1. Summary

- **General information on meningococcal disease and vaccines:** Meningococcal meningitis is a bacterial infection. Disease incidence is concentrated in West and Central Africa, where historically, serogroup A has been the most important cause of disease. More recently, meningitis outbreaks have increasingly been associated with serogroup C, and to a lesser extent, serogroup W.
- Two types of vaccines are available against meningococcal meningitis: conjugate and polysaccharide vaccines. UNICEF procures meningococcal A conjugate vaccines for use in Gavi-funded campaigns, paediatric routine immunization (RI) programmes, and a variety of meningococcal conjugate and polysaccharide vaccines for use in emergency outbreak response. The International Coordinating Group (ICG) on Vaccine Provision for Epidemic Meningitis Control brings together several partners involved in emergency health programmes and disease outbreak response. It forecasts meningococcal vaccine needs, and coordinates and prioritises the use of limited meningococcal vaccine availability based on disease epidemiology. Since 2009, UNICEF has procured meningococcal vaccines on behalf of the ICG.
- **Meningococcal A conjugate vaccines:** A meningococcal A conjugate vaccine, extensively used in mass campaigns across targeted regions in Africa since 2010, has dramatically decreased meningococcal A disease incidence. However, meningococcal A conjugate vaccine country demand remains uncertain given that national immunization programme adoptions are predicated on the timing of Gavi funding decisions, country readiness, and competing vaccine introduction priorities.
- Since 2010, UNICEF meningococcal A conjugate vaccine supply security has been dependent on one manufacturer, which supplies 90-98% of all meningococcal A vaccine.
- **Meningococcal C- and W-containing vaccines:** Demand for meningococcal C- and W-containing vaccines is uncertain, as serogroup C and W disease epidemiology for sub-Saharan Africa is not well known, and previous outbreaks have been infrequent and sporadic. WHO prequalified meningococcal C-containing vaccine availability was insufficient to meet recent outbreak requirements as a result of inaccurate serotype forecasting.
- UNICEF and other partners will work closely with industry to develop solutions to secure meningococcal vaccine supply availability.
- UNICEF will tender on behalf of the ICG for serogroup C- and W-containing meningococcal vaccines during 3Q 2015 to procure quantities for an emergency stockpile to cover 2016 and 2017 outbreak response.

2. General Brief and Background

Meningococcal meningitis, also known as cerebrospinal meningitis, is caused by *Neisseria meningitides (Nm)* bacteria. It is a contagious infection of the membranes surrounding the brain and spinal cord and transmits from person to person through respiratory droplets.\(^1\) It can cause severe brain damage and is fatal in 50% of the cases if not treated; and can leave persistent neurological defects in as many as 10-15% of survivors. Globally, it has caused an estimated 700,000 cases and 70,000 deaths over the past 10 years.\(^2\) Twelve strains (serogroups) of *Nm* have been identified, of which six (A, B, C, W, X and Y) are known to cause meningitis in humans, and can lead to disease outbreaks. Whereas serogroup A has traditionally been associated with most epidemic outbreaks, other serogroups cause epidemics at a lower frequency.\(^3\) The geographic distribution and epidemic potential differs according

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to the serogroup. Twenty-six African countries in sub-Saharan Africa (SSA), known as the “meningitis belt”, carry the highest epidemic risk and burden of disease. It has an aggregate at-risk population of 300 million people (Figure 1). Mass vaccination campaigns with meningococcal A conjugate vaccine have dramatically decreased serogroup A incidence.\textsuperscript{4} Subsequently, most cases were until recently associated with serogroup W, and since 2013, cases associated with serogroup C have spread gradually from Nigeria to other areas (Burkina Faso, Mali and Niger).

Figure 1 Countries or areas at high risk of meningococcal meningitis 2015\textsuperscript{5}

Two types of vaccines are available against meningococcal meningitis: conjugate and polysaccharide vaccines (Table 1).\textsuperscript{6} Conjugate vaccines have several advantages over polysaccharide vaccines. Besides offering longer-term protection, they reduce resident bacteria in the throat, and by consequence, its transmission. As a result, at appropriate levels of coverage, these vaccines confer longer-term population protection, i.e. protecting not only vaccinated individuals but also other unvaccinated individuals exposed to the bacteria.

