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Afriflu2—Second international workshop on influenza vaccination in the African continent—8 November 2012, Cape Town (South Africa)

Barry D. Schoub,

National Institute for Communicable Diseases/National Health Laboratory Service, Department of Virology, University of the Witwatersrand, Johannesburg, South Africa

Bradford D. Gessner,

Agence de Médecine Préventive – AMP, 13, chemin du Levant, 01210 Ferney-Voltaire, France

William Ampofo,

Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Ghana

Adam L. Cohen,

Influenza Program, Centers for Disease Control and Prevention, Pretoria, South Africa

Influenza Division, Centers for Disease Control and Prevention, Atlanta, USA

Christoph A. Steffen*

Agence de Médecine Préventive – AMP, 13, chemin du Levant, 01210 Ferney-Voltaire, France

Abstract

The second meeting of the Afriflu conferences took place in Cape Town, South Africa, with over 60 participants from 15 countries in Africa and also outside the continent. Significant progress in surveillance has been made in better understanding the illness burden of influenza on the continent, which limited evidence suggests is greater than that in the developed world. In southern Africa HIV and TB coinfections play a major role in increasing hospitalisation and mortality, while elsewhere in Africa other cofactors still need to be determined.

There is currently no indigenous vaccine production in sub-Saharan Africa and only one facility, based in South Africa, capable of filling imported bulk. Innovative vaccine strategies will need to be explored, such as maternal immunisation, and also the possibility of other influenza vaccine options, such as live attenuated influenza vaccine for young children. Sustained indigenous vaccine production is essential for the continent to have vaccine security in the event of a pandemic even though establishing local production faces considerable challenges especially ensuring adequate markets on the continent. There is an urgent need to develop effective communication messages for decision makers as well as healthcare workers addressing the importance of influenza even in the face of the major competing health burdens of the continent.

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*Corresponding author. Tel.: +33 1 53 86 89 20; fax: +33 4 50 42 98 07. csteffen@aamp.org (C.A. Steffen).

Keywords

Conference report; Influenza; Africa; Illness burden; Vaccines; Priority groups; Vaccine security

1. Introduction

At the time of the first Afriflu conference which was held in Marrakech, Morocco 1–2 June 2010, Africa was seen as a continent where relatively little attention has been paid to influenza and the least empowered part of the planet for influenza surveillance and control [1]. Significant progress has been made in the 2 years since then. More and more countries are carrying out surveillance and some 24 African countries now contribute specimens to WHO, 5 of them contributing about 1000 or more specimens annually. The median positivity for ILI is 15.6% and for SARI is 8.9% reflecting a progressively more productive surveillance programme throughout the continent [2]. Recent publications, including a complete supplement of the *Journal of Infectious Diseases*, are now starting to throw considerably more light on the regional burden of influenza and also on regional responses to vaccination [3]. Another African influenza initiative, that of the African Network for Influenza Surveillance and Epidemiology (ANISE), held its third annual meeting in February 2012 in Nairobi, Kenya [4]. This meeting dealt comprehensively with recent progress in the development of surveillance programmes on the continent.

This, the second of the Afriflu conferences, was held immediately preceding the first International African Vaccinology Congress in Cape Town, 9–11 November 2012. Afriflu2 was organised jointly by the Agence de Médecine Préventive (AMP, www.aamp.org) and the National Institute for Communicable Diseases (NICD) of South Africa (www.nicd.ac.za). Over 60 delegates from 15 African countries and from several non-African countries met to focus on influenza vaccines and vaccination with relevance to the African continent. The meeting was divided into three streams – first, the burden of influenza and effectiveness of influenza vaccines in Africa; second, defining the risk groups for prioritisation to receive vaccine; and third, vaccine security, an issue of especial importance to the African continent.

This paper is a report of the deliberations of the meeting which sought to answer four fundamental African public health questions regarding influenza: (1) How important is influenza in Africa? (2) In whom is it of particular importance? (3) How well do vaccine interventions work on the African continent? (4) How secure is Africa for supplies of seasonal and pandemic influenza vaccines given that there is currently almost no indigenous influenza vaccine production on the continent?

