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Position paper:

The use of a Pediatric Prophylactic Vaccine for Respiratory Syncytial Virus in Kenya

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Executive summary

The objective of the present paper is to document the burden of disease and associated costs due to respiratory syncytial virus (RSV) and perceived use of a future pediatric prophylactic vaccine for RSV in Kenya in order to inform local decision-makers as well as to evaluate whether the context is favorable for RSV vaccine trials to protect young children in Kenya.

A brief literature review was done in order to identify gaps in available data of the epidemiology of RSV in developing countries. The burden and costs associated with RSV in Kenya were estimated. The state of pediatric prophylactic vaccine development was reviewed. Finally, perceptions of key stakeholders at the international and national levels regarding feasibility and desirability of an RSV vaccine were also documented.

There remain information gaps regarding RSV associated burden, particularly in developing countries where the vast majority of severe cases and deaths occur. There are insufficient long term studies and few studies that look at within country variation geographically and factors relating to this. More information is needed on the incidence of RSV in young children as current estimates vary considerably between studies. Post-mortem assessment of children dying of respiratory infections should be considered as the mortality due to RSV is poorly defined and in all likelihood underestimated. Potential long term sequelae of RSV must be verified. Data on costs associated with the disease are limited.

In Kenya, RSV was estimated to be the cause of a substantial disease burden in young children resulting annually in 77,539 cases of lower respiratory tract infection (LRTI), 49,207 cases of severe LRTI, 37,278 outpatients visits and 9,311 hospitalizations among infants, as well as 10,162 hospitalizations and 2,376 deaths in children aged 0-4 years old. Although causing 47% less mortality than rotavirus, RSV results in 16% more hospitalizations than rotavirus. The total cost in health care attributable to RSV among children less than 5 years old for the Kenyan government in 2009 was US$ 3 million (252,398,234 KSh); while the societal cost represents an additional US$ 2 million (175,582,763 KSh). These costs represent close to half of the costs associated to rotavirus. However, they do not take into consideration costs for episodes occurring in the community and loss of productivity from the caretakers when they do not seek formal medical advice.

Vaccines appear like a most promising means of control and current progress in the research for an RSV prophylactic vaccine to protect young children provides hope that such a vaccine can be developed. There is consensus among national and international stakeholders that after rotavirus and malaria, RSV vaccine should be the next to be made available. Most stakeholders were favorable of a RSV vaccine trial in Kenya on the basis that it would be beneficial to have local data for an eventual larger campaign.

Interest in RSV and a preventive vaccine for young children from local authorities was however low. Underlying this could be the numerous competing health priorities, the absence of a vaccine candidate and the lack of knowledge of the RSV burden. An information campaign might be beneficial to foster a more informed opinion regarding a vaccine trial. It is hoped that the data gathered in this study can serve that purpose and in the assessment of an eventual vaccine candidate.

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APPENDIX

List of Acronyms

ALRI	Acute Lower Respiratory Infection
ARI	Acute Respiratory Infection
CYO	Child years of observation
GAVI	Global Alliance for Vaccines and Immunization
HDSS	Health and Demographic Surveillance System
HIS	Health Information System
IFAT	Immunofluorescent Antibody Test
KDHS	Kenya Demographic and Health Survey
LRTI	Lower Respiratory Tract Infection
MoPHS	Ministry of Public Health and Sanitation
PCR	Polymerase Chain Reaction
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcriptase polymerase chain reaction
WHO	World Health Organization

Introduction

The objectives of the present paper are to document the burden associated with respiratory syncytial virus (RSV) globally and more specifically in Kenya, as well as the current developments of pediatric prophylactic vaccine for the disease and the opinions of key stakeholders at the international and national levels regarding feasibility and desirability of an RSV vaccine.

The first section discusses the virus in general and the evidence documenting the burden attributable to RSV in all age groups, but particularly in developing countries. It will further enable identification of data gaps on RSV epidemiology and disease burden. The subsequent sections concentrate on RSV in children. The second section attempts to evaluate the health, social and economical consequences of RSV in children in the Kenyan context. The third section describes the vaccines to protect young children currently under development and their state of advancement. The fourth section reviews the perceptions of the experts in the field of RSV and immunization. Finally, conclusions are presented accompanied by recommendations for actions including research needs. Contacts of experts contacted, methods of literature reviews as well as burden and cost estimates are presented in appendix.

The elements presented in the following pages will inform decision-makers in Kenya about the burden associated with RSV in the country and will contribute to determining whether the context is favorable for the trial of a RSV vaccine to protect young children in Kenya.

Respiratory Syncytial Virus and Global Burden

Respiratory syncytial virus (RSV) is a single-stranded negative-sense RNA virus of to the genus *Pneumovirus* within the subfamily *Pneumovirinae* and the family *Paramyxoviridae*. There are two subtypes of RSV, A and B, differentiated primarily on the variability of the G gene and encoded protein. RSV produces large, usually annual, epidemics (P. Collins, Chanock, & McIntosh, 1996).

RSV is the single most important etiological agent causing respiratory disease in infancy (Pediatrics, 2009). It is the leading cause of severe lower respiratory tract infections (LRTI) in infants and young children, in particular causing pneumonia and bronchiolitis (Hall, 2001). It is the principal cause of pneumonia after the bacteria *Streptococcus pneumoniae* and *Haemophilus influenza*, and consequently RSV is the main viral cause of pneumonia (Berkley et al., 2010).

Primary RSV infection usually occurs early in life (Glezen, Taber, Frank, & Kasel, 1986). Two thirds of infants are infected with RSV during their first year and infection is usually universal by the age of two (P. Collins et al., 1996). The peak of hospitalization for RSV is between the ages of 2 and 4 months (P. Collins & Murphy, 2006), which coincides with diminishing titer of maternally derived antibodies (P. Collins et al., 1996). Repeated infections are common due to incomplete immunity and are correlated with lower levels of serum neutralizing antibodies (Glezen et al., 1986). However, respiratory tract symptoms are more severe with primary infection than in subsequent infections and more severe in young infants than in older children (Henderson, Collier, Clyde Jr, & Denny, 1979). Most infections are symptomatic (C. Hall et al., 1976). RSV-infected infants almost universally experience upper respiratory tract symptoms, and 20% to 30% develop lower respiratory tract disease with their first infection (Pediatrics, 2009). In older children and adults, RSV infection usually manifests as upper respiratory tract illness (Pediatrics, 2009).

The incubation of RSV is 4-5 days (P. Collins et al., 1996). In newborns, infants and young children RSV causes upper and lower respiratory tract disease characterized by fever, coryza, cough, expiratory wheezing and respiratory distress (Schickli, Dubovsky, & Tang, 2009). The symptoms last between 7 to 12 days (P. Collins et al., 1996). It is not clear from the literature whether strain A causes more severe disease than B. A community study of Kenyan children found a median duration of shedding of 4 days (Okiro et al., 2010). Shedding lasts longer in more severe hospitalized cases and in infancy, presumably associated with primary infections (Okiro et al., 2010). Children with a history of RSV infection have a shorter duration of shedding. Although most re-infections occurred in separate epidemics, 23% of re-infections

occurred during the same epidemic (Nokes et al., 2008). Ohuma et al. suggest partial protection to re-infection of 60-70% for up to 6 months following infection (Ohuma et al., n.d.).

Up to 40% of infants experience symptoms of bronchiolitis or pneumonia during their first episode of RSV infection (Holberg et al., 1991). RSV bronchiolitis is the leading cause of infant hospitalization in industrialized countries (C. Hall, 2001). During their first RSV infection, between 25% and 40% of infants and young children have signs or symptoms of bronchiolitis or pneumonia and 0.5% to 2% require hospitalization (Pediatrics, 2009). In Canada, it was estimated that approximately 75% of hospitalizations for RSV disease occur in infants and children who were previously healthy (P. Collins et al., 1996) . Among children aged less than five years of age, RSV is associated with 20% of hospitalizations, 18% of emergency department visits and 15% of office visits during the winter respiratory viral season in US (C. B. Hall et al., 2009). It is believed an acute episode of RSV may cause long term sequelae such as further episodes of wheezing, of pneumonia and asthma. It is not clear whether children affected already had predisposing conditions to such respiratory problems or if the acute RSV episode would be the real cause. Studies from the United States and Australia suggest that many children who develop bronchiolitis and asthma are born with narrow airways that predispose to these problems (Hament, Kimpen, Fleer, & Wolfs, 1999; Poulsen, Benn, Roth, Lisse, & Aaby, 2006). A short term (3 years) increased risk of pneumonia was observed in Gambian children following severe RSV infection (Weber et al., 1999).

It is not clear whether RSV infection may contribute to secondary bacterial pneumonia. While enhanced bacterial adherence has been documented for respiratory cells infected with RSV (Hament, Kimpen, Fleer, & Wolfs, 1999), the incidence of concomitant or secondary serious bacterial infection in association with RSV infection appears to be quite low (< 1%), except for otitis media, which may occur in as many as 40% of cases (R. Welliver & Cherry, 2006). In a study from Kenya, in children admitted with pneumonia, bacteremia was significantly less common among RSV-positive children than RSV-negative children (Nokes et al., 2009). Otitis media is not observed in association with RSV in Kenya.

In addition to young children, RSV can cause diseases in people of all ages, most severely in the elderly and in immune-compromised individuals (Kim et al., 2010). Asthma, cystic fibrosis and chronic cardiopulmonary disease may be severely exacerbated by RSV infection (Meissner, 2003; Thompson et al., 2003). RSV causes higher mortality among elderly than influenza in non-pandemic years (Falsey et al., 1995).

Data from developing countries are scarce relative to that from industrialized countries. They have been summarized by Weber (Weber, Mulholland, & Greenwood, 1998) and Nokes (D. Nokes, 2006). Since the last review covering articles published before 2005, five denominator-based studies in developing countries have been published from urban poor South Africa (Madhi, Kuwanda, Cutland, & Klugman, 2006), rural India (Broor et al., 2007), rural Thailand (Fry et al.,

2010) and rural Kenya (3 studies) (Berkley et al., 2010; Nokes et al., 2008, 2009); see literature search strategy *Burden* in appendix 1). Only two of these involved active surveillance in the community which captures more cases than passive hospital surveillance (Broor et al., 2007; Nokes et al., 2008).

Nokes et al. (Nokes et al., 2008) found that only between 20 and 25% of patients presenting to outpatient health facilities with RSV-associated severe lower respiratory tract infections (LRTI) were hospitalized (RSV-associated hospitalization), while the World Health Organization (WHO) guidelines recommend hospital admission for all such cases. While the study may have influenced the decision to refer, because the patients were able to return free of charge if the child's condition deteriorated, it still demonstrates that hospital data clearly underestimate the burden of severe pneumonia due to RSV. As for RSV burden in adult populations, only the study in Thailand evaluated it through passive surveillance (Fry et al., 2010). None of the studies estimated the cost associated to RSV.

Recently, Nair et al. estimated that RSV results in an estimated 33.8 (95% CI 19.3–46.2) million new episodes of RSV-associated acute lower respiratory infections (ALRI) worldwide in children younger than 5 years (22% of ALRI episodes), with at least 3.4 (2.8–4.3) million episodes of severe RSV-associated ALRI necessitating hospital admission in 2005 (Nair et al., 2010). Although associated with greater uncertainty than for morbidity estimates, it was estimated that RSV might be responsible for 53,000 to 199,000 deaths annually in the children under 5 years old age group; 99% of which occur in developing countries (Harish Nair et al., 2010). The burden could however have been underestimated in the past with the use of conventional techniques of cell culture or immunofluorescent antibody tests (IFAT) which have, individually, lower sensitivity than nucleotide amplification methods. Further, conventional serologic testing of acute convalescent serum specimens cannot be relied on to confirm infection in young infants in whom sensitivity may be low (Pediatrics, 2009). Modern molecular methods such as reverse transcription polymerase chain reaction (RT-PCR) offer greater sensitivity. In some studies, PCR assays have increased RSV detection as much as twofold over viral isolation or antigen detection (Pediatrics, 2009). Thus these methods may require re-evaluation of the epidemiological portrait for RSV.

