OK, welcome to this tutorial on the UNIVAC decision support model. Which is a universal framework for evaluating vaccine policy options in low- and middle-income countries.

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There are a couple of things I want to go through with this tutorial, and the first is I'll straight away get into how you access, navigate and run the Model. Then I'll jump back to the slides and we'll talk about the main calculations in the model. So, how UNIVAC inputs are used to generate the main outputs of the model.

OK, so first of all how do we actually access, and navigate, and run UNIVAC? For this I’m going to jump into my internet browser and go to the URL: www.univac-toolkit.com. This website gives much more information about the ProVac Initiative. It tells you where the models have been used in the past, in support, with Ministries of Health to sort of inform decisions. But the main section you need to go to, to get to the model, is this “Tools” section and “Register to download UNIVAC”. Here you’d enter a bunch of information and then submit that. An email would then go to PAHO, who will send you back a username and password. Once you have that you go to “Download Tools”, and then you would enter your details, log in, and you can then download the model to your hard drive. It’s important to do that, mainly because PAHO then has a list of registered users and can send email updates to those users as we post new versions of UNIVAC on this website.

OK, so what I’m going to do now is, I’ve actually save UNIVAC to my desktop so I’m actually going to run it from there. It’s quite a large Excel file, Excel workbook, so it does take a little while to load up. And if you haven’t enabled macros you need to do that before the model will run correctly. OK, so the first screen you see is this, and you can see the options for language are English and Spanish. The next version of the model will have French included as well. I’m going to leave it on English for this tutorial. There is also a bunch of license terms that PAHO have put together, so just make sure you’re happy with those before you agree to sort go in and use the model.

The first thing I’m going to do is set the zoom on the model using this section, to 150, just so that we can see the model a bit better as I go through. There are seven tabs in the model: instructions, set up, inputs, results, charts, uncertainty and calculations.

Now the sort of important feature of the model is that on the left-hand side of each of these tabs you see this plus button. If you hit that it will open a section so you can read it, and then if you hit it again it will close that section.

OK, I’ll quickly just run one analysis so that you can get an idea of how to use the model. So “Step 1” in the “Set up” tab asks you to choose a country. It’s currently set on “India”, but I’ll choose one in the PAHO Region. Let’s choose “Cuba”. Everything in yellow are cells that you need to do that before the model will run correctly. OK, so the first screen you see is this, and you can see the options for language are English and Spanish. The next version of the model will have French included as well. I’m going to leave it on English for this tutorial. There is also a bunch of license terms that PAHO have put together, so just make sure you’re happy with those before you agree to sort go in and use the model.

So, if we go to “Input”, what we’ll see are a bunch of steps of inputs. I’m just going to open one of them. This is the incidence rate for non-severe Rotavirus gastroenteritis cases and the incidence rates for non-severe
Rotavirus gastroenteritis visits or clinic visits. And you see there are yellow cells, which are what the user would need to enter. There is a mid-value and then an uncertainty range, which you might want to include for later uncertainty analysis, a low and a high. Then a source you can use to enter, or document your data.

But choosing Cuba here, as soon as you select that, what it does is transfer everything we have for Cuba into these yellow cells. And everything we have is shown on this right-hand side as recommended inputs. OK? So that’s what that’s doing. I’ll close that one on the set-up sheet and move to the second step, which is to choose the vaccine.

UNIVAC currently includes HPV vaccines, PCV, rotavirus, meningococcal and Hib vaccines. But the idea is that the model is flexible to be, the framework’s design to be flexible so that we can add new vaccines as required. I’m going to leave this on rotarix at the moment. But if you were to choose a new vaccine, it would change all of the set-up assumptions to things that are reasonable for that vaccine. OK, so we have Cuba and Rotarix. And then I’m going to go to the Results tab.

I’ll come back to the inputs later on, but just if you want I can quickly show you all of them. So if you hit the three (3) at the top here it will open everything, hit the one it will close everything. Hit the three, we’ll see all the different inputs the model. And that runs quite a way down. OK, for rotarix, so we’ve got things on price, on healthcare costs, and so on. And coverage, disease incidence, OK.