Table 1 Meningococcal conjugate and polysaccharide vaccines

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Conjugate** | - Polysaccharide antigen from serogroups A, C, W, and/or Y conjugated to a carrier protein.  
- Available in monovalent (A, C), bivalent (AC) and tetravalent (ACWY) forms, as well as in a combination (HibMenC) form.  
- Although comparatively more expensive, offers longer-term protection, particularly in children under two years of age.  
- Used in RI programmes, preventative campaigns and emergency outbreak response. |
| **Polysaccharide** | - Based on purified, heat-stable, lyophilized capsular serogroups A, C, W, and/or Y polysaccharides.  
- Available in monovalent (A), bivalent (AC), trivalent (ACW) and tetravalent (ACWY) form.  
- Confers shorter-term protection and commonly used for outbreak response and travellers.  
- Not recommended for use in children under two years of age as not effective in this population. |

Source: WHO.

\textsuperscript{4} WHO, *Meningococcal Meningitis Fact Sheet*.  
WHO recommends countries, with high or intermediate endemic rates of infection and frequent outbreaks, introduce vaccination into national RI programmes in accordance with national epidemiology and programme considerations. Countries with less frequent rates of infection should target defined groups considered at-risk. WHO recommends using meningococcal conjugate vaccines in RI programmes, particularly as they confer a higher immunogenic response in children <2 years of age. WHO recommends the use of meningococcal polysaccharide vaccines for emergency outbreak control in resource-limited settings, except in confirmed serogroup C outbreaks, when meningococcal conjugate vaccines should ideally be used due to increased effectiveness of the vaccine. At present, seven WHO prequalified vaccines are available from four manufacturers, of which three are polysaccharide and four are conjugate vaccines (Table 2).

Table 2 WHO prequalified meningococcal vaccines

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Manufacturer</th>
<th>Type</th>
<th>WHO PQ</th>
<th>Formul.</th>
<th>Vial</th>
<th>Shelf Life</th>
<th>VVM</th>
<th>Cold Chain Capacity</th>
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</thead>
<tbody>
<tr>
<td>MenA</td>
<td>Serum Institute of India</td>
<td>Conj.</td>
<td>2010</td>
<td>Lyophilised</td>
<td>10 ds</td>
<td>36 months</td>
<td>Type 30</td>
<td>2.60 cm³</td>
</tr>
<tr>
<td>MenA (pediatric)</td>
<td>Bio-Manguinhos (Brazil)</td>
<td>Conj.</td>
<td>2014</td>
<td>Lyophilised</td>
<td>10 ds</td>
<td>36 months</td>
<td>Type 30</td>
<td>2.60 cm³</td>
</tr>
<tr>
<td>MenAC</td>
<td>Bio-Manguinhos (Brazil)</td>
<td>Polysac.</td>
<td>2007</td>
<td>Lyophilised</td>
<td>10 ds</td>
<td>24 months</td>
<td>Type 14</td>
<td>2.6 cm³</td>
</tr>
<tr>
<td>MenAC</td>
<td>Sanofi Pasteur (France)</td>
<td>Polysac.</td>
<td>1997</td>
<td>Lyophilised</td>
<td>10 ds</td>
<td>36 months</td>
<td>n/a</td>
<td>2.46 cm³</td>
</tr>
<tr>
<td>MenACWY</td>
<td>GlaxoSmithKline (Belgium)</td>
<td>Con.</td>
<td>2013</td>
<td>Lyophilised</td>
<td>1 ds</td>
<td>36 months</td>
<td>Type 14</td>
<td>32.60 cm³</td>
</tr>
<tr>
<td>MenACWY</td>
<td>Sanofi Pasteur (France)</td>
<td>Polysac.</td>
<td>2014</td>
<td>Lyophilised</td>
<td>10 ds</td>
<td>24 months</td>
<td>Type 7</td>
<td>54.88 cm³</td>
</tr>
<tr>
<td>MenACWY</td>
<td>Sanofi Pasteur (France)</td>
<td>Polysac.</td>
<td>2014</td>
<td>Lyophilised</td>
<td>10 ds</td>
<td>24 months</td>
<td>Type 30</td>
<td>11.13 cm³</td>
</tr>
</tbody>
</table>

Source: WHO.