Kenyan context

There are reports on RSV seasonal patterns from only two areas in Kenya: Nairobi (Hazlett et al., 1988) and Kilifi (Nokes et al., 2009). The pattern in Kilifi was quite regular over the last 7 or so epidemics. In that region, they started around November or December and finished in April or June. The epidemic's average duration is 18 weeks (range 13–27 weeks) (Nokes et al., 2009). More data from elsewhere in the country is awaited to determine variation throughout the country.

There is currently limited information available in Kenya on the epidemiology of RSV, as well as burden and costs estimates attributable to RSV infections.

Estimation of the burden of RSV in Kenya

Using available data, it was sought to estimate the burden attributable to RSV.

Methods of estimation

Incidence rates of RSV associated events and prevalence of RSV may vary according to the case definition, methods of sampling, assays, period, area of the study, type of surveillance (active or passive), sample size and concurrent illnesses (HIV, malnutrition, etc.).

RSV associated events may be estimated in terms of the proportion of cases of acute respiratory infections (ARI), LRTI or pneumonia in which RSV was identified. ARI includes respiratory infections in both the upper and the lower tract, but not infections which are not considered acute such as tuberculosis for example. LRTI which is often used as a synonymous for pneumonia, can however also apply to other types of infection including lung abscess and acute bronchitis, depending on the case definition. Pneumonia is an inflammatory condition of the lungs which may have various causes, including RSV. When assessing epidemiological studies, it is preferable to refer to case definitions as for example, pneumonia may be defined in numerous ways.

The only RSV incidence rate estimates currently available for Kenya are from the research accomplished in Kilifi District (Berkley et al., 2010; Nokes et al., 2008, 2009). They are presented in appendix 4. Selected Kilifi District rates were thus used to estimate provincial and national incidence of RSV associated events (from references (Nokes et al., 2009; 2008); see rates in blue in appendix 6). Provincial data from the Kenya Demographic and Health Survey 2008-2009 (KDHS) were used to adjust the rates from Kilifi District Hospital to each region (Kenya National Bureau of Statistics, 2010).

KDHS is a household-based population and health survey, with a sample of 10,000 households distributed over the provinces of Kenya. In the 2008-9 survey a total of 3,973 mothers of 5,481 children born in the preceding five years were asked for each child if he or she experienced acute respiratory infection (ARI)[1] in the two weeks preceding the interview and whether they sought medical care. The ratio of each province-specific likelihood to the Coast likelihood was calculated using this 2-week prevalence of ARI in children under 5 years old from the KDHS converted to annual incidence (see method in reference (Division for the Control of Diarrhoea and Acute Respiratory Disease, 1994)). The likelihood of ARI alone was used to adjust the LRTI and severe LRTI rates while the combined likelihood of ARI and seeking medical care rates was used to adjust the rates of hospitalizations and outpatient visits. The crude incidence was then calculated applying the obtained rates to Kenya 2009 Population Census data (Government of Kenya, 2010).

Such a method of calculating the likelihood ratio assumes that Kilifi district rates apply to the whole Coast region and further that the likelihood ratios calculated using KDHS ARI data are close to real epidemiology of RSV which cannot be verified in the absence of regional data. Further, these likelihood ratios calculated using the 0-4 year-old age group are applied to the infants for certain indicators, while the epidemiology of RSV by age group may differ regionally.

Community data on RSV were available for children under the age of 30 months and not for the full range of children under 5 years old. Thus, to estimate the total incidence of RSV associated events in the children under 5 years old (including the community burden), KDHS 2 week prevalence of children under 5 years old with symptoms of ARI for each Province was converted into annual incidence using the method presented earlier. It is important to note that in KDHS, ARI are defined as cough accompanied by short, rapid breathing, which was chest-related and thus might be considered a proxy for pneumonia. The incidences were transformed into incidence rates using Kenya 2009 Population Census data (Government of Kenya, 2010).

To estimate the outpatient consultations of children under 5 years old, two different methods were used. Another source of information was used namely Kenya Health Information System (HIS) (Kenya MoPHS, n.d.). HIS is a national system at the Ministry of Public Health and Sanitation (MoPHS) obtaining data for outpatient consultations in all health care institutions by districts (Gessner, Shindo, & Briand, 2011). The data was collected in 2010. The pneumonia incidences were adjusted for underreporting. The recorded pneumonia outpatient consultations from the HIS and the reported pneumonia cases seeking medical advice or care KDHS were each multiplied by the proportion of pneumonia associated to RSV (see discussion and table below).

The RSV associated hospital mortality of children under 5 years old was calculated by multiplying the number of children under 5 years old hospitalized with RSV by Kilifi mortality

[1] defined as cough accompanied by short, rapid breathing, which was chest-related, considered a proxy for pneumonia.

rate among children hospitalized with severe or very severe pneumonia. Finally the total mortality, including the community mortality, was obtained by multiplying the KDHS mortality rate by the prevalence of pneumonia associated deaths (Ombok et al., 2010) and then by the RSV associated pneumonia prevalence.

Table 1 below summarizes the estimation methods employed for each indicator.

Table 1: Methods employed to estimate the incidence of various RSV associated events.

Indicator	Estimation Methods
LRTI <1 year old	Kilifi rate of RSV associated LRTI from reference (Nokes et al., 2008)(104/1000 CYO) multiplied by regional likelihood ratios (region/Coast) calculated using KDHS data (with symptoms of ARI in the preceding 2 weeks; (Kenya National Bureau of Statistics, 2010)).
Severe LRTI <1 year old	Kilifi rate of RSV associated severe LRTI from reference reference (Nokes et al., 2008) (66/1000 CYO) multiplied by regional likelihood ratios (region/Coast) calculated using KDHS data (with symptoms of ARI in the preceding 2 weeks).
Pneumonia <5 years old	Incidence rate obtained from KDHS 2 week prevalence of children < 5 years old with symptoms of ARI converted into annual incidence multiplied by RSV prevalence (see discussion and table below).
Outpatient consultations <1 year old	Kilifi rate of RSV associated LRTI from reference (Nokes et al., 2008) (50/1000 CYO) multiplied by regional likelihood ratios (region/Coast) calculated using KDHS data (seeking medical advice).
Outpatient consultations <5 years old	Pneumonia incidence from HIS and KDHS multiplied by RSV prevalence (see discussion and table below).
Hospitalizations <1 year old	Kilifi rate of RSV associated LRTI from references (Berkley et al., 2010; Nokes et al., 2008) (13-20.4/1000 CYO) multiplied by regional likelihood ratios (region/Coast) calculated using KDHS data (seeking medical advice).
Hospitalizations <5 years old	Kilifi rate of RSV associated LRTI from references (Berkley et al., 2010; Nokes et al., 2009)(2.93-5.35/1000 CYO) multiplied by regional likelihood ratios (region/Coast) calculated using KDHS data (seeking medical advice).
Hospital mortality <5 years old	Incidence of hospitalization of children <5 years old multiplied by Kilifi mortality rate among children hospitalized with severe or very severe pneumonia from reference (Nokes et al., 2009) (0.22 deaths per 1000 hospitalizations).
Total mortality <1 year old and <5 years old	Mortality rate from KDHS multiplied by the prevalence of pneumonia associated deaths (Ombok et al., 2010) multiplied by the RSV associated pneumonia prevalence (see discussion and table below).

[1] extrapolated from hospitalizations which are 26% of all consultations, 13*100/26=50.
Notes : CYO child-years of observation
The grey background indicates the same method was employed.

RSV prevalence

As mentioned previously, the proportion of respiratory infections associated with RSV may vary according to the case definition, methods of sampling, assays, period and area of the study among other factors. Table 2 summarizes the most relevant estimates available from the literature.

Table 2: RSV Prevalence Estimates from the Literature

Population	RSV Prevalence	Period	Area	Collection; Assay	Reference
< 5 years old hospitalized for severe pneumonia	15.3% (20% among infants)	2002-2007	Kilifi District Hospital, Kenya	NW or NPA; IFAT	(Nokes et al., 2009)
< 5 years old hospitalized for severe ARI	12%	1981-1982 (1 year)	Kenyatta National Hospital, Nairobi, Kenya	NPA & TS; IFAT	(Hazlett et al., 1988)
< 12 years old hospitalized for severe pneumonia	34%	2007	Kilifi District Hospital, Kenya	NPA; PCR	(Berkley et al., 2010)
< 5 years old hospitalized for severe pneumonia	6.2%	2006-2007 (one year)	Manhiça District Hospital, Mozambique	NPA; PCR	(O'Callaghan-Gordo et al., 2011)
Children outpatient and/or hospitalized for ARI	2-25% (median 12%), Hospitalized 1-13% (median appr. 8)	11 hospital based studies in sub-Saharan Africa between 1980 and 2009. Various collection methods and assays.			(Gessner et al., 2011)

Notes:
Severe pneumonia includes very severe.
IFAT Immunofluorescent Antibody Test
NPA Nasopharyngeal aspirate
NW Nasal washing
PCR Polymerase Chain Reaction
TS Throat swab

RSV prevalence monitored over 5 years in children less than 5 years of age hospitalized for LRTI was 15.3% (20% among infants) and 27% during epidemics (32% among infants) in Kilifi District Hospital screening for antigen using an IFAT (Nokes et al., 2009). In a community study in the same area, RSV was identified in 13% of all LRTIs, 19% of severe LRTIs and 5% of hospitalizations in children aged less than 30 months (Nokes et al., 2008). In a one year study, the prevalence of RSV in children under 12 year-old hospitalized at Kilifi District Hospitals for severe pneumonia was 34% using PCR assay (Berkley et al., 2010). In another one year study in rural Mozambique, this proportion was 6.2% of the severe pneumonia cases using PCR (O'Callaghan-Gordo et al., 2011).

Nokes and al. (Nokes et al., 2009) study covers a long period and hence is less subject to chance variation than the other reported studies. However, it is based on IFAT which, though quite sensitive, is thought to be less so than PCR. Nokes et al. RSV prevalence is further supported by another study based at Kenyatta National Hospital (Hazlett et al., 1988). The prevalence of RSV among children under 5 years old admitted with severe ARI (for which the case definition was similar to Nokes et al. severe pneumonia definition) was 12% in that study. Thus a 15.3% RSV prevalence among severe pneumonia cases appeared like an appropriate compromise. This however assumes the RSV prevalence does not change from one region to another and is the same in children no matter the outcome of interest (severe LRTI, hospitalization for severe pneumonia, death, etc). Finally, the estimates obtained using these methods and data are presented in appendixes 5 and 6. They are discussed below. National estimates are presented in Table 3.

Table 3: Key Estimates of RSV Associated Events Incidence in Kenya, 2009 (see estimation methods in table 1 above).