And then I’ll go to “Results”, and I’m going to run the model here. So, you just hit this button here “Run Model”. And what that is doing is churning through all of the cohorts that I’ve specified that I want to run in this analysis. So, it’s going through cohorts one, two three, four, five, running fourteen cohorts here. And then the progress bar tells me it’s done. I choose OK. And the primary outcome measure of the model is the cost-utility ratio. Which is the cost per DALY averted. So, in this particular example, based on data which probably isn’t brilliant for Cuba, just a very rough example. Is that the cost-utility ratio is 942, and this is would be in dollars usually but if you want to put your local currency in for everything it would also be reflected in local currency. So, this is $942 dollars per DALY averted, and that’s calculated by taking the difference in vaccine program costs, between your comparator (which is no vaccine) and your new intervention (which is adding the vaccine). So about $8.6 million. You then subtract your difference in healthcare costs between those two scenarios, with and without vaccine, to get $7.8 million. And then you divide that by the total health benefit, the difference in DALYs averted or difference in DALYs, which would give you 808 DALYs averted. So, the ratio, the cost-effectiveness would be 942 in this particular example.

There are charts and uncertainty analyses that you can do in addition to that.

But what I want to do is to jump back to the slides now quickly to explain some of these other outputs. So, if I go to table three it gives you a very sort of high level summary of the number of cases without the vaccine and with, and the difference. The number of visits without the vaccine and with, and the difference. Hospitalizations without and with, difference. And deaths as well. And you can drill down and get a bit more detail on those. Even look at them by calendar year, if you want, or cohort. But just to explain how the model is actually calculating events with and without vaccine.

So, I’m going to go back to the slides to do that. OK.

Right, so as I said the main outcome measure or output is the cost-utility ratio (cost per DALY averted). But there are a bunch of other outputs of UNIVAC. You get vaccine costs (with and without the vaccine), healthcare costs (with and without), disease events (with and without). And, what we define as cases in the model are community cases. So, they may or may not reach healthcare, it’s all cases. Clinic visits, or outpatient visits,
hospitalizations, and deaths, and also DALYs (disability adjusted life years). The model also calculates adverse events. And benefit risk ratios as well, if relevant to the vaccine you're interested in.

So, without vaccination, how man disease events can we expect over the lifetime of a birth cohort. So, the first thing UNIVAC does is to generate or pull-in (look up) United Nations Population Division projections of the number of individuals that will be alive in each single year of age and calendar year as the birth cohort ages through time.

So, just to sort of represent that graphically here you see the 2013 birth cohort, and the number of children that are aged zero (0) was a thousand (1000) initially in this case and every year we are sort of losing numbers of the population as that cohort ages. So, this is age one, two, three, four, five, six and so on. And you could see we would go on to a hundred years, but just for convenience I've cut that quite short.

OK, so we start with populations and what is that aging population look like for that particular cohort?

The second thing we do is multiply those population estimates by age specific rates of disease per hundred thousand per year, to estimate the number of disease events.

So, we would multiple them by a mortality rate to get the number of deaths in each of those single years as the cohort ages. So, in this case, we might be looking at rotavirus or a disease that mainly affects young children because we only have deaths in the under-five age group. And then no deaths are expected in the older age population as the cohort ages.

So, for convenience, for this example I'm just going to focus on the under-fives to keep this as simple as possible. So, you see there's more deaths in the early age groups, and sort of the age distribution tends to show there's less deaths as you get to older, two, three, four-year-old children.

OK, the next thing we do is, if you want to account for changes in inputs over time. So, things like demography are changing, mortality rates may be declining in the absence of a vaccine, vaccine coverage might be changing over time, and price of the vaccine may change, things like that. Then what you would need to do is repeat that process for a number of birth cohorts. And UNIVAC allows you to specify up to thirty birth cohorts.