The International Federation of Red Cross and Red Crescent Societies (IFRC), Médecins Sans Frontières (MSF), UNICEF and WHO, following the devastating meningitis outbreak in 1995-1996, established the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control (ICG) in 1997. It coordinates the use of meningococcal vaccines in response to emergencies.

With the support of the Bill and Melinda Gates Foundation (BMGF), the Meningitis Vaccine Project (MVP) developed a meningococcal A conjugate vaccine for use in SSA through the collaboration between WHO, the Program for Appropriate Technology in Health (PATH) in partnership with Serum Institute of India Ltd (SII) and Ministries of Health across Africa. The MenAfriVac® was introduced into selected countries in 2010 (Burkina Faso, Mali and Niger) with the support of Gavi, the Vaccine Alliance (Gavi). Gavi supports the elimination of serogroup A epidemics in Africa, funding meningococcal A conjugate vaccine introductions in eligible countries through mass campaigns targeting persons between 1-29 years of age and national introduction into paediatric RI programmes. Gavi also provided one-time support to the ICG’s meningococcal vaccine emergency stockpile, which has included meningococcal conjugate and polysaccharide vaccines for use in epidemic response.

3. Current Market Situation

3.1. Demand and Forecast

UNICEF anticipates all 26 African countries in the “meningitis belt” will complete mass campaigns by 2016, achieving expected high coverage rates. By end-2015, seventeen countries are projected to have introduced meningococcal A conjugate vaccine through mass campaigns accounting for a target population of 223 million. Nine countries remain with a total target population of 1.3 million. Serogroup A disease incidence is disappearing as a result of the efforts to date. With the support of the Bill and Melinda Gates Foundation (BMGF), the Meningitis Vaccine Project (MVP) developed a meningococcal A conjugate vaccine for use in SSA through the collaboration between WHO, the Program for Appropriate Technology in Health (PATH) in partnership with Serum Institute of India Ltd (SII) and Ministries of Health across Africa. The MenAfriVac® was introduced into selected countries in 2010 (Burkina Faso, Mali and Niger) with the support of Gavi, the Vaccine Alliance (Gavi). Gavi supports the elimination of serogroup A epidemics in Africa, funding meningococcal A conjugate vaccine introductions in eligible countries through mass campaigns targeting persons between 1-29 years of age and national introduction into paediatric RI programmes. Gavi also provided one-time support to the ICG’s meningococcal vaccine emergency stockpile, which has included meningococcal conjugate and polysaccharide vaccines for use in epidemic response.

Following the mass campaigns, WHO recommends meningococcal A conjugate vaccine introduction into national RI programmes, targeting infants aged 9-18 months with a 1-dose schedule, within 1-5 years upon the completion of mass campaigns. The recommendation includes a one-time mini catch-up campaign to vaccinate children born in the intervening period between completion of the initial mass campaign and national RI introduction.

8 WHO, Meningococcal Meningitis Fact Sheet.
Demand for meningococcal A conjugate vaccine introduction into national RI programmes depends upon confirmation of Gavi funding decisions, timing of Gavi approvals, country programmatic readiness, and competing vaccine introduction priorities facing many countries.

UNICEF anticipates all 26 countries to introduce meningococcal A conjugate vaccine during 2016-2018 (Figure 2). Ghana will be the first country to introduce the vaccine into its RI schedule during 2016, subject to Gavi confirmation. Four other countries (Mali, Niger, Nigeria and Sudan) may introduce the vaccine into RI programmes during 3Q-4Q 2016, while the timeline for RI introductions in other countries remains uncertain.