2. Is influenza of importance in Africa?

Reports from the four subregions of the WHO African Region – southern, central, eastern and western – were presented. Uniformly, influenza has been commonly associated with respiratory illness throughout the continent, involving both the upper and lower respiratory tract. The estimated burden of illness in Africa was usually but not always greater than that of developed countries. For example in a comparative study of excess mortality in the elderly (65 years) between South Africa and the USA, it was found that the relative risk

of all-cause deaths in South Africa was 4.1 times that of the USA, while pneumonia and influenza-related deaths and all-cause respiratory deaths were 3.0 and 3.5 times, respectively [5]. However rates of hospitalisation from a study in Kenya were comparable with an equivalent USA study [6,7], despite overall diverging health seeking behaviour patterns.

2.1. Surveillance

The quality of surveillance in Africa has improved dramatically in all subregions since 2006 when less than 5000 specimens were processed, mainly in South Africa. In 2010, over 40,000 specimens from all regions were processed. Of some 33,357 specimens processed by 24 African countries in 2012 (up to 2nd November) 11% were positive for influenza with the medians in 15 of these countries for ILI being 15.6% and SARI 8.9% [2]. The percent of isolates collected from patients with mild or severe respiratory disease that yielded influenza was similar throughout the continent, although there was a wide range. Major challenges to obtaining good surveillance data still remain, particularly in many countries in the central and western subregions where high-level commitment from government is lacking and, at present, the major portion of funding for surveillance still comes from outside sources. The difficulty in obtaining good data is also compromised by variations in health seeking behaviour seen in different countries. The great majority of ILI patients do not seek medical care and very few of those who do, get tested for influenza. There has, nevertheless, been a significant increase in the number of countries in Africa reporting data, as well as providing influenza strains to WHO. Surveillance is currently most extensive in South Africa with 250 ILI sites while SARI is investigated in six hospitals representing urban and rural populations [8]. In Kenya surveillance for both ILI and SARI has been undertaken at several sites from the coastal region to inland urban populations and rural sites in the west of the country [2,6–8]. Cameroon has also established 20 ILI sites in nine regions and two SARI sites in one region [9]. In West Africa, Ghana has surveillance programmes in all of its 10 regions, with 22 ILI and 4 SARI sites [10].

2.2. Burden of disease

Relatively good consistency was found between the various methods used for burden of disease measurement. Severe disease and death in SARI patients was strongly associated with coinfection with HIV [11], tuberculosis [12] and *Streptococcus pneumoniae* [13] in South Africa. However, the role of coinfection was not apparent in SARI patients in Malawi where a preliminary analysis found that malaria coinfection with HIV and tuberculosis also did not appear to be independent risk factors [14]. Similarly in Kenya there is limited evidence of an increased influenza risk in HIV patients and patients with chronic diseases [15]. In all studies young children and infants were at particular risk. For example, in medically attended and home-reported ILI in Kenya (2007–2010) the burden of illness was highest in children less than two years of age and lowest in adults over 50 years of age [8]. In a similar study of SARI patients in Kenya, influenza hospitalisations were 1–8/1000 for children <5 years compared to 0.5–0.6/1000 for children 5 years of age [6,7]. Surveillance in the Cameroon showed that 40–70% of ILI cases visiting sentinel sites were in children <5 years of age [9]. These data underline the importance of immunising young children as well as maternal immunisation to protect the very young before they can be vaccinated. Efforts to determine disease burden are underway in Ghana by the Ghana Health Service Public

Health Division following a desktop pilot of a WHO manual for disease burden estimation in January 2012 [10]. Cases of hospitalizations from respiratory illness are now reviewed nationally against influenza infections detected.

2.3. Seasonality of influenza

The seasonal distribution of influenza in Africa differs regionally and by country. Thus in the temperate weather of South Africa, influenza seasons monitored since 1984 have shown a sharp winter prevalence with a mean onset in week 23 (second week of June) and mean peak in week 27 (second week of July); the mean duration of the season is 11 weeks [16]. In all other African countries that presented data, with the exception of Zambia, which follows South Africa's pattern [17], influenza appears to occur throughout the year with various countries on the continent having their own specific pattern. In other southern African countries two peaks within the winter season were observed [2,18,19]. In the more tropical countries of central, eastern and western Africa influenza peaked in the corresponding rainy seasons [9,10].