Indicator	RSV cases per annum	RSV incidence (cases/ 1000 CYO)
LRTI <1 year old	77,539	63.2
Severe LRTI <1 year old	49,207	40.1
ARI <5 years old (Kenya National Bureau of Statistics, 2010)	1,069,735	180
Outpatient consultations <1 year old	37,278	30.4
Outpatient consultations <5 years old (Kenya MoPHS, n.d.); (Kenya National Bureau of Statistics, 2010)	101,460; 597,982	17.1; 101
Hospitalizations <1 year old	9,311	7.6
Hospitalizations <5 years old	10,162	1.7
Hospital mortality <5 years old	224	0.04
Total mortality < 1 year old ; <5 years old	2,138; 2,376	1.8; 0.4

Notes: CYO child-years of observation

RSV associated LRTI among infants

The national rate of RSV associated LRTI in infants is 63 per 1000 child-years of observation (CYO) for a total of 77,539 cases annually in children aged less than 1 year old. The region with the highest rate is the Coast with 104 cases per 1000 CYO (one infant in 10), followed by Nyanza with 66 per 1000 CYO, and finally Rift Valley with 65 per 1000 CYO (see appendix 6). However, the region which is the most affected in terms of annual number of cases is the Rift

Valley with a total of 22,171 cases, followed by Nyanza with 13,093 cases and the Coast with 12,008 cases.

In terms of severe LRTI cases, the national rate is 40 /1000 CYO, causing a total of 49,207 cases among infants. The Coast with the highest rate of 66 cases per 1000 CYO is followed by Nyanza which has a rate of 42 cases per 1000 CYO and the Rift Valley with 41 cases per 1000 CYO. The regions with the highest toll are again Rift Valley with 14,070 cases, Nyanza with 8,309 cases and Coast with 7,621 cases among infants each year. Rift Valley, Nyanza and Coast regions respectively account for 29%, 17% and 16% of the national total of RSV associated LRTI cases.

RSV associated ARI among children under 5 years old

The national annual incidence of RSV associated ARI obtained from KDHS prevalence is 1,069,735 among children less than 5, for a rate of 180 per 1000 CYO (see column *Annual incidence of RSV associated ARI* in Appendix Table 5). The Coast has a rate of 296 cases per 1000 CYO, is followed by Nyanza which has a rate of 187 cases per 1000 CYO and the Rift Valley with 185 cases per 1000 CYO. The regions with the most cases are the Rift Valley with 300,515 cases, Nyanza with 177,456 cases and Coast with 159,291 cases among infants each year.

Outpatient consultations among infants

The rate of outpatient consultations for infants in Kenya is 30 per 1000 CYO for a total of 37,278 consultations of infants per year. If we consider all cases consulting are severe, it means only about 76 % of the 49,207 severe cases among infants seek medical care (see Appendix Table 6).

The Coast is again the region with the highest rate of outpatient consultations for infants with 50 consultations per 1000 CYO. The Rift Valley comes in second rank and Nyanza in third rank; with respectively 32 and 31 infant consultations per CYO. This translates into 10,659 consultations per year in the Rift Valley, 6,295 in Nyanza and 5773 on the Coast.

Outpatient consultations among children aged less than 5 years old

The number of outpatient visits of children less than 5 which would be RSV associated using the prevalence of 15% of all pneumonia cases recorded in HIS is about 101,460 cases, for an annual incidence rate of 17 per 1000 CYO (see column *Annual incidence of RSV associated pneumonia recorded in HIS* in Appendix Table 5).

In HIS, the Rift Valley province has the highest number of outpatient consultations with a total of 22,899. It is followed by the Western and the Eastern provinces with respectively 18,248 and 15,497 outpatients consultations. The incidence rates are 24 per 1000 CYO for the Western province, followed by the Coast region with 22 per 1000 CYO and the Central province with 20 per 1000 CYO.

On the other hand, according to KDHS proportion of children sick seeking health care, there would be 597,982 cases of RSV associated pneumonia throughout Kenya, for an incidence rate of 101/1000 CYO (see column *Annual incidence of RSV associated ARI seeking advice* in Appendix Table 5).

When the HIS estimate is put in relation with the 37,278 outpatient consultations of infants estimated previously using KDHS data, it would mean only about 37% of these consultations for children aged less than 5 years old would be for infants. This proportion is still much lower when the KDHS estimate for the consultations of children aged less than 5 years old (same estimation method) is used as the denominator (6%). This is not consistent with the epidemiology of RSV associated pneumonia, which is usually more severe in infants. Reasons for that might be that KDHS data collection occurred during the ARI seasonal increase as well as the conversion from 2 week-prevalence to annual incidence both leading to overestimation. There may be over reporting still in KDHS due to desirability bias possible in declaring seeking health care when it was not, but this bias should have been consistent in the two age groups. The HIS data might not be exhaustive causing underestimation in the under 5 years old consultations rate, however this would lead to an even smaller proportion of infants' consultations.

The infants' rate of consultations seems more reliable as it is based on an incidence rate, but the regional likelihood ratios might not be adequate leading to a poor national estimate. The likelihood ratios were based on children aged less than 5 data for both age groups. If likelihood ratios would have been calculated using HIS data, the proportion of infants consulting among the less than 5 years old would have been lower still. It may also be possible that most the less than 1 year old constitute a weak proportion of consultations, but account for a majority of hospitalizations. Given these estimates were obtained using different methods, they are hardly comparable. However, their comparison may provide insight into the weaknesses of the estimation methods. See the *Possible biases* section below for further discussion.

Hospitalizations among infants and children aged less than 5 years old

The national rate of hospitalizations is 8 per 1000 CYO for infants, resulting in 9,311 hospitalizations in 2009. This rate is of 2 per 1000 CYO for children aged less than 5 years old for a total of 10,162 hospitalizations in 2009. The rate of hospitalizations of infants is thus about 4 times greater that of the 0-4 years old age group. Infant hospitalizations thus constitute 91.3% of the under 5 years old hospitalizations.

The Coast has a rate of 13 infant hospitalizations per 1000 CYO, followed by the Rift Valley and Nyanza with both about 8 hospitalizations per 1000 CYO. Due to its large population, the Rift Valley experiences 2,850 hospitalizations of infants annually, while Nyanza and the Coast region have about 1500 each.

As for the children under 5 years old, the incidence is 3 hospitalizations per 1000 CYO on the Coast, followed by the Rift Valley and Nyanza which have rates of about 2 hospitalizations per 1000 CYO each. This results into over 3000 hospitalizations in Rift Valley, 1,699 in Nyanza and 1,576 on the Coast.

Among infants, considering all hospitalized cases are severe cases, the incidence of 9,311 hospitalizations out of the 49,207 severe LRTI cases means that only 20% of all infants with RSV associated severe LRTI are being hospitalized while WHO recommends hospitalization for all such cases (Nokes et al., 2009). It is not possible to estimate this proportion among children aged less than 5 years old because the incidence of ARI in that age group obtained using KDHS self-reported data appears overestimated. However the fact many cases deserving to be admitted are not is probably due to access issues. Nokes et al. (Nokes et al., 2009) found that incidence estimates of hospital admissions are influenced by distance decay ie further away from the hospital then the lower the estimated incidence. In Nokes et al. study (Nokes et al., 2009), 92% of all hospital admissions of patients with RSV-associated pneumonia occurred during an epidemic period.

RSV Mortality among hospitalized children under 5 years old

The RSV associated mortality in hospitalized cases found in Nokes et al. was 2.2% in children aged less than 5 years old (Nokes et al., 2009). When applied to the number of hospitalizations in that age-group, it means there is a total of 224 deaths associated with RSV annually in the country (see column *Mortality hospitalized cases* in Appendix Table 6). The regions experiencing the most deaths are the Rift Valley with 67 deaths annually, 37 in Nyanza and 35 on the Coast; respectively 30%, 17% and 16% of the national total.

The hospital surveillance study by Nokes et al. (Nokes et al., 2009) found that the risks of very severe conditions, risk factors, and concurrent illness were significantly higher among RSV-negative patients. This is consistent with a case fatality rate of 4.7% for RSV-negative patients versus 2.2% for RSV-positive ones. However, there is a concern for a bias in sampling of less severe cases as 18% of eligible children were not tested, and the case fatality among the enrolled patients was less than one-half that observed among all eligible children (4.4% vs 9.9%). Therefore, it is possible that the true case fatality rate associated with RSV is significantly higher than that observed, and consideration should be given to collecting a specimen post-mortem to address this unknown factor.

The other problem of extrapolating mortality rates from a research hospital setting to all hospitals is that most of other hospitals will be less resourced and thus mortality may well be higher in non-research settings. On the other hand, cases seen in research hospitals and higher level hospitals, better resourced, are generally more serious and at higher risk of dying.

Total mortality among infants and children under 5 years old

According to a case-control study which documented places of death of children under 5 years of age in the Gambia, only about one-third die in a hospital while 9% die in a health center and over half die at home (Rutherford et al., 2009). Thus from the 224 hospital deaths we would expect a total mortality of 672 among children aged less than 5 years old.

In the KDHS household survey, the under 5 mortality in Kenya was 74 per 1,000 live births in 2009, of which 52 (70%) occur in the first year of life (Kenya National Bureau of Statistics, 2010). This is equivalent respectively to 1,566 and 5,485 deaths per 100,000 children per year.

From a study in rural western Kenya, it was determined through verbal autopsies that 16.8 % of 2954 children under 5 died of pneumonia, while this proportion increases to 20.9% when only children aged less than one year old are considered (n=1460) (Ombok et al., 2010). Pneumonia was the second cause of mortality after malaria. This means the annual pneumonia mortality rate in children aged less than 5 years old is 263 per 100,000 children while it is 1,146 per 100,000 infants.

When the RSV prevalence of 15.3% is applied, this means RSV was responsible for an estimated 40 deaths per 100,000 children aged less than 5 years old per year and 175 deaths per 100,000 children aged less than 1 year old per year. RSV would thus cause 2,376 deaths among children aged less than 5 years old, including 2,138 deaths among children aged less than 1 year old (90%) in Kenya in 2009 which is far in excess of the 672 cases we would expect if only 1/3 of deaths occur in hospitals as mentioned previously (3x 224 deaths occurring in hospital calculated previously).

This rate may be overestimated as the prevalence of RSV is probably lower in children who die than in those who are only sick as mentioned previously. In Nair et al., between 3 and 9% of acute lower respiratory infections deaths were RSV associated worldwide (Harish Nair et al., 2010).

In summary, according to the estimates presented here, RSV is expected to result annually in 77,539 cases of LRTI, 49,207 cases of severe LRTI, 37,278 outpatients visits and 9,311 hospitalizations among infants, as well as 10,162 hospitalizations and 2,376 deaths in children less than 5. These numbers are lower than those previously presented by Nokes et al. (Nokes et al., 2008) of 135,000 cases of LRTI, 85,000 cases of severe LRTI, and 17,000 hospitalizations of

infants. This difference is largely explained by the fact the Coast has double the prevalence reported in other regions in KDHS which had a great impact on likelihood ratios and thus provincial estimates.

The estimates done directly from HIS and KDHS, namely the RSV associated pneumonia and the outpatient visits incidences among the children aged less than 5 years old, are not discussed further as the confidence in these estimates is limited (see possible biases section below). The mortality estimates are also of limited confidence because of all the potential biases discussed previously, they should be interpreted with much caution.

Possible biases

The incidences calculated directly from KDHS data might be overestimated because part of the data collection took place during the seasonal ARI increase (13 November 2008 to late February 2009), the prevalence was self-reported (e.g. mothers overestimating the gravity of their child's condition, desirability bias in reporting having sought health care) and the 2-week prevalence was converted into an annual incidence.