Beyond the mass campaigns across all 1-29 year olds, and RI use in infants, UNICEF and Gavi forecast the needs for a limited number of “one time mini catch-up” campaigns. It is estimated that approximately 53 million meningococcal A conjugate vaccine doses could be used for one time mini catch-up campaigns in 14 countries in 2015-2016. Finally, UNICEF and Gavi also forecast “mop-up” campaigns in countries where RI coverage levels are insufficient to maintain necessary levels of population immunity (Figure 2).

Figure 2 Gavi’s strategic demand forecast (SDF) v10 meningococcal A vaccine requirements

In addition to the above, UNICEF procures meningococcal conjugate and polysaccharide vaccines for emergency outbreak response upon ICG request. From January to end-June 2015 an outbreak of Meningitis (serogroup C) in Nigeria and Niger produced 21,202 cases and resulted in 1,606 deaths. As a result, the ICG has significantly increased its demand for meningococcal C- and W-containing vaccine. The ICG has indicated the need to secure 5 million doses of meningococcal C- and W-containing vaccine and 1.5 million doses meningococcal A conjugate vaccine doses to replenish and expand the stockpile.

3.2. Supply and Procurement

From 2005 through 2008, overall supply, of all types and serogroups of meningococcal vaccines available through UNICEF, averaged approximately 4 million doses a year. From 2009 to 2014, available meningococcal vaccine supply through UNICEF grew five-fold, from approximately 14.5 million doses to 70 million doses. The meningococcal A conjugate vaccine for use in mass campaigns since 2010, accounts for most of the increase of supply (Figure 3).

To date, emergency response has accounted for approximately 1% of total meningococcal vaccine volumes (doses) procured through UNICEF (Figure 4). The ICG requests meningococcal vaccine procurement corresponding to emergency outbreak response requirements. The quantities that the ICG initially requests of manufacturers to make available under emergency stockpile arrangements have not always translated into the total volumes eventually procured in large part due to the inherent uncertainty in forecasting emergency outbreaks. The arrangement has often left manufacturers to bear the financial risk of any quantities not procured. Accordingly, manufacturers have responded more recently by reducing availability of meningococcal vaccines for emergency response.

Figure 4 Meningococcal Vaccine Emergency Outbreak Procurement through UNICEF, 2011-2015

For example, in 2015, the ICG had requested 3 million doses of meningococcal vaccine (and specifically 1.5 million was for meningococcal A conjugate, and 1.5 million for meningococcal W-containing doses) be secured in an emergency stockpile for procurement upon request. However, supply availability and initial offers from manufacturers to the tender were insufficient to meet the demand for
W-containing doses. Furthermore, one manufacturer experienced technical difficulties, restricting the volume of the stockpile to respond to requests by countries channelled through the ICG.

As a result of this, UNICEF procurement of meningococcal C- and W-containing polysaccharide vaccines during 2015 exhausted WHO prequalified available supply. UNICEF had to mobilise at short notice and rely on meningococcal conjugate vaccines as well as non-WHO prequalified polysaccharide vaccines, in response to outbreaks in Nigeria and Niger. Looking ahead, there are concerns about the availability of meningococcal polysaccharide vaccines may to meet the demand identified by the ICG to respond to outbreaks – particularly of serogroup C disease.

Based on indications from manufacturers, UNICEF anticipates that the supply of meningococcal polysaccharide vaccine will remain constrained over the next few years. Manufacturers use meningococcal polysaccharide bulk to produce meningococcal conjugate and polysaccharide vaccines. There is a risk that internal competition for limited bulk product could increasingly favour production of meningococcal conjugate vaccines (at the expense of polysaccharide vaccines), given that meningococcal conjugate vaccine markets are generally characterized by less volatile and increasing demand, and higher prices especially in higher income countries.

UNICEF is reliant on one manufacturer of Meningococcal A conjugate vaccines that has supplied 90-98% of all meningococcal vaccines made available through UNICEF over the past decade (Figure 5).

