begun just prior to the RSV season and continued for 5 months. Palivizumab does not interfere with response to routine immunization with live virus vaccines

Palivizumab is the only product approved for prevention of serious RSV disease. The effectiveness and safety of palivizumab in reducing the risk of complications (hospitalization due to RSV infection) in high-risk infants and children was assessed in a systemic review. Palivizumab prophylaxis reduced the risk of RSV hospitalization by 50% when compared to placebo.[29]

Immunoprophylaxis is currently recommended for preventing severe RSV infection in infants and children with prematurity, bronchopulmonary dysplasia (BPD)-chronic lung disease of prematurity and congenital heart disease.[30]

Palivizumab has benefits and limitations. One of the draw backs apart from cost is the fact that five injections are required. It may have an impact for high risk infants in urban settings with access to health care facilities. There will also be a need for preterms to benefit from maternal antibodies (active transport of maternal antibodies occurs during the third trimester), and too young for paediatric vaccines. Preterm birth rates are increasing in almost all countries with reliable surveillance data.[31]

Future prospects
For RSV therapeutic interventions, palivizumab is not a standard health-care intervention in the majority of low- and middle-income countries because of high cost. The World Health Organization (WHO) presented its plans for therapeutics for high risk infants in low income countries. Palivizumab having been proven to be effective and safe, immunoprophylaxis for RSV is to come off patent in 2015. The development of a "biosimilar" of palivizumab is planned which will reduce costs for the 5 doses. One of the WHO's role in RSV vaccine development is the publication of guidance on trial design for RSV vaccines, to include guidance on clinical development pathways to support global use. A surveillance system to support vaccine introduction in young children would be established later.

Conclusion

There have been recent advancements in research on the epidemiology, pathogenesis, immunology and vaccine development of RSV infection, and yet the absence of an licensed vaccine persists. The development of a safe and effective vaccine against RSV is critical to protect children from the disease but there are biological challenges and safety concerns which have prolonged the RSV vaccine development process. With many candidates at various stages of the RSV vaccine pipeline, it is hoped that a successful vaccine will be achieved in the near future As the majority of the burden of RSV disease lies in low-middle-income countries, these populations need to be factored into product development to ensure that affordable interventions become available.

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JOURNAL WATCH

Poliovirus type 3 – eradicated?

Review completed by Stephen Korsman

Since 1988, the eradication of poliovirus has been planned. Smallpox had previously been eradicated, and subsequently Rinderpest virus, a bovine morbillivirus, was declared eradicated in 2011. The last natural infection with wildtype poliovirus type 2 was seen in 1999 in India. Now there is the possibility that wildtype poliovirus type 3 has also been eradicated, as no cases have been reported since November 2012. The announcement comes after a 2-year absence of detection. However, it is likely that it will be only after 3 or more years without detection that eradication will be formally declared – in some countries still affected by polio, surveillance is not adequate, and cases may be missed.

In 2014, 9 countries reported wildtype poliovirus detection – Afghanistan; Cameroon; Equatorial Guinea; Ethiopia; Iraq; Nigeria; Pakistan; Somalia; Syrian Arab Republic – of which only Afghanistan and Pakistan reported more than ten cases.

While the trivalent vaccine (containing Sabin viruses 1, 2, and 3) has, in many places, been replaced with a bivalent vaccine or two monovalent vaccines, it is too early to consider removing Sabin virus 3 from circulation, and it is likely that it will continue to be used for several more years.

Reference: Kew OM, Cochi SL, Jafari HS, et al. Possible eradication of wild poliovirus type 3 - worldwide, 2012. MMWR Morb Mortal Wkly Rep 2014;63:1031-3.

Impact of vaccination on invasive pneumococcal disease

Review completed by Brian Eley

Until recently, the benefits of pneumococcal conjugate vaccines have not been quantified at a national-level in Africa. This situation has now changed. A recent report describes the impact of pneumococcal conjugate vacine (PCV) in South Africa. South Africa introduced PCV7 into its exapnded program on immunization (EPI) in April 2009 using a novel 2 + 1 schedule at 6 weeks, 14 weeks and 9 months of age. In April 2011 PCV7 was replaced with PCV13. In this publication the researchers used data from a laboratory-based surveillence system to calculate the change in incidence of invasive pneumococcal disease (IPD) from a pre-vaccine period (2005-2008) to a post-vaccine period (extending to 2012) in high-risk age groups. The analysis showed that rates of IPD declined substantially in children and adults, reflecting both the direct and indirect effects of the national childhood immunization programme.

Reference: von Gottberg A, de Gouveia L, Tempia S, et al. et al. Effects of vaccination on invasive pneumococcal disease in South Africa. N Engl J Med 2014; 371: 1889-99.

CONFERENCE & SOCIETY NEWS

4th Congress of the African Society for Immunodeficiencies (4th ASID): This conference takes place from 27 - 29 May 2015. For more information visit the ASID website: http://www.asid.ma/

7th SA AIDS conference takes place from 9 – 12 June 2015 at the International Convention Centre, Durban, South Africa. For more information consult the conference website: http://www.saaids.co.za

3rd International Conference on Prevention & Infection Control (ICPIC 2015) takes place from 16 – 19 June 2015 in Geneva, Switzerland. For more information visit the conference website: http://www.icpic.com/index.php/conference/icpic-2015

7th International Workshop on HIV Pediatrics: This annual workshop takes place on 17 & 18 July 2015 in Vancouver, Canada. For more information consult the conference website: www.virology-education.com

6th FIDSSA Congress takes place from 5 – 8 November 2015 at the Champagne Sports Resort, Drakensberg, KwaZulu Natal, South Africa. For more information consult the FIDSSA website: http://www.fidssa.co.za

18th International Conference on AIDS and STIs in Africa (ICASA) takes place from 8 – 13 November 2015 in Tunis, Tunisia. For more information consult the conference website: http://www.icasa2015tunisia.org

9th WSPID conference takes place from 18 – 21 November 2015 in Rio de Janeiro, Brazil. For more information visit the Paediatric Infectious Diseases Society website: http://www.pids.org/ AfSPID will once more host a dedicated symposium at this conference.

46th Union World Conference on Lung Health: This conference takes place from 2 – 6 December 2015 in Cape Town, South Africa. For more information visit the conference website: http://www.theunion.org/what-we-do/conferences/world-conference-on-lung-health/46th-union-world-conference-on-lung-health

17th International Congress of Infectious Diseases (ICID 2016) takes place from 2 – 5 March 2016 in Hydrabad, India. For more information consult the conference website: http://www.isid.org/icid/

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Research feature: Research feature should be preceded by a 200 - 300 word biosketch of the featured young researcher. The research commentary should have a maximum of approximately 3000 words and 40 references.

Conference report: An introductory paragraph is recommended in which the conference details and focus is described. The conference report should focus on new developments and what they mean for African settings. Maximum of approximately 2500 words, 40 references, and 6 tables, illustrations or pictures.

Case report: The main elements should be an introduction, the case report and the discussion. Maximum word count of approximately 1500 words, 15 references and 3 tables, illustrations and/or pictures.

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