KDHS was preferred over HIS to estimate the likelihood ratios because HIS thoroughness appears uncertain. The fact KDHS might be overestimated would not affect the ratios obtained. In HIS, the rate for the Coast is not the highest of the country while it is the case in KDHS. The Coast rate also differs less from that of the other regions. Thus lower estimates would have been obtained if HIS had been used for the calculation of the likelihood ratios. KDHS was further based on a limited sample especially for the percentage of those who sought advice (see notes in appendix 6).

The use of the RSV prevalence of 15.3% to estimate the number of pneumonia deaths associated with RSV is debatable because RSV prevalence may vary according to the health outcome considered as illustrated by Nokes et al. results and discussed previously (Nokes et al., 2008). It is usually thought to be less, however we cannot be certain in the absence of post-mortem assessment.

Comparison with rotavirus burden

The 10,162 hospitalizations resulting from RSV among children under 5 years old are more than the 8781 hospitalizations due to rotavirus according to Tate et al. (Tate et al., 2009). However, with its 2,138 deaths in total, RSV would cause the equivalent of about only half (53%) of the

4471 deaths resulting from rotavirus estimated by Tate et al. among children aged less than 5 years (Tate et al., 2009). The mortality rate of 40 per 100,000 children per year for the children under 5 years old is about two-thirds of the mortality rate of 68 per 100,000 per year for the children under 5 years old attributable to rotavirus (Tate et al., 2009).

Concurrent illnesses

In a longitudinal study of RSV hospital admissions in Kilifi, concurrent malaria parasitemia, severe malnutrition, and bacteremia were all significantly less common among RSV-positive children with pneumonia. Furthermore, a history of premature birth among infants and a discharge diagnosis including heart disease were marginally less frequent among RSV-positive children (Nokes et al., 2009).

The incidence of hospitalization for RSV-LRTI was 2.5-fold (95% CI 2.04–3.03) greater in HIV infected children than in non-infected children in South Africa (Madhi et al., 2006). In rural Mozambique, this incidence was also 2.2 to 6.5 times higher in HIV infected children under 5 years old than in non-infected children of the same age group (O'Callaghan-Gordo et al., 2011).

However, these co-morbidities might make patients at increased risk of complication and death before an RSV investigation can be performed, as mentioned previously.

Economic burden

Costs were estimated for the outpatient visits of infants and hospital admissions of children less than 5 years of age. Costs were based on WHO Choosing Interventions that are Cost Effective (WHO-CHOICE) and Ayieko et al. estimates (Ayieko, Akumu, Griffiths, & English, 2009; World Health Organization, n.d.). In Ayieko et al. (Ayieko et al., 2009)[2], cost estimations to health care system and caretakers were available specific for pneumonia diagnosis and by level of governmental hospitals. Outpatient visit cost estimates were taken from CHOICE. The cost of medication, investigation, transportation and loss of income[3] not being available from that reference, those costs in district hospitals from Ayieko et al. (Ayieko et al., 2009) were applied. This might have caused a certain overestimation. For hospitalizations however, the conservative costs applicable for district hospitals were used. Costs were adjusted to 2011 inflation using the Consumer Price Index of Kenya (Kenya National Bureau of Statistics, 2011). Unit costs were

[2] Estimates based on the treatment cost of 205 pneumonia cases in 7 hospitals throughout the country.

[3] Ayieko et al. reported caretakers spent an average of 1 hour and 49 min travelling to seek health care services for. Consequently, an average round trip would last 3 hours and 38 min, or approximately 0.5 working days.

estimated in 2011 US$. The 2011 exchange rate of 86.655 Kenyan shillings to the US$ was used (OANDA, 2011). Those estimated costs are detailed in Appendix Table 7.

Cost to governmental health care system

Only costs of consultations in governmental institutions were included. The proportion of patients in governmental institutions were based on the observed health care seeking behaviour for children under 5 as recorded in the 2007 Household Health Expenditure and Utilisation Survey; which is a cluster randomized household survey among 8,453 households from all regions of Kenya (Ministry of Medical Services and Public Health, 2009). The unit cost for an outpatient visit was US$32.82 (2,844 KSh) and hospitalisation was US$98.39 (8,526 KSh). Because 64.6% of outpatients and 76.2 % of hospitalizations were done in governmental institutions, the total cost in health care attributable to RSV for the Kenyan government is US$ 2,912,676 (252,398,234 KSh) (see Appendix Table 7).

Societal costs

The costs to caretaker include transportation and lost income. Pre-admission user fee and pre-admission cost is added for hospitalizations. The total is US$15.89 (1,377 KSh) for an outpatient visit and US $40.74 (3,531 KSh) for a visit to the hospital. All patients considered this represents a cost of US$ 2,026,225 (175,582,763 KSh) to the Kenyan society. Despite the free health care services to all children under 5 years in government institutions policy in Kenya, user fees are still charged in district hospitals and those can be significant to caretakers (Barasa, Ayieko, English, & Cleary, n.d.).

When Ayieko et al. used WHO CHOICE estimates to determine treatment costs, those were between 25% to 47% lower for pneumonia across the seven hospitals. However, Ayieko et al. estimates were preferred over CHOICE as they are mainly based on field data and are specific for pneumonia ; thus appear closer to reality. For example, the authors found that over half the children with pneumonia as a stand-alone diagnosis received at least 4 drugs when national treatment guidelines for severe pneumonia recommend that inpatients be treated with a single antibiotic only and those with very severe disease receive a combination of two antibiotics. This lack of adherence to clinical guidelines prevents rational resource use and increases costs of treatment. Further, while the mean cost for essential drugs in their sample would be US$ 0.36 for severe pneumonia and US$ 0.9 in a case of very severe pneumonia, the mean cost of a drug prescription for a child with pneumonia across the hospitals was between US$ 3.0 – US$ 31.2.

Comparison with rotavirus burden

Thus, the total health care costs associated with RSV in Kenya are US$ 4,938,901. These costs do not take into consideration costs for episodes occurring in the community and loss of productivity from the caretakers even when they do not seek formal medical advice. They equate to about half the US $10.8 millions associated to rotavirus estimated by Tate et al. (Tate et al., 2009).

Prevention strategies and vaccines

The virus spreads via large respiratory droplets from contaminated nasal secretions, so close contact with an infected individual or contaminated surface is required for transmission. However, RSV can persist for several hours on toys or other objects, which explains the high rate of nosocomial RSV infections, particularly in pediatric wards (Girard, Cherian, Pervikov, & Kieny, 2005). Frequent and careful hand washing might reduce transmission (Schickli et al., 2009). However, the virus being so transmissible, vaccines might be the best option to control the disease.

Vaccines

Some vaccines for passive immunization such as motavizumab and palivizumab already exist. They are used as monoclonal antibodies for prophylaxis and treatment. However, due to their high cost, vast use is not possible in developing countries. Discussions will thus focus mainly on active immunization. Such vaccines are under development; however no vaccine is currently available. Due to the low mortality and wide uncertainty in its estimation, but severe morbidity from primary infection in early life and significant disease following re-infection in the elderly, the rationale for an RSV vaccine is mainly on the basis of prevention of morbidity rather than mortality.

Challenges to the development of a safe effective vaccine

RSV-specific antibodies are transmitted from the mother to the child through transudation of the placental barrier and breast milk (P. L. Collins & Murphy, 2006). They mainly protect the children's lower respiratory tract (P. L. Collins & Murphy, 2006). Their half-life is 3 weeks and as their quantity decreases, the children susceptibility to RSV increases (P. Collins et al., 1996). As mentioned previously, the first infection is generally the most serious, especially at a young age. The peak incidence of serious RSV thus occurs between the ages of 2 and 4 months (P. L. Collins & Murphy, 2006). A pediatric RSV vaccine must thus ideally be capable of stimulating effective resistance before the second month of life (P. Collins et al., 1996). The immunosuppressive effects of maternally derived serum RSV-neutralizing antibodies, as well as the children's immunologic immaturity both pose challenge to the development of an efficacious

vaccine for that population (Schickli et al., 2009). Moreover, even natural infection does not trigger lasting immunity, so booster immunization might be required. Further, much care must be taken into the development of the vaccine to avoid disease enhancement as it was experienced with a formalin-inactivated vaccine candidate in the mid-1960s, impediment to breastfeeding which would be unacceptable in that age group, interference with other vaccines given at that age or any other serious side effect.

Intranasal vaccines

Intranasal vaccines offer many advantages for RSV immunization of young infants. First, they provide direct stimulation of the respiratory tract, RSV's infection site, which may be critical for the development of long-term memory at the site of infection through homing of effector cells to the site of immunisation (van Drunen Littel-van den Hurk, Mapletoft, Arsic, & Kovacs-Nolan, 2007). In addition to cell-mediated immunity, mucosal infection induces systemic immunity as secretory immunoglobulin A antibodies are normally synthesized, thus providing a strong first line of defense against invasion of deeper tissues (van Ginkel, Nguyen, & McGhee, 2000).

Second, the route of vaccine administration has been found to play a significant role in both avoiding enhanced disease by immunization. Immunity resulting from intranasal inoculation appears to be less Th2 biased than that acquired through parenteral delivery (van Drunen Littel-van den Hurk et al., 2007).

Furthermore, intranasal administration avoids interference with maternal antibodies since the concentrations of maternal antibodies that reach mucosal surfaces are significantly lower than levels in serum (van Drunen Littel-van den Hurk et al., 2007). While a live vaccine administered parenterally was neutralized by maternal antibodies, an intranasal vaccine could replicate in upper respiratory tract (van Drunen Littel-van den Hurk et al., 2007). Maternal antibodies partly suppress the immune response to infection, primarily through the humoral rather than cell-mediated immunity (P. L. Collins & Murphy, 2006).

Finally, mucosal delivery of vaccines is non-invasive, easy to administer, and avoids the use of needles, which facilitates compliance and is more practical in developing countries setting (van Drunen Littel-van den Hurk et al., 2007).

However, because the site of inoculation, replication and subsequent inflammation is in the respiratory tree, intranasal vaccines must not impede breathing and feeding in infants, the targeted group (Schickli et al., 2009).

Alternative immunization strategies

As it has proven difficult to develop a safe vaccine for that age group, alternative immunizations strategies have been put forward.

Cocoon-type strategy

The cocoon strategy consists of immunization of parents and siblings to protect the infants. It may be an interesting approach in developing countries where infants' main contacts are his family versus children in developed countries who are placed in nurseries.

Because even natural infection does not confer complete nor lasting immunity, benefits of immunization will probably be partial and of limited duration. Still it would diminish the risk of reinfection and thus reduce the likelihood contacts will infect an infant. Repeated immunization would be required, on a yearly basis before epidemics, making cost-effectiveness of this strategy difficult to attain. However, a single immunization boost to protect the most at-risk period, namely the epidemic occurring during the first year of life, might suffice to limit consequences.

Secondly, Crowcroft et al. found that in over 60% of the infants' admitted to hospital intensive care units families, the infant was the primary or co-primary case (Crowcroft et al., 2008). This suggests that a vaccine targeted to household members will not prevent a majority of RSV infections to naïve infants, but the fact households were visited retrospectively might have biased the study. However, this observation may not apply to settings in the developing work where the pattern of who acquires infection from whom may well be different to the United Kingdom setting.

Vaccine in pregnant mothers

Theoretically, boosting the level of maternal RSV IgG should result in transfer of maternal antibodies across the placental barrier and in the breast milk, enhancing short-term immunoprophylaxis against RSV in young infants (Schickli et al., 2009). Thus, maternal vaccination could serve to protect very young children.

Vaccination of older children

A delay in vaccination, to an age when children are more immunologically mature, interference from maternal antibodies is avoided and safety concerns are decreased might constitute an effective immunization strategy.