Figure 5 Meningococcal Vaccine Supply through UNICEF by Manufacturer, 2005-2015 YTD (November)

Currently, UNICEF has two existing long-term arrangements (LTAs) to supply approximately 68 million meningococcal A conjugate vaccine doses for use in campaigns, and in emergency outbreaks (Table 3).

Table 3 UNICEF meningococcal vaccine LTA awards, 2014-2016

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Vaccine</th>
<th>Type</th>
<th>Use</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Institute of India</td>
<td>Men A</td>
<td>Conjugate</td>
<td>Campaigns</td>
<td>69,207,600</td>
<td>66,875,690</td>
<td>44,252,520</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conjugate</td>
<td>Emergency outbreaks</td>
<td>1,500,000</td>
<td>1,500,000</td>
<td>*</td>
</tr>
<tr>
<td>Sanofi Pasteur (France)</td>
<td>Men ACWY</td>
<td>Polysaccharides</td>
<td>Emergency outbreaks</td>
<td>*974,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>71,681,800</td>
<td>68,375,690</td>
<td>44,252,520</td>
</tr>
</tbody>
</table>

Source: UNICEF Supply Division.

Note*: 274,200 doses procured for use in 2015.

Note**: UNICEF launched a tender in 3Q 2015 to secure quantities for 2016 and beyond.
In addition, UNICEF launched two separate tenders in 2015, to secure quantities of meningococcal A conjugate vaccines for use in paediatric RI programmes mainly in 2016, and for conjugate and polysaccharide vaccines for use in emergency outbreaks also in 2016 and January to June 2017.

In order to mitigate the anticipated polysaccharide C- and W-containing vaccine supply constraints in 2016, UNICEF is exploring exceptional procurement of non-WHO prequalified meningococcal vaccines from manufacturers to meet demand for use in outbreak response, should manufacturers with WHO prequalified vaccine not have sufficient doses available. For UNICEF to procure non-WHO prequalified meningococcal vaccine, manufacturers must:

- Have one other existing prequalified vaccine;
- Ensure that the vaccine to be procured must be licensed by a national regulatory authority (NRA), having met WHO’s regulatory system strengthening (RSS) assessment in country of origin, and take responsibility for the regulatory oversight of the vaccine, including lot release certificates for UNICEF;
- Ensure that the vaccine is licensed in at least two additional countries with WHO RSS assessed NRAs.

3.3. Pricing

The terms specified in the aforementioned technology transfer agreement between PATH and SII largely govern the meningococcal A conjugate vaccine weighted average price (WAP) per dose that UNICEF has secured to date. Accordingly, the introduction price for the meningococcal A conjugate vaccine was relatively low and price changes from year to year have been small in nominal terms (Figure 3). However, those annual increases when viewed cumulatively since the vaccine’s introduction appear more significant – A 41% increase from US$ 0.41 in 2010 to US$ 0.60 in 2014.

The WAP per dose for Meningococcal AC polysaccharide vaccines available through UNICEF has also increased since 2010 – rising by 31% from US$ 0.93 to US$ 1.22 between 2010 and 2012. However since that time, the WAP has remained at US$ 1.22 per dose (Figure 3).

By contrast, the WAP per dose for Meningococcal ACWY polysaccharide vaccine WAP decreased by 76% over the period 2008 to 2010, from US$ 15.50 to just under US$ 4.00 (Figure 3). The marked decrease was likely the result of a number of factors: First, the introduction of meningococcal A conjugate vaccine and the demand volumes this vaccine created (e.g. with several large catch-up campaigns) led to increases in total meningococcal polysaccharide bulk production (since manufacturers use polysaccharide bulk to manufacture meningococcal A conjugate vaccine). Second, the introduction of meningococcal A conjugate vaccine led to some direct competition with Meningococcal ACWY polysaccharide vaccines.

While less visible in Figure 3, there was an unanticipated 25% increase in the WAP from US$ 4.00 in 2012 to US$ 5.00 in 2013. The increase related to UNICEF’s dependence on a single manufacturer and a price premium levied unexpectedly by that manufacturer to mitigate perceived demand uncertainty risks.