OK, and then, the next thing we'd do is to repeat that process for each disease type and each outcome. So, the outcomes that the model uses are community cases (whether they reach care or not), clinic visits, hospitalizations, and deaths. And again, those are deaths irrespective of whether they’ve reached the hospital or not.

OK, and you then specify each disease type. So, this might be meningitis, might be pneumonia, might be rotavirus diarrhea. For whichever sort of pathogen you’re interested in, you can specify the types you want to look at. So, the model allows you to specify up to ten types of disease if required. OK, and you would repeat this process by entering rates of cases, rates of visits, rates of hospitalizations, and rates of death.

So, just to give you an example of different configurations you might want to use for rotavirus, this might be one. You just use a very simple one category of type of disease called “any rotavirus gastroenteritis”, and you’d estimate cases, visits, hospitalizations, and deaths.
Another configuration might be to drop community cases and think, well this isn’t likely to really drive my cost-effectiveness ratio, so I’m going to focus only on the visits, hospitalizations, and deaths. You may be very uncertain about this estimate anyway, so can just drop that.

Another configuration might be to look at any gastroenteritis. That would mean you need enter different efficacy estimates, that are obviously lower and reflect the fact that you’re only considering gastroenteritis cases. That’s possible as well.

A more common approach is to split rotavirus into non-severe rotavirus and add another disease type called severe rotavirus. And in this case you can see the non-severe rotavirus cases are assumed not to reach hospital or death, so we don’t have rates for those. And you can configure that in the UNIVAC set-up tab. Whereas severe cases will reach all of those different outcomes.

And the main configuration we recommend for rotavirus, is to include non-severe, server, and also intussusception, because UNIVAC allows you to specify severe adverse events in this section as well. And there’s a section where you can define whether it’s a severe adverse event or not. And in the case of intussusception you’re entering the background rate of intussusception and later on in the model there are inputs for relative risk that you can use to say by how much that background rate might be elevated with the introduction of the vaccine. And here you see we are only considering hospitalizations and deaths for intussusception.

OK, so every time you choose a vaccine in the model we will provide a recommended configuration but it doesn’t mean that you can’t change that. Just to be aware that if you do change it the inputs we have recommended might not be available so it might just show “no data” for a given configuration that you’ve set up.

OK, so, that’s without vaccination. What happens with vaccination? How many disease events can we expect over the lifetime of the cohort if we introduce the vaccine? The first thing we do is specify the period of vaccination.

So, in this example I’m going to vaccinate all children or all infants born between 2017 and 2026, so over a ten-year period.

The next thing the model does is multiply the age-specific disease events by one minus the impact of the vaccine. And the impact calculated by coverage of infant individuals that only have one dose, in the particular age group that we’re interested in, multiplied by the efficacy of that first dose in the particular age we’re interested and then we add to that the incremental benefit you get from individuals that only had two doses times the efficacy of that vaccine (or that number of doses) and we add on coverage of individuals that have had only three doses and he efficacy of that. And then so on, reflecting all of the doses that are considered in a given analysis.

One important thing to mention here is that we treat children under five years of age differently to individuals aged over five years of age. So, for everyone aged over five, we’re just doing his calculation in a simple way for entire years of age (as single years of age). But for everyone aged under five we’re dividing these calculations into weeks of age. So, we try and get a bit more of a precise estimate of what the impact would be in different weeks of age. And what that means is that you’ll see as we go through the inputs some quite detailed inputs on things like the age distribution of disease by week of age under five, vaccine coverage and timeliness of vaccination by week of age under five, and vaccine efficacy by time in weeks since the dose is given. And all three of those are actually distribution shapes that are fitted to your data, so that we can get a nice sort of smooth curve, estimating numbers by week of age.

OK, so then what happens is introducing the vaccine will reduce these numbers without vaccine to reflect a scenario with vaccine in each cohort. And then we have, for each of those cohorts we are tracking the benefits over
the future lifetime that cohort. In this case it’s only necessary to track them for five years, but if you were looking at cervical cancer or something, you’d obviously need to track them over the entire lifetime of the cohort.