Although the estimated incidence of RSV-associated LRTI, severe LRTI, and hospitalization was highest in the group aged <6 months, significant disease incidence was observed in older groups continuing into the third year of life. In fact, 55%–65% of significant disease due to RSV in the wider community would occur in ages outside the age range typically designated as the vaccine target (Nokes et al., 2009).

This approach could be combined with vaccination of pregnant women to extend the period of protection from birth.

Furthermore, if there is an effect of vaccination of elder children on the overall spread of virus in the population, this would provide indirect protection to the infant.

Vaccines currently under development

The only pediatric prophylactic RSV vaccines currently under clinical evaluation are live intranasal vaccines based on i) attenuated RSV (*rA2cp 248/404/1030ΔSH* or MEDI-559) or ii) attenuated PIV3 expressing the RSV F protein as a bivalent RSV/HPIV3 vaccine (b/hPIV3/RSV F2 or MEDI-534). Both are being developed by MedImmune.

Another vaccine targeted at mothers to temporarily boost young infants' immunity was also under development. It is a subunit vaccine, called RSV purified F protein (PFP)-2.

A summary table of these three vaccines is presented in Appendix Table 8.

rA2cp248/404/1030ΔSH

rA2cp248/404/1030ΔSH is a cold-passaged, genetically engineered by reverse genetics live attenuated RSV vaccine. Its predecessor, *cpts*248/404, was the first live attenuated RSV vaccine candidate evaluated in the target population of infants as young as one month old. However, the vaccine caused significant nasal congestion that interfered with feeding and sleeping, which was inacceptable (Wright et al., 2000). The mutation of nucleotide 1030 appears to have successfully attenuated the vaccine while retaining immunogenicity in the *rA2cp248/404/1030ΔSH* version.

In a previous study, only 44% of infants who received two $10^{5.3}$-pfu doses of *rA2cp 248/404/1030ΔSH* vaccine had detectable antibody responses (Karron et al., 2005). However, even though a neutralizing antibody response could not be detected in young infants (1-3 months old) infected with the RSV vaccine, the vaccinees had diminished virus shedding after receipt of a second dose, indicating that an immune response capable of restricting RSV replication had occurred (Karron, 2011). This surrogate for vaccine efficacy was further supported in Wright et al. (Wright et al., 2007) study in which the frequency of total respiratory illness and RSV-associated upper respiratory illness was compared between vaccinees of live attenuated virus vaccines all derived from RSV A2 including *cpts*248/404 and *rA2cp 248/404/1030ΔSH* and controls in the RSV season following vaccination. Both symptoms were more frequently observed in controls than in RSV vaccinees, suggesting that receipt of a RSV vaccine had decreased replication of wild type RSV sufficiently to modify illness. Indeed, the rate of RSV associated upper respiratory tract illness in the 388 children was 14% in RSV vaccinated children versus 20% in controls in the 6–24 month old group and 16% versus 25% in infants. This trend of decreasing RSV-associated illness in vaccine recipients during the subsequent RSV season is suggestive of vaccine efficacy, but authors recognized this conclusion would be premature since

the studies involved multiple vaccines over multiple years and were not designed to evaluate efficacy (Wright et al., 2007). This finding may not be confirmed when *rA2cp 248/404/1030ΔSH* will be examined on its own.

Further, live attenuated vaccines may potentially revert to wild type virus (van Drunen Littel-van den Hurk et al., 2007). Sequence analysis performed on 9 viruses recovered from 5 recipients revealed that in 5 instances, single nucleotide substitutions were observed at either the 248 or 1030 codons, with reversion to the wild type coding assignment. A sixth isolate had a mixed population of nucleotides at the 1030 codon. Each isolate had nucleotide substitutions at no more than 1 codon. The 5 *cp* mutations, the 404 mutation, and the DSH mutation were present in all isolates tested, demonstrating the stability of these mutations after replication in RSV-naive children (Karron et al., 2005).

However, according to a recent publication, infection with a series of live attenuated RSV vaccines, including *rA2cp 248/404/1030ΔSH,* did not lead to enhancement of disease upon infection with wild type RSV in children between 1 and 24 months old (Wright et al., 2007).

A phase 1/2a, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, immunogenicity, and viral shedding of MEDI-559, a live attenuated intranasal vaccine against RSV in healthy 1 to <24 month-old children is currently undergoing. The study comprises 2 cohorts with each a treatment arm and a placebo arm of 80 children in each. The first cohort includes RSV seronegative children between the ages of 5 to <24 months, while the second cohort is of infants between 1 to <3 months of age regardless of their baseline serostatus. Doses of vaccines or placebo were administered at 0, 2, and 4 months. The primary outcome measure was the incidence of solicited adverse events from administration of study vaccine through 28 days following each dose, considered a safety issue. The secondary outcome measure is the incidence and magnitude of MEDI-559 shedding at days 7, 12, and 28 after each dose. The study started in October 2008. The final data collection date for primary outcome measure was planned for May 2011. The study should be completed by January 2012 (United States National Institutes of Health, 2011).

To date, *rA2cp 248/404/1030ΔSH* is the only attenuated RSV strain with a demonstrated safety profile in infants suitable for further study. Whether the vaccine may induce immunity against wild type RSV remains to be verified (Wright et al., 2007). However, results are very encouraging and thus it appears that a pediatric live RSV vaccine candidate that is sufficiently attenuated, optimally immunogenic and not overly reactogenic is an achievable goal (Schickli et al., 2009).

b/hPIV3/RSVF2

The second vaccine candidate is *b/hPIV3/RSVF2*, in which RSV F is expressed from a bovine/human chimeric PIV3 wherein the antigenic F and HN PIV3 genes are derived from human PIV3 and the internal PIV3 genes are derived from bovine PIV3 (Schickli et al., 2009). It is thus a replicating vectored vaccine (van Drunen Littel-van den Hurk et al., 2007). Such vaccines may cause disease in immunocompromised individuals (van Drunen Littel-van den Hurk et al., 2007).

A phase 1 clinical trial to assess the safety of the *b/hPIV3/RSVF2* vaccine in healthy RSV seropositive children between 1-9 years-old was completed in May 2007. Participants are currently being recruited for a phase 1/2a study to evaluate the safety, tolerability, immunogenicity and vaccine-like viral shedding of the vaccine in healthy 6 to < 24 month-old seronegative children and in 2 month old RSV immunity unscreened infants. The cohorts and doses received are described in the table below. Doses of vaccines or placebo were administered at 0, 2, and 4 months. The primary and secondary outcome measures are the same as in the MEDI-559 trial. The study started in October 2008. The final data collection date for primary outcome measure is planned for December 2011, while the study should be completed by January 2012 (United States National Institutes of Health, 2011).

	Age, number of participants, dose
Cohort 1- Experimental	6 to < 24 mos, N = 80, 10:5 TCID:50
Cohort 2- Experimental	6 to < 24 mos, N = 80, 10:6 TCID:50
Cohort 3- Experimental	2 mos, N = 40, 10:4 TCID:50
Cohort 4- Experimental	2 mos, N = 80, 10:5 TCID:50
Cohort 5- Experimental	2 mos, N = 80, 10:6 TCID:50
Cohort 6- Placebo	N = 40 (for Cohort 3); N = 80 (for Cohorts 1,2,4 & 5)

RSV-PFP 2 vaccine

A PFP-2 has been evaluated in 35 women in the third trimester of pregnancy (Munoz, Piedra, & Glezen, 2003). The vaccine was administered intramuscularly. F-specific IgA and IgG in the milk were higher in the F-vaccinated women. 75% vaccine recipients had a response to PFP-2 by Western blot and 95% had a ≥4 fold rise in IgG ELISA Ab after immunization versus none in the placebo group (Munoz et al., 2003). Geometric mean concentrations of IgG ELISA Ab were 4 fold higher in infants of vaccine recipients at birth, 2 and 6 months after delivery than in infants of placebo recipients ($P < 0.01$) (Munoz et al., 2003). A little increase in neutralization Ab (0.5 log 2) was observed in vaccine recipients and their infants, there was no increase in T-cell or cytokine activity and there were no differences between babies of placebo and vaccine recipients

in rate or severity of RSV disease during the subsequent RSV season (Munoz et al., 2003). A substantially more immunogenic subunit RSV vaccine is needed to further evaluate this approach (Schickli et al., 2009).

Subunit vaccines, such as PFP, stimulate a bias toward a Th2 immune response, which may theoretically predispose RSV-naïve recipients for enhanced disease, according to animal studies (Schickli et al., 2009). There is further evidence in mice that the quality of the immune response induced in the vaccinated mothers influences the bias of the immune response of newborns once they get vaccinated (Blomqvist, Lövgren-Bengtsson, & Morein, 2003). If this proves to be applicable to RSV as well, it is important that mothers are vaccinated with a vaccine that induces a balanced Th1:Th2 response. This could be attained through the use of a Th1 immune response biased adjuvant (Schickli et al., 2009). Though administration of adjuvants may increase the generation of neutralizing antibodies and improve the Th1:Th2 balance of subunit vaccines, they would likely be too reactogenic in children and infants.

Also, inherent bias of the neonatal immune system towards a Th2 immune response, which can often lead to a Th2-dominant memory response which persists into adulthood (van Drunen Littel-van den Hurk et al., 2007).

Thus, subunit vaccines are usually considered more appropriate for RSV experienced individuals, such as mothers. In young infants, subunits vaccines are further of limited efficacy due to the presence of maternal antibodies unless administered through mucosal delivery (van Drunen Littel-van den Hurk et al., 2007). Subunit vaccines offer limited duration of immunity (van Drunen Littel-van den Hurk et al., 2007). The development of the PFP-2 vaccine was abandoned by Wyeth in 2005.

Perceptions of stakeholders

National stakeholders

A survey was prepared for Kenyan paediatricians. The objectives were to:

1) understand how RSV is treated in the medical system versus other LRTIs;
2) document the knowledge of Kenyan paediatricians on a few key epidemiological aspects of RSV;
3) document the perceptions of Kenyan paediatricians regarding the burden attributable to the virus, immunization and clinical trial for a paediatric RSV vaccine in Kenya.

The data collection was held between November 10th 2011-December 9th 2011. Kenya Paediatricians Association accepted to circulate the survey (see questionnaire in appendix 9) through email to all of its members (numbering nearly 200). A reminder was sent 3 weeks after the initial sent out. Unfortunately, the response rate was very low with only 10 respondents, 3 of which abandoned before the end of the survey. Because there were so few respondents, no cross-analysis could be performed. However, the responses to the three open questions on 1) whether greater attention should be paid to RSV disease and prevention in Kenya; 2) if a vaccine to protect infants should be considered a priority for routine use within the country; and 3) whether Kenya should participate in an RSV vaccine trial all generated unanimously supportive responses.

However, it is important to note this sample might not be representative of the whole Kenya paediatrician community as those who decided to answer the questionnaire might have had an interest for the disease. Most worked in a national hospital and in Nairobi. This might also explain why the respondents had a relatively good knowledge of the epidemiology of RSV. Most underestimated the mortality associated to RSV in hospitalized LRTI cases. Moreover, only two out of seven reported being able to recognize annual RSV epidemics.

Respondents' characteristics

The median number of years of practice in peadiactrics of the respondents was 6 years (n=10, IQR=2), with a minimum of 2 and a maximum of 24. Out of the 8 who provided details regarding their current work, 7 work in the national hospital, 1 in a district hospital. Five are in the public sector, while 3 are in private for-profit organizations and 1 is in the private not-for-profit sector. Seven are in Nairobi, while 1 works in the Rift Valley.