3. In whom is influenza of particular importance?

In considering priority groups for seasonal influenza immunisation, two issues need to be taken into account. Firstly, a great deal of evidence has been accumulated since the WHO influenza vaccine recommendations of 2005 and, because of this, an updated (April 2012) set of recommendations has recently been published [20]. Five priority groups were identified; the highest being pregnancy, followed, in no particular order, by four others – health care workers, children less than five years of age (especially 6–23 months), the elderly and persons with defined underlying medical conditions. Secondly, both developed and developing countries need to regionally tailor their country-specific recommendations appropriate to their prevailing circumstances, basing them on WHO recommendations – this is particularly applicable to Africa.

3.1. Report of the influenza working group of the WHO strategic advisory group of experts (SAGE) working group on influenza vaccines and immunisation

The background to the new WHO position paper on influenza vaccines [20] was presented. Designating pregnancy as the highest priority was based on multiple sources of evidence that the risk of influenza in pregnant women without any other risk factors is equivalent to that seen in high-risk adults with underlying medical conditions that predispose them to the complications of influenza [21]. If underlying factors are added to pregnancy the risk becomes even greater. Both excess mortality as well as the increased risk of hospitalisation have been reported in pregnancy in Africa [22]. There is also evidence that influenza vaccination of pregnant women may result in increased birth weight of the infant [23]. Thus, women in the third trimester without any other risk factors are over five times more likely to be hospitalised for influenza-related conditions than non-pregnant women – 10.5 vs. 1.91 per 10,000 women months, respectively [21]. A further very valuable benefit of vaccination in pregnancy is the protection afforded to the newborn and young infant less than six months of age who are not eligible for influenza vaccination. For example, a study in Bangladesh demonstrated a 29% reduction in ILI and a 63% reduction in laboratory

confirmed influenza in infants born to mothers vaccinated in pregnancy [24]. These infants also had significantly higher birth weights [25]. Furthermore the safety profile of influenza vaccination in pregnancy is excellent.

Health-care workers were identified as one of the target groups because of the direct and indirect benefits. Since health care workers are often healthy young adults, they generally respond well to the vaccine and are at an increased occupational risk of infection. In addition indirect benefits exist from decreasing the risk of transmitting infection to vulnerable patients as well as reducing absenteeism in healthcare workers who may be part of essential personnel in times of crisis.

Young children have the highest incidence of infection with influenza, and school-aged children have the highest rates of transmission [26]. Complications are highest in the very young with hospitalisation rates in infants less than two years of age being equivalent to those seen in the elderly. Unfortunately, vaccine efficacy of non-adjuvanted trivalent inactivated influenza vaccine (TIV) is lower in children less than two years of age and this is also the case for the elderly who account for the highest rate of hospitalisation and up to 90% of all influenza related deaths in the developed world [27].

Although these five priority groups would also be applicable in general to the African setting, comorbidities substantially contribute to influenza burden and mortality on the continent and would significantly affect regional influenza vaccine recommendations. Specifically, human immunodeficiency (HIV) and tuberculosis (TB) co-infections have been shown to play important roles in aggravating influenza outcomes in southern Africa [11]. Sub-Saharan Africa is home to 2/3 of all persons in the world living with HIV (22.5 of 33.3 million), with South Africa having the largest number in the world, 5.6 million, and Swaziland the highest prevalence in the world, 25.9%. A similar situation exists with TB. South Africa has the third highest burden in the world, 400,000–600,000 affected and 1% of the population developing TB disease every year [28]. In children, HIV infection increases the risk of deaths associated with influenza and influenza-related pneumonia [29] and in adults (25–54 years) the excess mortality is increased 150–200 times that of age matched HIV-negative persons [11]. This is equivalent to what was found in the USA in the pre-HAART era and is currently 2–4 times that seen in the elderly in South Africa. Data from South African SARI surveillance sites showed that 45% of patients hospitalised for acute lower respiratory tract infection were HIV positive. In the H1N1 pandemic of 2009 53% of the deaths in South Africa were in HIV-infected persons and 10% in patients with active TB [22].