OK, so, our competitor was no vaccine and we just basically sum up all of these deaths attributed to the vaccination period that we are considering, which is 2017 onwards. And we have 50 thousand deaths or so. And then we have the new option, with the vaccine, and we sum up the same number and compare them head-to-head. And we can say that roughly 50 thousand future deaths would be prevented if all children born in that period were tracked over their lifetimes.

OK, so that is essentially the main calculations that the model is going through. I just want to give you a quick sort of summary of the main benefits of this model, and its drawbacks. It’s purposefully been developed for use by Ministries of Health in low- and middle-income countries where data quality isn’t always perfect. So the main advantages of a sort of decision support model like this is that it is accessible, it’s been developed in Excel, it’s transparent, it can be easily explained, simple. It’s flexible so that you can quickly adapt the UNIVAC to look at different vaccines or different vaccine policy questions within a vaccine and do that in a timely way so you’re not spending a lot of time developing a new model from scratch, and making it sort of perfect representation of the world. It’s really aiming to guide decisions that will be made in the near future. And it’s also comparable because it shares common data on population, vaccine timeliness, and all of those kinds of things. It means the methods for discounting, all those things. It means that your comparisons between vaccines are likely to be more reliable. It’s one major drawback, is that it’s a static model. So, unlike dynamic models, it doesn’t track the number of susceptible, infectious, and immune individuals over time so it can’t directly simulate herd immunity and other indirect effects. So, that’s an important limitation of the model. In mitigation, calibration of dynamic models can be a lengthy/complex process. They might not always be defensible by Ministry of Health staff if they’re complicated and if they’re based on poor quality data. If you haven’t got the data you need to calibrate those models to fit the sort of missing transmission parameters, then the overall quality may be a bit uncertain. And then finally, it might not actually be necessary to develop a complicated model if plausible ‘what if’ scenarios can demonstrate that inclusion of indirect effects would be very unlikely to change a recommendation or decision. And it’s often the case with vaccines that simply showing the benefits among the vaccinated children is enough to recommend introduction of a vaccine because adding herd immunity will only vaccine look more cost-effective. It’s not always as simple as that, but that’s sort of a general principle. And there are features in the model for building different scenarios like that. And they may be based on real world impact from other settings, or from transmission dynamic models that have been developed similar countries (with similar epidemiological features.

OK, so, what I’m going to do now is go back to the model quickly and just go through it in a bit more detail.

So, for the set up tab, you’d obviously choose the country. And within the model there are these help buttons. Which, I’m not going to be able to have time to go through everything in great detail now, but if I’ve skipped over things then you can always go back and look at these help buttons to get a bit more information about a given section.

You choose the vaccine.

And you would choose the vaccine schedule. So, you can choose up to ten doses, in this case I’m only looking at two. I’m going to give the doses to both boys and girls, at ages two and four months. If you want to put in, in weeks, or whatever your particular schedules is, you can do that. If you’re looking at HPV vaccines you might want to enter in years. You say which vaccine it’s being given with, whether it’s BCG, DTP measles, or whether it’s being given at a new visit entirely (which it may be for HPV). Whether you want to include delays in vaccination
(realistic delays in vaccination) or whether you don’t want to do that. Whether you want to apply an age restriction. So, for rotavirus that might be relevant, that you want to apply an age restriction.

OK, disease categories. This should be a bit more familiar because we’ve been through this in the slides. So, these are the disease types, and you can specify up to ten. The configuration it’s given us for rotavirus are three diseases: non-severe rotavirus diarrhea, severe and intussusception.

One of them is labeled as an SAE (severe adverse event), just so that we’re aware that we need relative risk estimates for that and not efficacy.