Medical care of LRTI

Of 7 respondents none prescribed antibiotics for LRTI other than pneumonia. All prescribed antibiotics for pneumonia, severe pneumonia and very severe pneumonia. For severe and very severe pneumonia most would give it by intravenous means (6 and 7/7 respectively), rather than *per os* as in non-complicated pneumonia (6/7).

Knoweldge of RSV epidemiology

When asked whether RSV was the main cause of severe pneumonia (Q5), 4/6 rightfully answered it is. In Berkley et al. (Berkley et al., 2010) one year study, the authors found using molecular methods that the prevalence of RSV in children under 12 year-old hospitalized at Kilifi district hospitals for severe pneumonia was 34%. Two out of 7 identified this prevalence correctly and 5 did not know. The next question (Q7) was asking what percentage of children is infected with RSV during their first year. The answer is two-thirds, so respondents were expected to pick 60%. However, only one respondent selected this proportion, while 3 said 80% and 3 did not know. Four recognized the peak of hospitalization for RSV is between the ages of 2 and 4 months (Q8). One denied and 2 did not know.

All of five respondents recognized RSV infection does result in long lasting immunity (Q9). All of six respondents to the next question knew RSV repeatedly infects throughout life (Q10). The seven respondents knew the risk of disease from RSV infection decreases with age through childhood. When asked whether the risk of disease from RSV infection is greatest following primary exposure and less in subsequent exposures, six out of seven picked the right answer that it is true, while one said no (Q12).

Only two of the seven respondents reported being able to recognize RSV epidemics each year when they cause a seasonal high burden on hospital bed-space (Q13). Four of the seven respondents correctly picked all symptoms presented: fever, coryza, cough, expiratory wheezing, respiratory distress. Three others selected only four of the five symptoms. Two rightfully said RSV symptoms usually last between 7 to 12 days; the other five said between 5 to 10 days.

All seven respondents recognized RSV is the most important cause of bronchiolitis in children under 1 year of age (Q16). Four responded around 4-6% of infants and young children with signs of bronchiolitis or pneumonia during their first RSV infection require hospitalization. Three did not know. Three out of seven respondents said the mortality associated with RSV is 1%. While this is true in United States, Nokes et al. 2009 found a 2.2% mortality among children hospitalized for pneumonia in Kilifi district hospital (Q18). Four others said they did not know.

Four said RSV is a major cause of morbidity in children, while 3 said it was a major cause of both morbidity and mortality.

Their opinion

When asked whether greater attention should be paid to RSV disease and prevention in Kenya, respondents were unanimous (n=6). One mentioned for both its short term and long term outcomes. Another highlighted the fact RSV cases in children are under-recognized in comparison to bacterial pneumonias, yet RSV is a major cause of hospital visits. Prevention would result in reduced burden on health resources and families as well as better quality of life for affected children as noted by someone. The misuse of antibiotics and costs associated were also reported.

To the question: "If a vaccine was available to protect infants, do you think this should be considered a priority for routine use within Kenya?" Four out of the six respondents said yes, while one said not at this time. Another said maybe. Half mentioned it should come after rotavirus vaccine. One specified that rotavirus morbidity and mortality appeared more important. One added it should come after a malaria vaccine in addition to after the rotavirus one.

All six respondents felt Kenya should participate in vaccine trials (phase 2b or 3) for an RSV vaccine. Three specified it would allow to obtain good data on the effectiveness of the vaccine in our setup and community and thus advise rationale for future vaccination initiative. Another mentioned the benefits for Kenyan children.

International stakeholders

Many experts in the field of vaccine development or funding were consulted to document their opinion on the feasibility and desirability of an RSV vaccine. The list of people who were contacted at least twice each is presented in appendix. People who gave detailed responses were Dr Osman Mansoor, Senior Adviser EPI for Unicef (Mansoor, 2011); Professor Barney Graham from the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (Graham, 2011) and Professor Ruth Karron, Director of the Center for Immunization Research of the Johns Hopkins Bloomberg School of Public Health (Karron, 2011). A few others replied saying they did not feel comfortable answering the questions. Professor Salisbury's opinion as chair of the Research and Development Working Group of the Decade of Vaccine initiative was documented through a keynote presentation he made at Global Vaccines 202X conference in 2011 (Salisbury, 2011).

According to Professor Salisbury, RSV vaccine has a low feasibility at high cost. Dr Mansoor was concerned about the major immunological challenges to developing an RSV vaccine and that consequently the development will be driven by industrialized countries where there is documented and large impact on infants and young children. Dr Graham estimated it would take 5-10 years of clinical development for each new vaccine platform. Dr Graham said he noticed a heightened interest from industry for an RSV vaccine in the 2 last years.

Since, RSV has relatively little genetic variation the virus depends largely on immune evasion and modulation to successfully reinfect humans. Therefore, immunizing by an approach other than live virus infection has the potential to induce more durable immunity (Graham, 2011).

The experts were also asked which of the following immunization strategy might be most effective in a developing country setting:

1) the vaccination of pregnant mothers to boost newborns' immunity and thus delay the age of the first episode,
2) pregnant mothers' immunization followed by immunization of the child at an older age,
3) immunization of siblings before epidemics(cocoon strategy),
4) delayed immunization (at 6 months-old) to prevent future burden,
5) other.

According to Dr Karron, the approach of immunizing pregnant mothers to afford passive protection to young infants followed by active immunization of infants during the first 6 months of life seems reasonable while the cocoon would not be cost-effective due to repeated immunization required of parents and siblings. Dr Mansoor rather felt all of the vaccine strategy options need to be assessed based on population impact. However, he pointed the use of vaccine in older children to protect their younger sibling might be hard to 'sell' to parents.

Nair et al. (H Nair et al., 2011) also evaluated the emerging interventions against RSV associated lower respiratory infections in children through an expert opinions survey. As for active immunization, there were very low levels of optimism for low product cost (i.e. cost on the market), affordability (i.e. affordable in the population of interest at the time of introduction) and low cost of development. Levels of optimism regarding the criteria of answerability (i.e. likelihood that the emerging intervention would become available for implementation within the time period specified), likelihood of efficacy, deliverability, sustainability and acceptance to end users for the interventions were medium. While there were high levels of optimism regarding impact on equity (i.e. likelihood that it would improve equity in the population of interest; that the global poor will have access) and acceptance to health workers. They also examined levels of optimism regarding a vaccine for pregnant women. Levels of optimism for such a vaccine were low for low product cost, affordability, answerability and low development cost; moderate levels of optimism for likelihood of efficacy, deliverability, sustainability and impact on equity; and high for acceptance to end users and health workers.

Having an effective RSV vaccine would provide a significant public health benefit. It would be important for the vaccine approach to not interfere with polio, measles, meningitis, Hib and rotavirus vaccinations. Once an RSV vaccine is available, whether it is added to EPI then becomes a matter of cost, how the vaccine is offered (on its own or in combination) and availability of funding for developing countries (Graham, 2011; Mansoor, 2011). Dr Salisbury

described the global burden attributable to RSV as medium-high. Dr Graham suggested that phase I vaccine trials are typically conducted in the country where the vaccine product was developed. Advancing the clinical evaluation to developing countries would depend on the public health importance, the interest of the host country, and the available clinical trials infrastructure available. Prior demonstration of safety and efficacy, and efforts to reduce cost would improve the cost:benefit analysis and make to product more attractive.

Dr Mansoor felt it hard to see a place for RSV vaccine in the near future because of the challenges in the development of an RSV vaccine and later in making it available to developing countries. Yet, he thinks Unicef should be supportive of both the vaccine development and its testing in developing countries, because it is potentially of high impact. He specified that having data from developing countries will be important to plan for eventual use.

Conclusions & Recommendations

Recent progress has been made in estimating the disease burden of RSV. However, there remain important gaps in our knowledge. There are insufficient long term studies and few that look at within country variation geographically and factors relating to this. Potential long term sequelae of RSV which might be a major argument in favor of vaccination must further be verified. Data on the economic burden and the burden among adults are scarce.

In Kenya, RSV was estimated to result annually in 77,539 cases of LRTI, 49,207 cases of severe LRTI, 37,278 outpatient visits and 9,311 hospitalizations among infants, as well as 10,162 hospitalizations and 2,376 deaths in children less than 5. The hospitalizations resulting from RSV among children under 5 years old are more than the 8781 hospitalizations due to rotavirus. However, with its 2,138 deaths in total, RSV would cause the equivalent of about only half (53%) the 4471 deaths resulting from rotavirus among children aged less than 5 years old. While it causes 47% less mortality than rotavirus, RSV results in 16% more hospitalizations than rotavirus.

These estimates were done with the greatest rigor; however their level of confidence depends of the quality of the data they are based on, which are the data available. The results are greatly influenced by the likelihood ratios used to adapt the Kilifi rate in each region, consequently also affecting the national estimate. Though KDHS sample was small, it appeared like the most reliable source of information as HIS thoroughness is uncertain. However, if HIS had been used for the likelihood ratios, the results would have been very different, the national rate lower and not the same regional order. Moreover, the total deaths caused by RSV might be overestimated because the RSV prevalence used was that of hospitalizations for severe pneumonia. RSV is usually associated with low mortality and the prevalence of RSV may be lower in children dying of pneumonia than in those hospitalized. However, there is a possible bias in sampling of less severe cases, the most severe ones dying before a sample could be taken, thus leading to RSV mortality underestimation. Post-mortem assessments should be accomplished even though it may be challenging to obtain authorization from parents. And it would be important to verify whether RSV is responsible for greater morbidity than rotavirus as this may be another incentive towards RSV immunization.

The total health care costs associated with RSV in Kenya were estimated at US$ 4.9 million. These costs include both costs to the government and the population. However, they do not take into consideration costs for episodes occurring in the community and loss of productivity from the caretakers when they do not seek formal medical advice. This cost still represents close to half of the US $10.8 million associated to rotavirus. These costs estimates appear robust though

regional variation could not be accounted for. They could be used to determinate the minimal required efficacy of a vaccine candidate to attain cost-effectiveness in an immunization program.

Vaccines appear like a most promising means of control. Current progresses in the research for an RSV prophylactic vaccine to protect young children provide hope that such a vaccine can be developed. However, establishing a timeline is difficult as the candidate vaccines have to pass through meticulous clinical trials to ensure their security and efficacy. While developing a safe yet immunologic vaccine for naïve children appears challenging, vaccinating pregnant mothers to boost newborns' immunity and thus delay the age of the first episode appears a preferred option over immunization of siblings before epidemics. There was consensus among national and international stakeholders asked that after rotavirus and malaria vaccines, RSV vaccine should be the next to be made available. All stakeholders, including a representative of a funding agency, recognized the desirability of an RSV vaccine though it should not interfere with present EPI schedule.

In the context that severe cases and deaths concentrate in developing countries, it is essential that the global poor have access to an eventual RSV vaccine. Most stakeholders asked were favorable of a clinical trial for an RSV vaccine in developing countries/Kenya. The local data that could thus be generated would be most profitable for an eventual larger campaign. They noted much care should be paid to ethical considerations. While active immunization for RSV would improve equity in the population of interest, the cost of the product will have a great impact on the potential dissemination of the vaccine. It is anticipated that the market cost will be high. Availability of funding will thus be key in ensuring accessibility to the RSV vaccine in developing countries when it becomes available.

It should however be noted that the response from local authorities was very low, probably a symptom of numerous competing health and immunization priorities (introduction of a conjugate Pneumococcus vaccine in March 2011); further in the absence of an RSV vaccine contender while other vaccines such as for rotavirus are available. More information on the burden attributable to RSV within Kenya might serve to emphasize the importance of the disease. Countrywide prevalence estimates and denominator estimates if possible are needed, as well as better mortality estimates including post-mortem assessment. Morbidity attributable to RSV must not be neglected as there are societal costs associated, which are often ignored yet probably substantial.