4. How efficacious and effective is influenza vaccination in Africa?

4.1. Vaccine efficacy and effectiveness in the African setting

Few studies of vaccine efficacy and effectiveness have been carried out in Africa. In South Africa, a randomised double blind placebo-controlled trial of trivalent inactivated influenza vaccine efficacy in HIV-infected adults showed it to be satisfactory at 75.5% (9.2–95.0) [30]. However, another randomised double-blind placebo-controlled trial in HIV-infected children, also in South Africa, in children 6–59 months of age, demonstrated absence of

trivalent inactivated influenza vaccine efficacy – (from 19.1% [–61.0, 59.9] for laboratory confirmed influenza illness to 22.6% [–36.2, 56.6] for ILI [31]). Mention was made at this conference of a study in children 6 months to 10 years of age with unknown HIV status in 2 sites in Kenya. The study found that influenza vaccine was effective in preventing disease, and this was not unexpected because of the older age of the subjects. It should be pointed out that in the South African children’s study the vaccine was not well matched with circulating strains; nevertheless, over and above the mismatch, the immunogenicity in this population was intrinsically poor. In elderly South Africans poor effectiveness of influenza vaccination – 19.3% – was found in a small study in a health management setting [32].

5. How can vaccine security be established for Africa?

5.1. Challenges of influenza vaccination in Africa

Africa lags far behind the rest of the world, not only for influenza surveillance, but also for influenza vaccination. Very few countries in sub Saharan Africa (including South Africa and Mauritius) make provision for seasonal influenza vaccination in their national immunisation schedule. There is also only one country in sub-Saharan Africa, South Africa, which has any facility for local filling or the potential for future production of influenza vaccine. These challenges are compounded by serious logistical obstacles including delays in importation and distribution and insufficient buy-in from healthcare workers and decision-makers especially with the pressure of competing health priorities.

The vaccine donation initiative for the provision and distribution of the 2009 pandemic H1N1 vaccines to African countries illustrated many of these logistical problems. This initiative was established soon after the advent of the 2009 pandemic by a WHO – USAID partnership together with the respective governments of African countries. Some 44 of the 46 WHO African region member states were eligible for donation. In the eastern and southern African regions 3,391,800 doses were received and 2,048,225 doses were administered; in the western African region 6,483,300 doses were received and 5,309,855 administered: and the central African region received 864,000 doses with 587,164 administered. While the peak of the pandemic in Africa was in September of 2009, the average delay in the procurement process for the region was 261.4 days from signature of the letter of intent to implementation. Vaccine was therefore only available well after the pandemic had declined. Nevertheless much was learnt from the experience that will be of value in future planning. Firstly, there was almost unanimously a great willingness, responsiveness and commitment to the initiative, including financial, from a number of countries, even to the extent of urgently adjusting legal requirements and regulations. Secondly, rumours that circulated globally regarding the efficacy or safety of the H1N1 vaccine generally had little effect on the African continent. Thirdly, the exercise also improved the capacity to respond to future pandemic threats. National task teams have been established in several countries and an WHO African Region Crisis Management Team (CMT) has now been created. What does need improving for the future is the communication gap at a number of levels as was experienced during this exercise.

5.2. Challenges to the development of indigenous vaccine production in Africa

Sustainable vaccine production is dependent on reliable demand and reliable supply. The driver for demand is a sustainable vaccine procurement policy which itself depends on evidence of local disease burden, vaccine efficacy and effectiveness and the priority accorded to influenza in the face of competing health needs. In terms of supply, while global production of seasonal vaccine [at 1420 million doses per annum] may well fall far short of global needs [33], it is significantly in excess of demand and this surplus has grown from 250 million doses in 2007 to 584 million doses in 2012. What complicates indigenous African vaccine production even further is that the continent's market is largely that supplied from UNICEF and a local manufacturer would face stiff competition from multinational suppliers to UNICEF – unless some preferential supply agreement was made. The dilemmas facing a local vaccine manufacturer are therefore many, not least of which is the unpredictability of seasonal vaccine demand in a continent still struggling to afford routine vaccines costing a fraction of influenza vaccine.