And then we have the outcomes. So, this configuration of cases, visits, hospitalizations and deaths will reflect what I went through in the slides. So non-severe cases obviously don’t go on to get hospitalizations of deaths. And here we specify the age range we’re assuming they’re all under fives

Things that you do in the set up sheet will influence what happens in the inputs sheet.

OK, so, here we see the first step is the incidence of non-severe rotavirus and the incidence of non-severe rotavirus limits, and both of those are only for under fives. But if we were to change that, and say actually we want to look at the whole age range up to one hundred, what that does on the inputs sheet is give you a bunch of age inputs so that you need to then enter rates of cases and visits for all of those age groups. So, just to be aware that changes made here will have an influence on what’s show on the inputs page.

OK, and that’s the end of that step.

Step five is to choose the period of vaccination, so this is where I chose two thousand and seventeen to twenty-six or seven in the example in the slides, but here I’ve just bumped it up a bit and it’s two thousand and eighteen. And there’s a bunch of other inputs here which would be more complex to explain but you can use the help tab/help button to find out a bit more about those.

This is kind of a tricky step on the set up. What this is doing, is this is summarizing all of the disease types we choose and also the outcomes. So, we choose non-severe rotavirus cases and visits; we choose cases, visits, hospitalizations and deaths for severe; and we choose just hospitalizations and deaths for intussusception. And as I mentioned, in that under five age group we’re really trying to get to quite detailed estimates of age distributions by week of age. And one thing we can do is to say, well, let’s just assume that all of these different types of outcomes have the same age distribution. And to do that, you’d just set them all to A1, age distribution one. And that means you’ll only be presented with one set of inputs for one age distribution in the inputs page. But you may want to say, well, actually I think at least intussusception has a different age distribution so I’m going to choose A2, age distribution two, for that so that I get a new bunch of inputs for intussusception. And you can choose up to ten different age distributions if you want to maybe assume deaths for rotavirus are different, and you have data on that or something like that.

So, if I go to the inputs now, what we’ll see if we focus on step two which is looking at disease event rates under five, is that we now have two things, A one and A two. A one is asking for an age distribution in weeks of age, which is applied to all of the rotavirus outcomes at the moment. And A two is doing the same thing but it is being applied to intussusception. So, it’s telling the model which age distribution to use for each type of disease and outcome.

OK. And similar we also want to look at efficacy in quite narrow weeks of age or time since vaccination. And here we’re just assuming all of the outcomes have the same efficacy and it’s not applicable for intussusception.

So, when we go to efficacy assumptions…
Which will be in step nine of the inputs, what you see is just one set of assumptions called E one. If you added a bunch of new efficacy assumptions this would be repeated for each of the new assumptions you want to look at. So, in this case we’ve got efficacy of the first dose: 47 percent. Efficacy of the second dose: 93. Duration of efficacy, we’re saying it’s only lasting a couple of years and the standard deviation of that is nought (zero) point three, so it gives you some idea of the efficacy starting around 40 percent dropping off (waning) slowly over time.

And the same for dose two. It starts at 93 percent and then declines at a certain rate. And you can obviously change that based on evidence you might have, and adapt these things as required. OK, now…

The next thing on the set up sheet is to define your healthcare cost perspective. So, this is just defining the three types of disease non-severe, severe rotavirus, and intussusception. And if you remember from the non-severe, we only had visits. We didn’t have hospitalizations, so you see that’s greyed out. For intussusception we didn’t have visits, so they’re greyed out, but we did have hospitalizations. And you can choose up to three cost perspectives in the model. And here you’ve got government, system and society. But they could be, they could mean different things to you in terms of how you want to use those inputs. Typically a government perspective will include all the cost borne by the government. And a societal perspective will include all the cost borne by the government, as well as household costs and potentially other indirect costs like lost wages and things. But definitions for those perspectives can be found here in the popup. So, I’ve only chosen to look at a government perspective where this has been requested. And what that means is that on the inputs page, if I go to healthcare costs I’ll only have one input to put in from a government perspective for the average cost of a non-severe visit.