As noted by the stakeholders, RSV might well become the next priority after rotavirus vaccine is introduced and a malaria vaccine shows promise. It would be in the interest of local authorities to then have the most accurate field data to assess the cost-effectiveness of the new vaccine. Such data is not presently available and can only be collected through a large scale clinical trial to determinate efficacy of a safe vaccine candidate (phase 3 clinical trials) for which KEMRI has

the experience, namely in the field of malaria vaccine research. An information campaign among local stakeholders might be beneficial to inform them of the burden due to RSV and thus foster a more favorable climate for undertaking vaccine trials early in the development stage. It is hoped that the data gathered here can support this purpose.

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APPENDIX

1. List of contacts

National stakeholders:

- *Kenya Ministry of Public Health and Sanitation*

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- *World Health Organization and Unicef*

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2. Questions asked to vaccine stakeholders

A few questions on RSV

Dear,

I work with Professor James Nokes at the Kenya Medical Research Institute- Wellcome-Trust (KEMRI). We are doing a situation analysis to examine whether the climate is favorable for an RSV vaccine trial in Kenya. The document will be presented to the Kenyan Public Health authorities to inform them on the burden associated to RSV. We would also like to document the opinions of international and national actors in the field of RSV on RSV prevention means and in particular vaccines. We consider you are an expert on vaccines and would have a few questions to ask you. We would greatly appreciate if you could take a few moments of your time to let us know of your opinion. In case you do not wish to answer a particular question or do not have an opinion on it, please simply indicate it.

Do you think the development of an RSV vaccine is possible? In what time frame (in terms of years)?
And what about a vaccine which would confer a long lasting immunity (many years)?

Given the challenges in immunizing young infants, do you think other prevention approaches might be promising in a developing country setting?
Do you think alternative immunization strategies might be effective in a developing country setting, such as :
1) the vaccination of pregnant mothers to boost newborns' immunity and thus delay the age of the first episode,
2) pregnant mothers' immunization followed by immunization of the child at an older age,
3) immunization of siblings before epidemics(cocoon strategy),
4) delayed immunization (at 6 months-old) to prevent future burden (according to Dr Nokes researches a majority of the disease in the community occurs after the age 6 months-old though the peak of hospitalization is passed), etc.?

Do you think an RSV vaccine for children is relevant in a developing country? Under what conditions? Do you think it should eventually be added to EPI? If you are a funding agency, do you think your agency would support RSV immunization?

What is your opinion on a RSV vaccine trial in Kenya?

Finally, regarding vaccines currently under development, it appears there were some reversions in the vaccine 559 (rA2cp 248/404/1030 8710;SH). What is your opinion on the stability of the vaccine? To your knowledge, can anything be done to stabilize it?

To your knowledge, are there currently other vaccines under development (aside from pre-trial stage and MEDI 524 or b/hPIV3/RSV F2) for RSV in children?

Please confirm whether I can quote you in the report.

Thank you very much in advance for your collaboration.
Regards,

Genevieve Gravel
KEMRI intern
MPH Epidemiology Candidate
University of Toronto

3. Literature search strategies

BURDEN (Jul 15th 2011)

1. *Medline Ovid*
RSV (MeSH) or RSV or Respiratory syncytial virus
AND
Developing countries (MeSH) or GAVI 56 eligible countries 2011

- Humans, from 2005=87=> 35 selected

2011 56 GAVI eligible countries
(http://www.gavialliance.org/support/who/eligible/index.php)

- Afghanistan
- Bangladesh
- Benin
- Bolivia
- Burkina Faso
- Burundi
- Cambodia
- Cameroon
- Central African Republic
- Chad
- Comoros
- Congo, Dem Republic of
- Côte d'Ivoire
- Djibouti
- Eritrea
- Ethiopia
- Gambia
- Ghana
- Guinea
- Guinea-Bissau
- Guyana
- Haiti
- India
- Kenya
- Korea, DPR
- Kyrgyz Republic
- Lao PDR
- Lesotho
- Liberia
- Madagascar
- Malawi
- Mali
- Mauritania
- Mozambique
- Myanmar
- Nepal
- Nicaragua
- Niger
- Nigeria
- Pakistan
- Papua New Guinea
- Rwanda
- São Tomé e Príncipe
- Senegal
- Sierra Leone
- Solomon Islands
- Somalia
- Sudan
- Tajikistan
- Tanzania
- Togo
- Uganda
- Uzbekistan
- Viet Nam
- Yemen
- Zambia
- Zimbabwe

2. African Index Medicus, keywords: syncytial or RSV = 1not relevant

3. Africa Journals Online, keywords: syncytial or RSV= 1

4. Literature provided by Dr James Nokes, hand-picked

5. List of references of the articles.

VACCINE (June 8th 2011)

1. Medline Ovid

with keywords (RSV OR syncytial) AND (vaccine), since 2005

1. exp Respiratory Syncytial Virus, Human/
2. vaccine*.mp.
3. limit 2 to yr="2005"
4. RSV.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. limit 4 to humans
6. syncytial.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
7. limit 6 to humans
8. 5 and 7
9. 1 or 8
10. 3 and 9

2. Literature provided by Dr James Nokes, hand-picked

3. List of references of the articles.

4. *Clinical trials website*.

5. *Google* to find for news releases and grey literature, keywords: RSV vaccine OR syncytial vaccine

6. Contacts with developers and researchers involved for precisions.

4. Table 4: Rates of RSV associated LRTI in Kilifi District

Indicator	Rate /1000 CYO	Source of surveillance	Years of surveillance	Case definition	Assay	Reference
LRTI <1 yo	104	Community	2002-05	Acute cough or difficulty in breathing in association with one of the following: (1) increased respiratory rate for age, or (2) intercostal indrawing, or (3) inability to feed, reduced conscious level, or hypoxia	IFAT	10
Severe LRTI <1 yo	66	Community	2002-05	Acute cough or difficulty in breathing with: intercostal indrawing, and/or inability to feed, reduced conscious level, or hypoxia.	IFAT	10
Outpatient visits <1 yo	50	Community	2002-05	See LRTI case definition above.	IFAT	10
Hospitalizations[1] <1 yo	13	Community	2002-05	See LRTI case definition above.	IFAT	10
Hospitalizations <1 yo	11.1	Hospital	2002-07	Severe pneumonia: history of cough or difficulty in breathing for <30 days, and lower chest wall indrawing. Very severe pneumonia: history of cough or difficulty in breathing for <30 days, when accompanied by any 1 of prostration (inability to feed or drink), coma, or hypoxia.[3]	IFAT	18
Hospitalizations <1 yo	20.4	Hospital	2007	WHO criteria for severe and very severe pneumonia.[2]	PCR	3
Hospitalizations <5 yo	2.93	Hospital	2002-07	See severe and very severe pneumonia case definitions from same reference above.	IFAT	18
Hospitalizations <5 yo	5.35	Hospital	2007	WHO criteria for severe and very severe pneumonia.[2]	PCR	3
Mortality <5 yo	0.22	Hospital	2002-07	See severe and very severe pneumonia case definitions from same reference above.	IFAT	18

[1] extrapolated from outpatient visits,26% of which are hospitalized

[2] WHO criteria- Severe pneumonia: cough or difficult breathing plus lower chest wall indrawing and no signs of very severe pneumonia; very severe pneumonia: cough or difficult breathing plus at least 1 of hypoxia, defined as an oxygen saturation <90% by fingertip pulse oximetry, inability to drink or breast feed, inability to sit, or impaired consciousness at admission, including infants < than 2 months of age.

[3] Hypoxia is defined as an oxygen saturation level (pO2) of <90% determined by finger tip Oxymeter.

Notes:
- CYO Child-years of observation
- IFAT Immunofluorescent Antibody Test
- LRTI Lower Respiratory Tract Infection
- PCR Polymerase Chain Reaction
- YO year(s) old

5. Table 5: RSV associated events incidence, 2009 & 2010 - Using KDHS 2009 data and HIS 2010 data

	Birth cohort (<1 y)[1]	Total population < 5 y[1]	Annual cases of RSV associated pneumonia (15.3%)[6] recorded in HIS (outpatient department)[2]	Annual incidence rate of RSV associated pneumonia /1000 CYO (15.3%) from HIS data[2]	Percentage of <5 yo with symptoms of ARI[5] in prec 2 weeks (prev)[3]	Annual incidence of RSV associated ARI [5] (15.3%)[4]	Annual incidence rate of RSV associated ARI [5]/1000 CYO (15.3%)[4]	Percentage of the total population per region[4]	Likelihood ratios for symptoms alone[4]	Perc for whom advice or treatment was sought from a health facility or provider[3]	Annual incidence of RSV associated ARI[5] seeking advice[4]	Annual incidence rate of RSV associated ARI[5] seeking advice /1000 CYO[4]	Likelihood ratios for symptoms and seeking care[4]
Central	110,117	535,742	10,647	19.9	7.5	95,223	178	12.8	0.60	(45.2)	43,041	80	0.48
Coast	115,466	537,719	11,764	21.9	12.5	159,291	296	21.3	1.00	56.4	89,840	167	1.00
Eastern	160,668	809,563	15,497	19.1	6.0	115,114	142	10.2	0.48	(52.6)	60,550	75	0.45
Nairobi	94,647	397,161	5,289	13.3	6.5	61,179	154	11.1	0.52	55.9*	34,199	86	0.52
North Eastern	44,704	328,088	5,150	15.7	6.7	52,094	159	11.4	0.54	(60.9)	31,725	97	0.58
Nyanza	199,203	947,849	11,965	12.6	7.9	177,456	187	13.5	0.63	54.6	96,891	102	0.61
Rift Valley	341,645	1,625,721	22,899	14.1	7.8	300,515	185	13.3	0.62	58.0	174,298	107	0.64
Western	155,514	757,490	18,248	24.1	6.0	107,709	142	10.2	0.48	(45.4)	48,900	65	0.39
Kenya	1,221,937	5,939,333	101,460	17.1	7.6	1,069,735	180	12.9	0.61	55.9	597,982	101	0.60

[1] Source: Kenya Demographic Census 2009 (32)
[2] Source: Kenya MoPHS Health Information System, 2010 (34)
[3] Source: KDHS 2008-2009 (30)
[4] Estimated using KDHS data
[5] ARI: Acute Respiratory Infections. Symptoms of ARI (cough accompanied by short, rapid breathing, which was chest-related) is considered a proxy for pneumonia in KDHS (30).
[6] From reference 18, see table 2.

Notes: CYO Child-years of observation
LRTI Lower Respiratory Tract Infection
y years
An asterisk denotes a figure based on fewer than 25 unweighted cases which has been replaced by the national rate.
Numbers in parenthesis are based on 25-49 unweighted cases.