To date technology transfer of influenza manufacturing capacity has been exported to 13 countries globally. It may be appropriate for new start-up vaccine production in Africa to examine alternate technologies to the classical egg-based TIV. The choice of which technology to embark on will depend on cost and the time it would take for production to come on line. For example, to produce 20 million doses per year, egg-based live-attenuated influenza vaccine (LAIV) vaccine, which would be the cheapest option at approximately US\$ 1 million, would take two years to come online. Egg-based TIV would cost US\$10 million and take four years to production and TIV produced in an established cell culture line US\$100 million and six years to production.

5.3. The South African initiative for indigenous vaccine production in Africa

Despite the major challenges outlined above, the need for indigenous vaccine production is well recognised. A reliable and prompt supply of pandemic vaccine depends on sustained seasonal vaccine production. To address these needs, a network of manufacturers in a number of Latin American, Asian, African and Middle Eastern countries has been established under the banner of the Developing Country Vaccine Manufacturers Network (DCVMN – www.dcvmn.org). This network consists of a substantial number of indigenous vaccine producers especially in Asia and Latin America. In Africa, a modest amount of vaccines is produced in Egypt, Tunisia, Senegal and South Africa. The African Vaccine Manufacturers Initiative [AMVI] has been established with a mission to create sustainable vaccine manufacturing capacity on the continent to meet the needs of its peoples. AMVI's strategic objectives are to facilitate partnerships, high-level advocacy, mobilisation of the required resources, and development of appropriate skills.

In sub-Saharan Africa the only influenza production facility is at the Biovac Institute in Cape Town, South Africa, a public–private partnership between the South African government and private industry. At present, this facility has developed the capacity for multiproduct formulation and filling, including that for influenza vaccine imported in bulk. This facility will be inspected at the end of 2012 by the local regulatory authority, the South

African Medicines Control Council. A future licence for influenza vaccine manufacture is anticipated in 2015.

5.4. Influenza initiatives in Africa from non-governmental organisations

PATH (www.path.org) is a non-governmental organisation dedicated to improving the health of people throughout the world by advancing technologies, strengthening systems and encouraging healthy behaviours. Approximately 34% of its activities are dedicated to vaccine related projects, included in the latter are four influenza vaccine projects in Africa. PATH is involved in the collation and analysis of data from maternal immunisation projects and is currently collaborating on a large maternal immunisation study in Soweto, South Africa. Another programme involves the evaluation of LAIV using both the Ann Arbor and the Leningrad LAIV vaccine strains. The former has shown consistently better efficacy than inactivated vaccine in children < 2 years – 46% in a recent meta-analysis [34]. The technology to manufacture Leningrad LAIV, which PATH supports predominantly [35], has now been transferred to several developing countries and the safety and immunogenicity is currently being evaluated in Bangladesh and India. In Senegal a trial of TIV has been launched and in the future an adjuvanted TIV vaccine will also be tested. Adjuvanted TIV has recently been demonstrated to be superior to non-adjuvanted TIV in preventing laboratory confirmed influenza in children 6 to 72 months of age [36]. LAIV has been shown to be more effective than TIV in children – 54.9% fewer cases of culture-confirmed influenza than the group receiving TIV [37]. A suggested future influenza vaccination programme for children could consist of three phases—immunisation of pregnant women to protect young infants less than six months, followed by TIV with or without an adjuvant up to 2 years and then LAIV after two years for young children.

6. Conclusion

Influenza remains an enigmatic virus despite being one of the first human viruses isolated, in 1933, and many of its properties remain to be elucidated. Predicting antigenic changes and the consequences thereof for seasonal influenza outbreaks is still imprecise even in developed countries, as seen by the frequency of mismatches of vaccine strains. Anticipating pandemics is even more perplexing, as demonstrated by the unexpectedness of the 2009 H1N1 pandemic. Measuring the burden of disease is hampered by a lack of clear clinical endpoints, which similarly bedevils precision in measuring vaccine responses. Finally, influenza vaccine is unique among human vaccines in having changed little since its first licensure in 1945 and there is clearly much room for improvement. As an example, in three of the five priority groups designated by WHO's SAGE for influenza vaccination, i.e., young children, the elderly and those with underlying medical conditions, the efficacy of the vaccine is lower than in healthy young adults. In addition while a vaccine needing annual renewal and annual administration may be inefficient in a developed world setting, it is potentially unusable in most African settings. Importantly, public awareness and buy-in from decision-makers in African countries is still unpredictable.