Despite the high cost for meningococcal polysaccharide multivalent vaccines compared to monovalent meningococcal A conjugate vaccine, in general terms multivalent polysaccharide vaccine prices are lower than similar meningococcal conjugate multivalent vaccines. Meningococcal multivalent conjugate vaccines can be up to seven times higher than their polysaccharide equivalents, ranging between US$ 12.00 and US$ 40.00 per dose, and as such are often not affordable for many endemic countries.

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4. Issues and Challenges

- Demand for meningococcal A conjugate vaccines is shifting from campaign-driven volumes to paediatric RI programme needs. The demand for the latter is currently uncertain, as it depends on country requirement confirmation, timing of Gavi approvals, and country programmatic readiness for these new vaccine introductions.
- The procurement of meningococcal C- and W-containing polysaccharide vaccines through UNICEF during 2015 exhausted WHO prequalified available supply. UNICEF was not able to award any supply of these vaccines for emergency outbreak response activities, and has had to rely on non-WHO prequalified meningococcal polysaccharide vaccine, as well as meningococcal conjugate multivalent vaccines in response to outbreaks.
- The quantities that the ICG initially requests of manufacturers to make available under emergency stockpile arrangements have not always translated into the total volumes eventually procured in large part due to the inherent uncertainty in forecasting emergency outbreaks. The arrangement has often left manufacturers to bear the financial risk of any quantities not procured. Accordingly, manufacturers have responded more recently by responding by reducing availability of meningococcal vaccines for emergency response.
- The shortage of meningococcal C- and W-containing polysaccharide vaccines may not be sufficient to meet the ICG’s 5 million doses stockpile requirements for 2016.
- Few manufacturers producing WHO prequalified meningococcal polysaccharide vaccines exist on the market. Some manufactures have signalled they may no longer make them available in the near future, as they shift using their polysaccharide bulk towards producing conjugate vaccines over their polysaccharide vaccine equivalents.
- A high reliance on a single manufacturer for monovalent conjugate vaccines and a single manufacturer for multivalent polysaccharide vaccines has led to cumulative WAP increases over time in the former market seen some unexpected price increases in the latter market.
- Currently, the cost per dose for meningococcal conjugate multivalent vaccines can reach up to sixteen times the price of a polysaccharide multivalent vaccine.

5. Steps Forward

- UNICEF urges programmes to conduct meningococcal disease modelling, including potential serotype substitution dynamics, and include meningococcal C- and W-containing vaccines demand in forecasts.
- UNICEF launched a tender beginning-August 2015 to supply 13.6 million meningococcal A conjugate vaccine doses for 2015-2016 RI introduction. UNICEF anticipates issuing LTAs end-3Q 2015.
- For outbreak response preparedness, UNICEF is actively following developments of WHO prequalified meningococcal C- and W-containing vaccine manufacturers, as well as encouraging manufacturers with non-WHO prequalified vaccine to seek prequalification to increase supply security.
- UNICEF anticipates issuing a tender for meningococcal vaccines during 3Q 2015 to ensure emergency stockpile availability for 2016; final composition of the stockpile will be determined by the ICG.
For further questions or additional information, please contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>UNICEF Division</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heather Deehan</td>
<td>Chief, Vaccine Centre</td>
<td>UNICEF Supply Division</td>
<td>+45 45 33 58 90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><a href="mailto:hdeehan@unicef.org">hdeehan@unicef.org</a></td>
</tr>
<tr>
<td>Guillermo Gimeno</td>
<td>Contracts Specialist</td>
<td>UNICEF Supply Division</td>
<td>+45 45 33 58 79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><a href="mailto:ggimeno@unicef.org">ggimeno@unicef.org</a></td>
</tr>
<tr>
<td>Aadrian Sullivan</td>
<td>Information Management</td>
<td>UNICEF Supply Division</td>
<td>+45 45 33 57 68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><a href="mailto:asullivan@unicef.org">asullivan@unicef.org</a></td>
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</table>

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