If I was to choose to also add a societal perspective cost, when I go to inputs it will also have this additional societal perspective cost in there and I’ll need to enter a realistic value for that. Adding that will also give me in the results page an additional output. So, when I rerun the model I can actually have a cost-utility ratio from a societal perspective because it’ll use the costs that I’ve entered here instead of this government cost for that particular analysis. OK, so I’m going to switch that off. There are other things you can specify here again about the age range whether the costs happen yearly or only once, and that kind of thing.

Right, and finally I’ll quickly go through inputs as a whole. So, as I mentioned you have the incidence rates for non-severe cases and visits, and then incidence rates for cases and visits of severe disease as well as hospitalizations and then a mortality rate for deaths. OK.

And then we have our intussusception incidence rate and mortality rate. We then have the age distribution under five. And as I said, this is where you specify what the age distribution should be. And the distribution takes a scale and a shape parameter, which you can vary to better reflect what the age distribution is in your particular setting. And if you go to the help button it will talk you through the ways you can actually fit the best curve to your data, if you were to enter it in here.

OK. We then have disability weights. Which is the proportion of healthy time lost while living with disease, so these are important things we need to calculate the DALYs. And then also the average duration of illness, which is entered in years of age.

We then have vaccine coverage for dose one over time. Dose two over time.

Then we have vaccine timeliness. Again, it’s a distribution that requires a scale and shape. So, you can vary that and better reflect the local situation in our country. And we have reasonable defaults that will be included in a new version of the model shortly from demographic and health surveys and UNICEF MICS surveys.

We then have equity of coverage. So, the base case analysis would generally assume that there is perfect equity, which is typically what most models would assume as their default. But what you can do is to say, well
actually what if coverage in the population (say coverage of the program) is sixty percent, and if you just follow the blue line. But actually the effective coverage is the proportion of high risk children that might die from the disease is only forty percent. So, that’s sort of saying that most of the deaths are probably clustered in groups that are outside the EPI program, and this makes an adjustment for that at different coverage levels. As I said, there’s usually not a brilliant amount of data to support these assumptions so in general we set it to perfect equity, and then you can run different scenarios to show what influence it would have on the results if you tried different parameters for this. OK. Vaccine safety, so for this particular vaccine these shouldn’t be considered reliable. These are just in there for the moment to help the model run and they will be updated with more robust sort of COCHRAN estimates shortly. But, essentially, it’s the relative risk compared to the background risk of intussusception in the one to seven day risk period after getting dose one and two. And the eight to twenty one day period after dose one and two. So, to find a bit more about that it’s worth looking at this help button in a bit more detail.

Vaccine efficacy, I’ve already kind of been through that.

And then we have vaccine program costs. What the price is over time. Inputs about the syringe costs, and handling and delivery costs. Wastage. And then the incremental health system cost per dose. So, this is where you add in all the costs to the health system like expanding the cold chain, printing new vaccination cards, social mobilization, all of those things are wrapped up into one incremental cost which is added to the cost of the vaccine. And if you use the help button, that gives better definitions of each of these different things. OK.

And then finally the health care costs, which I’ve already described

And then you would run the model. And, if you go through each of these tables you’ll get a much more detailed break down of all of the costs. The visits, and cases and so on.

You can also have a look at the charts here. More or less as a sort of debugging to make sure your inputs are reasonable and they reflect what you’d expect in terms of cases and deaths with and without the vaccine. It also shows the vaccine costs over time. Your healthcare costs, incremental health care costs, and so on.

And then uncertainty analysis. This is how you build up a what if scenario analysis. And I haven’t got time to through that in this tutorial but I think we’ll probably post a new tutorial just on uncertainty analysis. Which, will focus on that and other things like probabilistic sensitivity analysis.

OK, so I’m going to stop there and hopefully that’s been a useful quick overview of model to get you started.

And I’ll just finish on this slide, which tells you if you want to know more about ProVac or the tools that we’ve developed these are the weblinks to go to.

OK, thanks very much.