6. Table 6: RSV associated events incidence, 2009 - Using adjusted Kilifi District rates

	LRTI (<1 yo)			Severe LRTI (<1 yo)				Outpatient visits (<1 yo)			Hospitalizations (<1 yo)			Hospitalizations (<5 yo)			Mortality hosp cases (<5 yo)	
	Incidence /1000 CYO	One-year risk ratio[1]	Annual number of cases	Incidence /1000 CYO	One-year risk ratio[1]	Annual number of cases	% of national cases	Incidence /1000 CYO	One-year risk ratio[1]	Annual number of cases	Incidence /1000 CYO	One-year risk ratio[1]	Annual number of cases	Incidence /1000 CYO	One-year risk ratio[1]	Annual number of cases	Annual number of deaths	% of national cases
Central	62.4	16	6,871	39.6	25	4,361	7.4	30.0	33	3,304	6.3	160	688	1.4	710	755	17	8.9
Coast	104.0	10	12,008	66.0	15	7,621	16.1	50.0	20	5,773	13.0	77	1,501	2.9	341	1,576	35	15.5
Eastern	49.9	20	8,021	31.7	32	5,090	10.0	24.0	42	3,856	5.8	172	935	1.3	762	1,062	23	10.3
Nairobi	54.1	18	5,119	34.3	29	3,248	6.8	26.0	38	2,461	6.7	149	634	1.5	662	600	13	6.6
North Eastern	55.7	18	2,492	35.4	28	1,581	3.6	26.8	37	1,198	7.5	133	336	1.7	590	556	12	3.2
Nyanza	65.7	15	13,093	41.7	24	8,309	17.0	31.6	32	6,295	8.0	126	1,584	1.8	558	1,699	37	16.9
Rift Valley	64.9	15	22,171	41.2	24	14,070	30.6	31.2	32	10,659	8.3	120	2,850	1.9	532	3,057	67	28.6
Western	49.9	20	7,763	31.7	32	4,927	8.4	24.0	42	3,732	5.0	199	781	1.1	883	858	19	10.0
Kenya	63.2	16	77,539	40.1	25	49,207	100.0	30.4	33	37,278	7.6	132	9,311	1.7	584	10,162	224	100.0

[1] Risk ratio: ratio of the risk in the exposed divided by the risk in the unexposed.

Notes: CYO Child-years of observation ; LRTI Lower Respiratory Tract Infection ; YO year(s) old

In blue are rates taken from Nokes et al. 2008 and 2009 to which the regional likelihood ratio was applied.

7. Table 7: Cost estimates associated with RSV disease burden

	Source	Per patient US$ (KSH)	Total US$ (KSH)
OUTPATIENT			
Public health care			
Cost of visit	38	13.59 (1178)	64.6% of patients
Investigation	39	13.72 (1189)	
Medication	39	5.50 (477)	2,150,843 (186,381,508)
Total		32.82 (2844)	
Societal			
Caretaker time[1]	39	13.45 (1165)	All caretakers
Transportation cost[2]	39	2.44 (212)	1,612,201 (139,705,478)
Total		15.89 (1377)	
INPATIENT			
Public health care			
Total including hotel cost, medication and investigations, but excluding fees recovered through user fee[3]	39	98.39 (8526)	76.2% of patients 761,833 (66,016,726)
Societal			
Total cost to caretaker including user fee, pre-admission cost, caretaker time and transportation	39	40.74 (3531)	All caretakers 414,024 (35,877,285)
TOTAL PUBLIC HEALTH CARE			**2,912,676 (252,398,234)**
TOTAL SOCIETAL			**2,026,225 (175,582,763)**

[1] Estimated as 33% of the caretaker cost in public district hospitals
[2] Estimated as 6% of the caretaker cost in public district hospitals
[3] Estimated as 15% of the treatment cost

8. Table 8: Vaccines currently under development

Vaccine	Type and delivery	Target population	Status	Objective of the trial and results if available	Study completion (and primary completion)	Advantages	Disadvantages	Developer and contacts	Ref.
rA2cp248/404/1030ΔSH (MEDI-559)	Live attenuated vaccine, intranasal	Young infants (from 2 months)	Phase 1/2a ongoing	To describe the 28-day post-final dose safety and tolerability of three doses of MEDI-559 at 10:5 FFU when administered to healthy RSV seronegative children 5 to <24 months of age and healthy infants 2 months of age regardless of baseline serostatus. Primary Outcome Measures: Incidence of symptoms through 28 days following each dose Secondary Outcome Measures: Incidence and magnitude of vaccine-like viral shedding of MEDI-534 at days 7, 12, and 28 after each dose	Jan 2012 (May 2011)	- Inexpensive - Induction of balanced immune responses - No needles needed as mucosal delivery - Safe in young RSV naïve infants - Potential efficacy in infants with maternal antibodies	- Potential for reversion to wild type - Over/under-attenuation - Disease in immunocompromised -Cold-chain necessary	MedImmune	48, 49, 51
b/hPIV3/RSVF 2 (MEDI-534)	Replicating vectored vaccine, intranasal	Young infants (from 2 months)	Phase 1/2a ongoing	To describe the safety and tolerability of multiple doses of MEDI-534 at 10:5 or 10:6 TCID:50 in RSV and hPIV3 seronegative children 6 to < 24 months of age and at dosages of 10:4, 10:5 or 10:6 TCID:50 in unscreened infants 2 months of age. Primary Outcome Measures: Incidence of symptoms through 28 days following each dose	Jan 2012 (Dec 2011)	- Inexpensive - Induction of balanced immune responses - No needles needed as mucosal delivery	- Antibody production to the vector - Disease in immunocompromised - Cold-chain necessary	MedImmune	57

				Secondary Outcome Measures: Incidence and magnitude of vaccine-like viral shedding of MEDI-534 at days 7, 12, and 28 after each dose					
PFP-2	Subunit	Pregnant women in 3rd trimester	Phase 1/2a	20 treatment/15 placebo Results: Geometric mean concentrations of IgG ELISA Ab were 4 fold higher in infants of vaccine recipients at birth, 2 and 6 months after delivery than in infants of placebo recipients ($P < 0.01$). 0.5 log 2 increase in neutralization Ab in vaccine recipients and infants. No increase in T-cell or cytokine activity. No differences between babies of placebo and vaccine recipients in rate or severity of RSV disease during the subsequent RSV season.	Completed.	- Stable - Induction of virus neutralization antibodies	- Not appropriate for young, naïve subjects - Potential for aggravated disease - Th2-biased immune responses unless formulated with Th1-promoting adjuvant	N/A, development abandonned	53

9. Questionnaire for Kenya paediatricians

Respiratory syncytial virus: A survey of the views of Kenyan Paediatricians

The objectives of the present questionnaire are to:

4) understand how RSV is treated in the medical system versus the other LRTIs
5) document the knowledge of Kenyan paediatricians on a few key epidemiological aspects of RSV
6) document the perceptions of Kenyan paediatricians regarding the burden attributable to the virus, immunization and clinical trial for a paediatric RSV vaccine in Kenya

The questionnaire is anonymous, we only ask you about some information on your practice.

It should not take you more than 10 minutes to answer the questionnaire. We would be grateful if you could answer all the questions. In order to indicate your answers, you may type them, bold or highlight them. Please note the questionnaire is also available online at:

https://www.surveymonkey.com/s/RSV_KEMRI

We thank you very much in advance for your collaboration which will greatly help us to better understand how RSV is perceived among Kenyan paediatricians.

Please do not hesitate to contact us for any inquiry at genevieve.gravel@utoronto.ca.

Genevieve Gravel, Mwanajuma Ngama and Dr James Nokes
KEMRI Wellcome-Trust Research Programme, Kilifi

IDENTIFICATION OF RESPONDENT

1. Please state the number of years of practice you have in paediatrics: _____

2. Please list the institutions (individually) where you currently work, their type and specify their region:

Name	Dispensary	Health Center, maternity, nursing home	District hospital (primary)	Provincial hospital (secondary)	Tertiary hospital (tertiary)	**Type**			**Region**							
						Public	Private for profit	Private not-for-profit	**Central**	**Coast**	**Eastern**	**Nairobi**	**North Eastern**	**Nyanza**	**Rift Valley**	**Western**
1.																
2.																
3.																
4.																
5.																

SECTION 1: MEDICAL CARE OF LRTI

3. What kinds of diagnostic tests are done and to approximately what proportions of patients with LRTI:

Diagnostic test	Approximate % of patients
Culture from sputum	
Molecular methods	
Colour of sputum	
Chest X-ray	
Sputum Gram stain	
S.pneumoniae antigen in urine	
Rapid test (e.g. influenza)	
Biomarkers	
Other:	

4. Would you prescribe antibiotics in case of the following types of LRTI and if so, specify the route of administration:

Types of LRTI	Prescribe antibiotics		Route of administration if applicable (IV, PO)
	Yes	No	
No pneumonia			
Pneumonia			
Severe pneumonia			
Very severe pneumonia			

SECTION 2: EPIDEMIOLOGY AND BURDEN OF RSV

5. List in order of frequency the causes of severe pneumonia among Kenyan children (*1 being the most common, 5 the least*):

_____ Human parainfluenza virus
_____ Pneumococcus
_____ Respiratory syncytial virus (RSV)
_____ Adenovirus
_____ Haemophilus influenza type b (Hib)

6. In a study of the viral etiology of severe pneumonia among Kenyan children over a full calendar year using molecular diagnostics, RSV was detected in about _____% of the cases (*identify the answer you think is right, one answer*).

- 15 %
- 25 %
- 35 %
- Do not know

7. _____%of infants are infected (irrespective of disease outcome) with RSV during their first year of life *(identify the answer you think is right, one answer*).

- 40%
- 60%
- 80%
- Do not know

8. The peak of hospitalization for RSV is between the ages of 2 and 4 months (*indicate whether the statement is right*). Yes/ No/ Do not know

9. An infection with RSV result in long lasting immunity (*indicate whether the statement is right*). Yes/ No/ Do not know

10. RSV repeatedly infects throughout life (*indicate whether the statement is right*). Yes/No/Do not know

11. Through childhood, the risk of disease from RSV infection decreases with age (*indicate whether the statement is right*). Yes/ No/ Do not know

12. The risk of disease from RSV infection is greatest following primary exposure and less in subsequent exposures (*indicate whether the statement is right*). Yes/No/Do not know

13. I can recognize RSV epidemics each year when they cause a seasonal high burden on hospital bed-space *(indicate whether you agree with the statement*). Agree/ Disagree/ Do not know

14. In newborns, infants and young children RSV causes upper and lower respiratory tract disease characterized by (*identify all those that apply*): fever, coryza, cough, expiratory wheezing, respiratory distress. Do not know.

15. RSV symptoms usually last (*identify the answer you think is right, one answer*):

- between 5 to 10 days
- between 7 to 12 days
- between 10 to 15 days
- Do not know

16. RSV is the most important cause of bronchiolitis in children under 1 year of age (*indicate whether the statement is right*). Yes/No/Do not know

17. During their first RSV infection, around ____% of infants and young children with signs of bronchiolitis or pneumonia require hospitalization *(identify the answer you think is right, one answer*).

- 1-2%
- 3-4%
- 4-6%
- Do not know

18. The associated mortality among hospitalized cases of children less than 5 years is around (*identify the answer you think is right, one answer*):

- 1%
- 2%
- 3%
- Do not know

19. RSV is a major cause of _____ in your children (*identify the answer you think is right, one answer*).

- Morbidity
- Mortality
- Morbidity and mortality

SECTION 3: YOUR OPINION

20. In your opinion, should greater attention be paid to RSV disease and prevention in Kenya (*identify your answer*)?

Yes/No/ Maybe/Do not know

Please briefly specify why?

_____

21. If a vaccine was available to protect infants, do you think this should be considered a priority for routine use within Kenya (*identify your answer*)?

Yes/No/ Maybe/Do not know

Please briefly specify why?

_____

22. Do you believe Kenya should participate in vaccine trials (phase 2b or 3) for an RSV vaccine (*identify your answer*)?

Yes/No/ Maybe/Do not know

Please briefly specify why?

_____

Thank you very much!

Do you have any further comments you may like to add?

_____

_____

_____