Influenza has long been neglected on the African continent, largely because of huge competing health problems. The proceedings of this, the second Afriflu conference, have

shown that there is an increasing awareness of the need for influenza surveillance and has also demonstrated the value of vaccine interventions in the African setting. Surveillance has improved and the burden of influenza and influenza related diseases shown to be high, and often greater than in the developed world. This suggests that the health value and cost-effectiveness of vaccine interventions could be high, if logistic, programmatic, production, dosing, and effectiveness issues can be addressed. In addition to the usual cofactors seen elsewhere in the world, the epidemiology of influenza and the influenza-associated illness burden in Africa is driven to a large degree by coinfections. In southern Africa this is especially true with HIV, TB and *S. pneumoniae*. Tropical diseases and other possible cofactors prevalent in African countries still need urgent investigation.

It is clear that vaccine strategies will need to be specifically tailored to Africa's needs. For example, although TIV vaccine appears to be adequately effective in HIV-positive adults, it may lack efficacy in infants who are HIV positive – a problem of significant importance in sub Saharan Africa. No data are available on the effectiveness among HIV exposed children. Innovative strategies are being developed for the continent's influenza problems, such as maternal immunisation, not only because pregnancy offers the highest priority but also for the protection of the young infant.

Currently LAIV has not been explored to any extent in Africa but its demonstrable superiority in young children elsewhere in the world needs to be examined with respect to Africa. Simultaneously, use of adjuvanted vaccine for young children in Africa needs to be further investigated. The final, and perhaps most important, African influenza barrier to be overcome is that of developing and implementing a communication initiative. This should be directed not only at political decision-makers, but also at the general public, especially healthcare workers who at present do not recognise influenza as a major problem when weighed against the enormity of the competing health problems of Africa.

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Conflicts of interest and Disclaimer

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of their institutions or organisations.

Appendix A.: Afriflu2 conference agenda

AGENDA
Afriflu workshop 2012
8 November 2012
Cape Town, South Africa
Influenza immunisation in Africa

Time	Topic	Presenter	
08:00	08:30	Workshop introduction	B Schoub (NICD, SA)
08:30	10:30	Disease burden session	<i>A Cohen (CDC, SA), P Ndumbe (Univ. Buea, Cameroon)</i>
08:30	08:50	Southern Africa perspective	A Cohen
08:50	09:10	Central Africa perspective	R Njouom (Centre Pasteur, Cameroon)
09:10	09:30	Eastern Africa perspective	J Mott (CDC, Kenya)
09:30	09:50	Western Africa perspective	W Ampofo (NMIMR, Ghana)
09:50	10:30	General discussion	
11:00	12:30	Session on priority groups	<i>W Ampofo, C Steffèn (AMP, France)</i>
11:00	11:20	SAGE global perspective	J Bresee (CDC, USA)
11:20	11:40	Local perspective	C Cohen (NICD, SA)
11:40	12:00	Global NGO perspective	J Ortiz (PATH, USA)
12:00	12:30	General discussion	
14:00	15:30	Vaccine security session	<i>B Schoub, B Gessner (AMP, France)</i>
14:00	14:20	Vaccine production in Africa	P Tippoo (Biovac Institute, SA)
14:20	14:40	WHO perspective	M Friede (WHO, Geneva)
14:40	15:00	Lessons learnt from the pandemic	P Ndumbe
15:00	15:30	General discussion	
15:30	16:00	Wrap up and conclusion	B Schoub

Abbreviations:

DCVMN	developing countries vaccine manufacturers network
ILI	influenza-like illness
LAIV	live-attenuated influenza vaccine
SAGE	strategic advisory group of experts on immunisation
SARI	severe acute respiratory illness
TIV	trivalent inactivated influenza vaccine
WHO	World Health Organization

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